

## Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure

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**Objectives.** This study was performed to assess the utility of inhaled nitric oxide as a selective pulmonary vasodilator in patients with severe chronic heart failure and to compare its hemodynamic effects with those of nitroprusside, a nonselective vasodilator.

**Background.** Preoperative pulmonary vascular resistance is a predictor of right heart failure after heart transplantation. Non-selective vasodilators administered preoperatively to assess the reversibility of pulmonary vasoconstriction cause systemic hypotension, limiting their utility.

**Methods.** Systemic and pulmonary hemodynamic measurements were made at baseline, during oxygen inhalation and with the addition of graded doses of inhaled nitric oxide or intravenous nitroprusside in 16 patients with New York Heart Association class III or IV heart failure referred for heart transplantation.

**Results.** Pulmonary vascular resistance decreased to a greater extent with 80 ppm nitric oxide (mean  $\pm$  SEM 256  $\pm$  41 to 139  $\pm$

14 dynes $\cdot$ cm $^{-5}$ ) than with the maximally tolerated dose of nitroprusside (264  $\pm$  49 to 169  $\pm$  30 dynes $\cdot$ cm $^{-5}$ ,  $p < 0.05$ , nitric oxide vs. nitroprusside). Pulmonary capillary wedge pressure increased with 80 ppm nitric oxide (26  $\pm$  2 to 32  $\pm$  2 mm Hg,  $p < 0.05$ ). Mean arterial pressure did not change with nitric oxide but decreased with nitroprusside. Seven of the 16 patients, including 1 patient who did not have an adequate decrease in pulmonary vascular resistance with nitroprusside but did with nitric oxide, have undergone successful heart transplantation.

**Conclusions.** Inhaled nitric oxide is a selective pulmonary vasodilator in patients with pulmonary hypertension due to left heart failure and may identify patients with reversible pulmonary vasoconstriction in whom agents such as nitroprusside cause systemic hypotension. Inhaled nitric oxide causes an increase in left ventricular filling pressure by an unknown mechanism.

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As heart transplantation has evolved as a treatment for refractory heart failure, it has been recognized that early postoperative right heart failure is a common occurrence associated with substantial morbidity and mortality (1-3). Elevations of transpulmonary pressure gradient and pulmonary vascular resistance are common in patients with chronic left heart failure, and their persistence through the peritransplantation period can lead to right ventricular failure, particularly if prolonged ischemia has occurred during harvesting and transportation of the donor organ. Severe, fixed elevation of transpulmonary pressure gradient or pulmonary vascular resistance is therefore considered a contraindication to orthotopic heart transplantation. The immediate response of the pulmonary circulation to intravenous vasodilators, such as nitroprusside (4), amrinone (5) and prostaglandin E<sub>1</sub> (6), has

been used to identify patients at acceptable risk for transplantation, but the effectiveness of these agents in predicting the reversibility of pulmonary vasoconstriction is limited by their systemic hypotensive effects.

Nitric oxide, an endothelium-derived relaxing factor (7) produced from L-arginine by endothelial nitric oxide synthase (8), has an in vivo half-life of 111 to 130 ms (9). Inhaled nitric oxide has been shown to reverse pulmonary vasoconstriction in hypoxic lambs (10) and pediatric patients with congenital heart disease complicated by pulmonary hypertension (11). In adults with pulmonary hypertension due to the adult respiratory distress syndrome, inhaled nitric oxide decreases pulmonary vascular resistance without altering systemic arterial pressure (12,13). It has been demonstrated that in patients with pulmonary vascular disease; inhaled nitric oxide also causes a reduction in pulmonary vascular resistance (14,15), accompanied by an improvement in right ventricular performance, as indicated by an increase in stroke volume despite a decrease in right ventricular end-diastolic pressure (14).

To assess the potential role of inhaled nitric oxide in identifying reversible pulmonary vasoconstriction in patients with severe heart failure referred for heart transplantation, we compared its effects on transpulmonary pressure gradient, pulmonary vascular resistance and systemic arterial pressure with those of intravenous nitroprusside.

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**Table 1. Patient Characteristics**

Pt No.	Age (yr)/ Gender	Diagn	NYHA Class	LVEF	Outcome
1	58/F	DCM	IV	0.17	Died, not listed for transplantation
2	49/M	DCM	III	0.25	Transplantation performed
3	37/M	DCM	IV	0.12	Transplantation performed
4	50/M	CAD	IV	0.23	Died 4 weeks after transplantation (renal, hepatic failure)
5	54/M	CAD	IV	0.13	Transplantation performed
6	47/M	CAD	III	0.18	Awaiting transplant
7	50/M	CAD	III	0.15	Awaiting transplant
8	56/M	CAD	III	0.17	Awaiting transplant
9	52/M	DCM	III	0.10	Transplantation performed
10	57/F	HCM/DCM	IV	0.16	Transplantation performed
11	49/M	DCM	III	0.17	Transplantation performed
12	63/M	CAD	III	0.14	CABG
13	44/M	DCM	III	0.27	Awaiting transplant
14	45/M	DCM	IV	0.09	Died awaiting transplant
15	59/F	DCM	III	0.10	Awaiting transplant
16	53/M	DCM	III	0.17	Awaiting transplant
Mean	51			0.16	
SEM	2			0.02	

CABG = coronary artery bypass grafting; CAD = coronary artery disease; DCM = dilated cardiomyopathy; Diagn = diagnosis; F = female; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; M = male; NYHA class = New York Heart Association functional class; Pt = patient.

### Methods

**Patients.** The study group included 13 men and 3 women (mean age  $\pm$  SEM  $51 \pm 2$  years) with chronic New York Heart Association class III or IV heart failure who were referred to the Massachusetts General Hospital for consideration of heart transplantation (Table 1). The cause of heart failure was dilated cardiomyopathy in nine patients, coronary artery disease in six and progression of hypertrophic cardiomyopathy to ventricular dilation and systolic dysfunction in one patient. No patient had a history of primary pulmonary disease, and the results of pulmonary function testing were consistent with chronic left heart failure, showing a mild restrictive pattern and a mild decrease in diffusion capacity (16). All patients were treated with digoxin, diuretic drugs and vasodilators, and three (Patients 1, 9 and 15) were treated with amiodarone for atrial or ventricular arrhythmias. Radionuclide left ventricular ejection fraction was  $0.16 \pm 0.02$  (range 0.09 to 0.27). Patients 1, 2 and 14 had chronic atrial fibrillation, and Patient 15 had a ventricular paced rhythm; the remaining 12 patients were in sinus rhythm. The study protocol was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital, and written informed consent was obtained from all patients.

**Hemodynamic measurements.** Digoxin, diuretic drugs and vasodilators were discontinued 12 to 24 h before catheterization, and amiodarone therapy was continued. No premedication was administered. Right heart catheterization was performed by way of the internal jugular vein with a triple-lumen balloon-tipped catheter. Systemic arterial pressure was measured from a radial artery cannula or from the side arm of a femoral artery introducer.

The following hemodynamic variables were recorded: heart rate, right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure and systemic arterial pressure. Cardiac output was determined by the Fick oxygen technique. Oxygen consumption was measured with an MRM-2 oxygen consumption monitor (Waters Associates). Derived hemodynamic variables were calculated using the following formulas: Cardiac index (liters/min per  $m^2$ ) = Cardiac output/Body surface area; Transpulmonary pressure gradient (mm Hg) = mean pulmonary artery pressure - Pulmonary capillary wedge pressure; Stroke volume index ( $ml/m^2$ ) = Cardiac index/Heart rate; Right ventricular stroke work index ( $g\cdot m/m^2$ ) =  $(0.0136)$  (Mean pulmonary artery pressure - Right atrial pressure)(Stroke volume index); Left ventricular stroke work index ( $g\cdot m/m^2$ ) =  $(0.0136)$ (Mean systemic arterial pressure - Pulmonary capillary wedge pressure)(Stroke volume index); Systemic vascular resistance ( $dynes\cdot cm^{-5}$ ) =  $80$ (Mean systemic arterial pressure - Right atrial pressure)/Cardiac output; Pulmonary vascular resistance ( $dynes\cdot cm^{-5}$ ) =  $80$ (Transpulmonary pressure gradient)/Cardiac output.

**Nitric oxide delivery.** Nitric oxide gas (800 ppm in nitrogen [ $N_2$ ]) (Airco) was mixed with room air with the use of a standard low flow blender (Bird Blender) and then titrated with 100% oxygen using standard high flow rotameters (Timeter Instruments) to achieve a mixture of >90% oxygen with 20, 40 or 80 ppm nitric oxide and the remainder  $N_2$ . The mixture was then introduced into a non-rebreathing circuit consisting of large-bore aerosol tubing and a modified continuous positive airway pressure mask (Respironics Inc.). The inspired concentration of nitric oxide and nitrogen dioxide was measured by chemiluminescence (17) (model 14A,

**Table 2. Acute Hemodynamic Effects of Oxygen, Inhaled Nitric Oxide and Nitroprusside**

	Baseline	O <sub>2</sub>	NO (80 ppm) +O <sub>2</sub>	O <sub>2</sub>	Nitroprusside +O <sub>2</sub>
Heart rate (beats/min)	93 ± 6	90 ± 6	96 ± 6	99 ± 6	98 ± 7
Mean systemic arterial pressure (mm Hg)	84 ± 2	87 ± 2	89 ± 2	90 ± 2	68 ± 1*†‡
Right atrial pressure (mm Hg)	9 ± 2	10 ± 2	8 ± 2	9 ± 2	4 ± 1*†‡
Mean pulmonary artery pressure (mm Hg)	38 ± 3	37 ± 3	39 ± 2	38 ± 4	19 ± 3*†‡
Pulmonary capillary wedge pressure (mm Hg)	25 ± 3	26 ± 2	32 ± 2*‡	26 ± 3	9 ± 2*†‡
Transpulmonary pressure gradient (mm Hg)	14 ± 2	11 ± 1*	7 ± 1*‡	11 ± 2*	10 ± 1*†
Cardiac index (liters/min per m <sup>2</sup> )	2.1 ± 0.2	2.1 ± 0.1	2.3 ± 0.2	2.2 ± 0.2	2.9 ± 0.3*†‡
Stroke volume index (ml/m <sup>2</sup> )	23 ± 2	24 ± 2	24 ± 2	23 ± 2	30 ± 4
RV stroke work index (g-m/m <sup>2</sup> )	9 ± 1	9 ± 1	10 ± 1	9 ± 1	7 ± 1†
LV stroke work index (g-m/m <sup>2</sup> )	19 ± 2	20 ± 2	19 ± 2	20 ± 2	24 ± 2*†
Systemic vascular resistance (dynes·s·cm <sup>-5</sup> )	1,648 ± 1,493	1,649 ± 119	1,625 ± 121	1,692 ± 144	1,121 ± 140*†‡
Pulmonary vascular resistance (dynes·s·cm <sup>-5</sup> )	323 ± 64	256 ± 41*	139 ± 14*‡	264 ± 49*	169 ± 30*†‡
PVR/SVR	0.19 ± 0.03	0.15 ± 0.02	0.09 ± 0.01*‡	0.15 ± 0.03	0.15 ± 0.02†
Oxygen saturation (%)	94 ± 2	99 ± 1*	99 ± 1*	100 ± 1*	99 ± 1*

\*p < 0.05 versus baseline. †p < 0.05 nitroprusside versus nitric oxide (NO). ‡p < 0.05 versus previous period of oxygen (O<sub>2</sub>). Data are presented as mean value ± SEM. LV = left ventricular; PVR = pulmonary vascular resistance; RV = right ventricular; SVR = systemic vascular resistance.

ThermoEnvironmental Instruments Inc.) and that of oxygen by polarimetry (Hudson Oxygen Meter). The total gas flow rate was maintained at 45 liters/min, a level that reduced the nitric oxide residence time within the breathing circuit and, hence, the time for the oxidation of nitric oxide to nitrogen dioxide. Nitrogen dioxide was not measurable in the expired gas at any dose of nitric oxide. Exhaled gases were scavenged and discarded to the atmosphere. Blood methemoglobin levels were determined spectrophotometrically (18) at baseline and during the inhalation of 80 ppm nitric oxide.

**Study protocol.** All measurements were made with the patient supine and wearing a face mask. Hemodynamic data were obtained during a baseline period with the patient inhaling room air; during inhalation of >90% oxygen; during inhalation of 20, 40 and 80 ppm nitric oxide in addition to >90% oxygen; during another period of >90% oxygen; and during the intravenous administration of nitroprusside in addition to the inhalation of >90% oxygen. We administered >90% oxygen during nitroprusside infusion to avoid hypoxemia due to intrapulmonary shunting. To allow valid comparisons among baseline, nitroprusside and nitric oxide periods, we administered >90% oxygen throughout the study protocol. The dosage of nitroprusside was titrated upward until a systolic arterial pressure of 85 mm Hg, a mean pulmonary artery pressure of 20 mm Hg or a maximal dose of 500 µg/min was achieved. Hemodynamic measurements were obtained 5 min after the dose of nitric oxide was altered or 5 min after the desired dose of nitroprusside was reached. The total duration of nitric oxide administration to each patient was ~40 min.

**Statistics.** Results are expressed as mean value ± SEM. A two-way analysis of variance with subsequent comparisons of group means by the Newman-Keuls test was used for comparisons among the treatment periods of room air, oxygen, 80 ppm nitric oxide with oxygen and nitroprusside with oxygen, as well as for evaluation of the dose response to 0 to 80 ppm of nitric oxide. Preoperative and postoperative hemodynamic variables

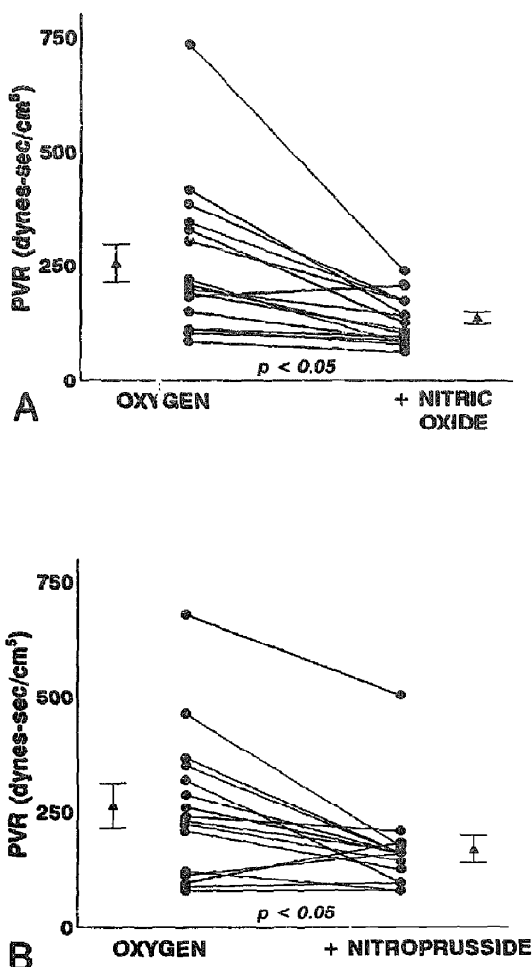
in those patients who underwent transplantation were compared by paired Student *t* testing. A linear regression was used to compare the changes in pulmonary vascular resistance produced by nitric oxide with those observed after transplantation. A *p* value < 0.05 was considered significant.

## Results

**Baseline measurements.** Right atrial pressure was elevated at 9 ± 2 mm Hg, as were mean pulmonary artery pressure at 38 ± 3 mm Hg and pulmonary capillary wedge pressure at 25 ± 3 mm Hg (Table 2). Cardiac index was depressed at 2.1 ± 0.2 liters/min per m<sup>2</sup>. Pulmonary vascular resistance was elevated at 323 ± 64 dynes·s·cm<sup>-5</sup>.

**Effects of >90% oxygen.** During inhalation of >90% oxygen, arterial oxygen saturation increased from 94 ± 2% to 99 ± 1% (*p* < 0.05), transpulmonary pressure gradient decreased from 14 ± 2 to 11 ± 1 mm Hg (*p* < 0.05), and pulmonary vascular resistance decreased from 323 ± 64 to 256 ± 41 dynes·s·cm<sup>-5</sup> (*p* < 0.05) (Table 2). There was no effect on mean systemic arterial pressure or systemic vascular resistance. There were no significant differences in hemodynamic variables between the two >90% oxygen periods.

**Effects of nitric oxide.** With the addition of 80 ppm nitric oxide to >90% oxygen, mean pulmonary artery pressure was unchanged, but pulmonary capillary wedge pressure increased from 26 ± 2 to 32 ± 2 mm Hg (*p* < 0.05) (Table 2). An increase in pulmonary capillary wedge pressure ≥ 5 mm Hg was observed in 9 of the 16 patients (Patients 1 to 3, 5 to 8, 10, 16). Transpulmonary pressure gradient decreased from 11 ± 1 to 7 ± 1 mm Hg (*p* < 0.05), and pulmonary vascular resistance decreased from 256 ± 41 to 139 ± 14 dynes·s·cm<sup>-5</sup> (*p* < 0.05, Fig. 1A). Cardiac output, mean systemic arterial pressure and systemic vascular resistance were unchanged. The ratio of pulmonary vascular resistance to systemic vascular resistance

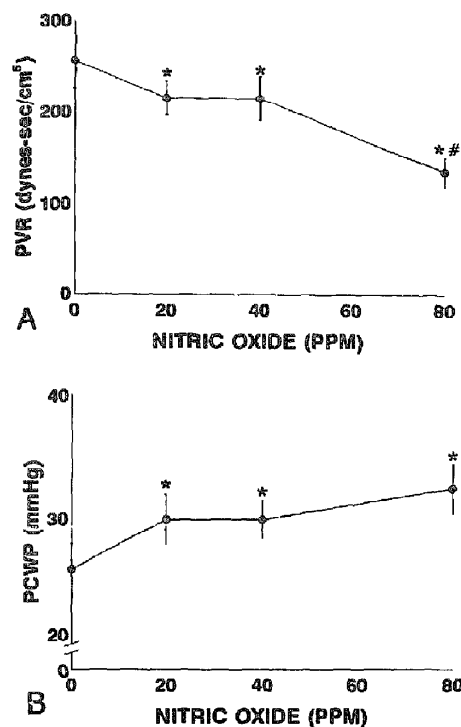


**Figure 1.** A, Pulmonary vascular resistance (PVR) during oxygen administration and after the addition of 80 ppm nitric oxide in each of the 16 patients. B, Pulmonary vascular resistance during oxygen administration and with the maximal dose of nitroprusside in each of the 16 patients. The mean value ( $\Delta$ ) and SEM are also shown.

decreased from  $0.15 \pm 0.02$  to  $0.09 \pm 0.01$  with nitric oxide ( $p < 0.01$ ).

The effects of nitric oxide dosage on pulmonary vascular resistance and pulmonary capillary wedge pressure are shown in Figure 2, A and B, respectively. The maximal reduction of pulmonary vascular resistance was seen at 80 ppm, although an effect was observed with doses of 20 and 40 ppm. Pulmonary capillary wedge pressure increased with a dose of 20 ppm of nitric oxide; there was no further significant increase with doses of 40 or 80 ppm.

**Effects of nitroprusside.** With the addition of nitroprusside ( $214 \pm 43 \mu\text{g}/\text{min}$ ) to  $>90\%$  oxygen, mean pulmonary artery pressure decreased from  $38 \pm 4$  to  $19 \pm 3$  mm Hg ( $p < 0.01$ ), and pulmonary capillary wedge pressure decreased from  $26 \pm 3$  to  $9 \pm 2$  mm Hg ( $p < 0.01$ ) (Table 2). Transpulmonary pressure gradient did not change, but cardiac index increased



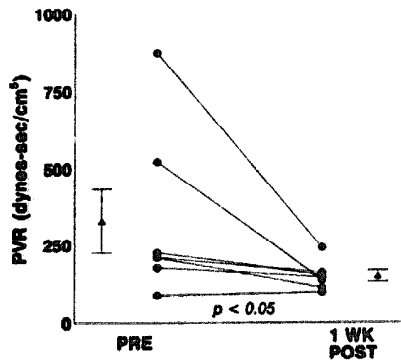
**Figure 2.** Relation between dose of nitric oxide and pulmonary vascular resistance (PVR) (A) and pulmonary capillary wedge pressure (PCWP) (B). Data are expressed as mean value  $\pm$  SEM. \* $p < 0.05$  versus oxygen alone. # $p < 0.05$  versus 20 and 40 ppm nitric oxide. PPM = parts per million by volume.

from  $2.2 \pm 0.2$  to  $2.9 \pm 0.3$  liters/min per  $\text{m}^2$  ( $p < 0.05$ ), and pulmonary vascular resistance decreased from  $264 \pm 49$  to  $169 \pm 30$  dynes $\cdot\text{sec}/\text{cm}^5$  ( $p < 0.05$ ) (Fig. 1B). Mean systemic arterial pressure decreased from  $90 \pm 2$  to  $68 \pm 1$  mm Hg ( $p < 0.01$ ). The dosage of nitroprusside was limited to  $<500 \mu\text{g}/\text{min}$  by a decrease in systemic arterial pressure in 7 of the 16 patients (Patients 1, 5 and 10 to 14). The ratio of pulmonary vascular resistance to systemic vascular resistance did not change.

**Comparison of the effects of nitric oxide and nitroprusside.** Right atrial, mean pulmonary artery and pulmonary capillary wedge pressure were all lower during administration of nitroprusside than during administration of nitric oxide. However, both transpulmonary pressure gradient and pulmonary vascular resistance decreased to a greater extent with nitric oxide than with nitroprusside. Mean systemic arterial pressure was lower with nitroprusside, as was systemic vascular resistance. The ratio of pulmonary vascular resistance to systemic vascular resistance was lower with nitric oxide than with nitroprusside.

**Side effects.** No side effects were observed during nitric oxide or nitroprusside administration. Despite the increased pulmonary capillary wedge pressure with nitric oxide, arterial oxygen saturation remained  $>95\%$  in all patients, in part





**Figure 3.** Pulmonary vascular resistance (PVR) at the time of initial evaluation (PRE) and 1 week postoperatively (1 WK POST) in the seven patients who have undergone heart transplantation. The mean value ( $\Delta$ ) and SEM are also shown.

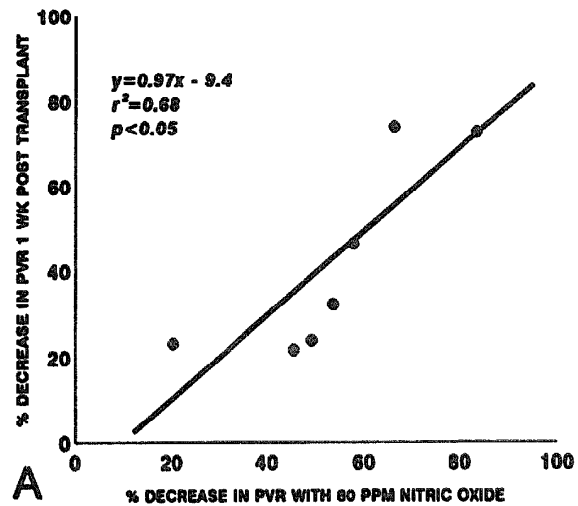
because of concomitant administration of  $>90\%$  oxygen. Methemoglobin levels did not increase to  $>1.5\%$  in any patient during nitric oxide administration.

**Clinical outcome.** In 13 of the 16 patients studied, pulmonary vascular resistance decreased to  $<200$  dynes $\cdot$ sec $\cdot$ cm $^{-5}$  with both nitroprusside and nitric oxide. In Patients 1 and 14, neither agent lowered pulmonary vascular resistance to  $<200$  dynes $\cdot$ sec $\cdot$ cm $^{-5}$ . These patients were thought not to be suitable transplant recipients on the basis of these data, and they died of progressive heart failure. Patient 9, whose pulmonary vascular resistance decreased to 240 dynes $\cdot$ sec $\cdot$ cm $^{-5}$  with nitroprusside and to 200 dynes $\cdot$ sec $\cdot$ cm $^{-5}$  with nitric oxide, underwent successful transplantation; his pulmonary vascular resistance was 146 dynes $\cdot$ sec $\cdot$ cm $^{-5}$  1 week postoperatively.

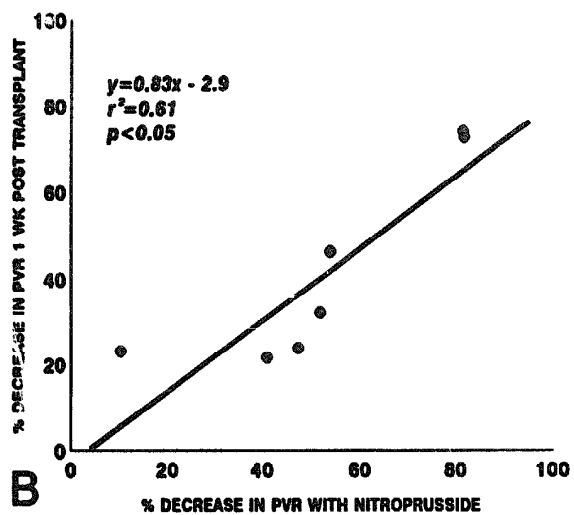
In all, seven study patients have undergone transplantation. Pulmonary vascular resistance decreased from  $328 \pm 104$  dynes $\cdot$ sec $\cdot$ cm $^{-5}$  preoperatively to  $157 \pm 18$  dynes $\cdot$ sec $\cdot$ cm $^{-5}$  1 week after transplantation ( $p < 0.05$ ) (Fig. 3). There was no additional change 4 weeks after transplantation. The decrease in pulmonary vascular resistance observed during inhalation of 80 ppm nitric oxide predicted the decrease measured 1 week after transplantation (Fig. 4A), as did the decrease in pulmonary vascular resistance observed with nitroprusside (Fig. 4B). Two patients (Patients 10 and 11), who had the highest preoperative pulmonary vascular resistance among those undergoing transplantation, were treated for early postoperative right heart failure with intravenous prostaglandin E<sub>1</sub> for the 1st 48 and 30 h, respectively. There were no deaths due to postoperative right heart failure.

### Discussion

Elevation of left atrial pressure in chronic heart failure is associated with an obligatory increase in pulmonary artery pressure to maintain a pressure gradient for forward flow in the pulmonary circulation. Further elevation of pulmonary artery pressure results from pulmonary vasoconstriction. The



**A**



**B**

**Figure 4.** Correlation between the decrease in pulmonary vascular resistance (PVR) observed during inhalation of nitric oxide (A) or infusion of nitroprusside (B) and that seen 1 week postoperatively in the seven patients who have undergone heart transplantation. PPM = parts per million by volume.

presence of pulmonary hypertension is of importance to patients undergoing heart transplantation because it is a risk factor for premature death in the postoperative period (1). The right ventricle of the donor heart undergoes ischemic injury during the harvesting and implantation procedures, making it particularly vulnerable to acute dysfunction and failure when confronted with an increase in afterload (19). Thus, patients with a fixed elevation of pulmonary vascular resistance are generally excluded as candidates for heart transplantation because of a high early postoperative mortality rate (2,3,20).

Pulmonary hypertension caused by either an elevation in

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