Inhaled Nitric Oxide Reduces Pulmonary Vascular Resistance More Than Prostaglandin E₁ During Heart Transplantation

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Heart transplantation in patients with increased pulmonary vascular resistance is often associated with postbypass right heart failure. We therefore compared the abilities of prostaglandin E₁ (PGE₁) and inhaled nitric oxide to reduce pulmonary vascular resistance during heart transplantation. Patients undergoing orthotopic heart transplantation for congestive heart failure were randomly assigned to either a PGE₁ infusion at a rate of 8 ng kg⁻¹ min⁻¹ starting 10 min before weaning from cardiopulmonary bypass (CPB) (n = 34) or inhalation of 4 ppm nitric oxide starting just before weaning from CPB (n = 34). Both treatments were increased stepwise, if necessary, and were stopped 6 h postoperatively. Hemodynamic values were recorded after the induction of anesthesia, 10 and 30 min after weaning from CPB, and 1 h and 6 h postoperatively. Immediately after weaning from CPB, pulmonary vascular resistance was nearly halved in the nitric oxide group but reduced by only 10% in the PGE₁ group. Pulmonary artery pressure was decreased approximately 30% during nitric oxide inhalation, but only approximately 16% during the PGE₁ infusion. Six hours after surgery, pulmonary vascular resistance and pulmonary artery pressure were similar in the two groups. The ratio between pulmonary vascular resistance and systemic vascular resistance was significantly less in the nitric oxide patients at all postbypass times. In contrast, the pulmonary-to-systemic vascular resistance ratio increased approximately 30% in the patients given PGE₁. Cardiac output, heart rate, mean arterial pressure, right atrial pressure, and pulmonary wedge pressure did not differ between the groups. Weaning from CPB was successful in all patients assigned to nitric oxide inhalation; in contrast, weaning failed in six patients assigned to PGE₁ (P = 0.03). **Implications:** Nitric oxide inhalation selectively reduces pulmonary vascular resistance and pulmonary artery pressure immediately after heart transplantation which facilitates weaning from cardiopulmonary bypass.

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Heart transplantation is a highly-effective, life-saving procedure for patients with severe congestive heart failure. Pulmonary hypertension secondary to chronic pulmonary venous hypertension in these patients may become nearly irreversible because of structural changes in the pulmonary vasculature. Increased pulmonary vascular resistance is associated with life-threatening risk of right heart failure after orthotopic heart transplantation and is a well-established predictor for early postoperative mortality in heart transplant patients (1–3).

For example, Kirklin et al. (4) have shown that early postoperative mortality progressively increases with increasing pulmonary vascular resistance, and special caution is warranted when considering patients with even moderately elevated pulmonary vascular resistance for heart transplantation. These findings were confirmed by single- and multicenter analyses (5,6).

After transplantation, the effects of ischemia, preservation, denervation, and surgical manipulations may impair right ventricular function of the donor heart (7,8). Additionally, cardiopulmonary bypass (CPB) is associated with release of vasoactive substances that may increase preexisting elevated pulmonary vascular resistance in heart transplant recipients (9). This, in turn, results in an acute increase in right...
ventricular afterload of the newly transplanted heart and may lead to right ventricular failure immediately after termination of CPB or in the early postoperative period (10,11). Weaning from CPB after heart transplantation is therefore often difficult and requires special caution.

Inotropic and vasodilating drugs are commonly required in patients undergoing heart transplantation. Isoproterenol and dobutamine, for example, are often given to increase contractility and heart rate. More importantly, a reduction of pulmonary vascular resistance may improve right ventricular performance and prevent right heart failure after heart transplantation. Prostaglandin E1 (PGE1) is a potent but nonselective pulmonary vasodilator and is extensively metabolized in pulmonary vessels. PGE1 has thus become a standard treatment in many hospitals, including ours, for treatment of elevated pulmonary vascular resistance during heart transplantation. Nonetheless, PGE1 typically produces substantial simultaneous reductions in systemic vascular resistance, which restricts its utility (12–14).

Recently, nitric oxide inhalation has been used to reduce pulmonary hypertension in a number of pathological conditions. In contrast to PGE1, inhaled nitric oxide induces relatively selective pulmonary vasodilation while producing minimal systemic vasoconstriction because its half-life is only 5 to 10 s (15–22). Some authors similarly report that nitric oxide markedly decreases pulmonary vascular resistance and transpulmonary gradient without substantial effect on the systemic vasculature in heart transplant candidates or after heart transplantation (23–25). Kieler-Jensen et al. (26) demonstrated that nitric oxide inhalation produced a selective reduction of pulmonary vascular resistance without effects on systemic vascular resistance, which may be helpful in severe right heart failure after heart transplantation.

The use of PGE1 for reducing pulmonary vascular resistance during weaning from bypass has been an established standard practice at our institution since 1991. We developed this practice because our experience has been that our late-phase transplantation patients often do poorly without PGE1. The aim of this study was to compare this standard treatment with inhaled nitric oxide, a relatively selective pulmonary vasodilator during weaning from CPB and perioperatively in patients undergoing orthotopic heart transplantation. We thus tested the hypothesis that nitric oxide inhalation provides more selective reduction in pulmonary vascular resistance than PGE1 infusion after orthotopic heart transplantation.

Methods

After approval from the Ethics Committee at the University of Vienna and written informed consent, we studied 70 adult patients (59 men, 11 women) undergoing orthotopic heart transplantation. All but two had congestive heart failure resulting from ischemic cardiomyopathy or dilated idiopathic cardiomyopathy. One patient had left heart failure after aortic valve replacement, and another was receiving a second transplant. Preoperative medications included a combination of digoxin, diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and nitrates. Additionally, some patients in both groups required a continuous preoperative infusion of PGE1 and/or dobutamine.

Patients were randomly assigned to a PGE1 infusion or inhalation of nitric oxide. Patients assigned to the prostaglandin group (n = 35) were given an IV infusion starting 10 min before weaning from bypass, at an initial rate of 8 ng · kg⁻¹ · min⁻¹. The dose was increased, stepwise, to 16 ng · kg⁻¹ · min⁻¹ and then to 24 ng · kg⁻¹ · min⁻¹, as required, to limit pulmonary hypertension. The study protocol specified that the PGE1 dose would be increased as required to maintain mean pulmonary artery pressure <25 mm Hg.

Patients assigned to the nitric oxide group (n = 35) were given nitric oxide in nitrogen inhalation at a starting concentration of 4 ppm. The concentration was increased, stepwise, as required, to treat pulmonary hypertension, up to a maximal concentration of 24 PPM. Again, the study protocol specified that the dose would be increased as required to maintain mean pulmonary artery pressure <25 mm Hg. Nitric oxide (1000 ppm in nitrogen) was delivered directly from a cylinder to a site 10 cm past the outlet of the ventilator; fresh gas flows were adjusted to avoid rebreathing.

Patients were switched to the alternative study drug when pulmonary artery pressure was consistently elevated at the highest permitted dose, and weaning from bypass proved difficult because of right heart failure. Right heart failure was defined by a high mean pulmonary artery pressure, an increase in right atrial pressure to more than 15 mm Hg, a decrease in mean pulmonary artery pressure <40 mm Hg, and a decrease in mixed venous oxygen saturation to <40%. Additionally, right heart failure was detected by dilation and hypocontractility of the right ventricle as observed in the surgical field.

Radial-arterial, central-venous, and flow-directed pulmonary-artery catheters were inserted in all patients. Anesthesia was induced by IV administration of etomidate (0.2 mg/kg), midazolam (0.1 mg/kg), fentanyl (5 μg/kg), and pancuronium (0.1 mg/kg). Patients were intubated, and mechanical ventilation was adjusted to maintain an arterial Pco₂ near 35 mm Hg. Anesthesia was maintained with fentanyl (0.3 mg/h), midazolam (4 mg/h), and repeated doses of pancuronium.

CPB was performed at a core temperature of 32°C with a bypass flow of 2.5 L · min⁻¹ · m⁻². The bypass circuit was primed with 2000 mL of lactated Ringer’s
solution, 100 mL of 20% mannitol, and 5000 IU of heparin. A membrane oxygenator (BARD Cardiopulmonary Division, C.R. BARD, Inc., Haverhill, MA) was used in all patients. Myocardial preservation techniques included crystalloid cardioplegia and topical cooling.

Isoproterenol was administered to all patients to achieve a heart rate between 100 and 120 bpm and to improve cardiac output. The infusion was started 10 min before weaning from CPB, at a dose of 0.02 µg·kg⁻¹·min⁻¹. Continuous infusions of norepinephrine or epinephrine were also given as required to maintain mean arterial pressure > 65 mm Hg.

Hemodynamic measurements were performed after the induction of anesthesia, 10 and 30 min after weaning from CPB, and 1 and 6 h postoperatively in the intensive care unit.

Mean arterial pressure, mean pulmonary arterial pressure, right atrial pressure, and heart rate were recorded continuously. Cardiac output was considered the average of three thermodilution measurements. Mixed venous oxygen saturation was recorded continuously during and after weaning from bypass. Pulmonary vascular resistance and systemic vascular resistance were calculated by using standard formulas. The transpulmonary gradient was considered to be the difference between mean pulmonary artery pressure and pulmonary wedge pressure. The relationship between pulmonary vascular resistance and systemic vascular resistance was calculated for all time points. Additionally, mixed venous and arterial blood gas tensions were measured at all time points.

Inspiratory concentrations of inhaled nitric oxide and nitrogen dioxide (NO₂) were measured with a chemiluminescence analyzer (MLU 8840, Monitor Labs United, USA) that had a response time of 3 s. Samples were obtained from the respiratory circuit near the Y-piece of the circle circuit. Co-oximetry was used to measure methemoglobin concentration.

Demographic and morphometric characteristics of the two study groups and potential confounding factors were compared by using unpaired, two-tailed t-tests. The same test was used to compare epinephrine use in the two groups. The ratio of pulmonary and systemic vascular resistance indicated the extent to which each study drug produced specific pulmonary vasodilation.

Our primary statistical analysis was multiple regression. The patients were nested random factors within the two study groups. The five time points were considered categorical factors. Comparison between groups was restricted to preplanned contrasts at the five specified time points. The fraction of patients switched from one study drug to the other was evaluated with a Fisher’s exact test. Patients switched to the alternative drug were statistically evaluated separately. A P value of 0.05 was considered statistically significant. All results were expressed as mean and least-square standard errors.

**Results**

One patient in each group was eliminated from statistical evaluation because phosphodiesterase inhibitors were given during the observation period, which violated the study protocol. Demographic and morphometric characteristics of the remaining patients were similar in each group (Table 1).

Immediately after the weaning from CPB, pulmonary vascular resistance in the nitric oxide group was nearly halved (from 326 ± 21 to 180 ± 15 dynes·s·cm⁻⁵, \( P < 0.0001 \)); resistance then remained essentially unchanged until 6 h after surgery. In contrast, pulmonary vascular resistance in the PGE₁ group decreased only approximately 10%, from 295 ± 30 to 264 ± 27 dynes·s·cm⁻⁵. However, resistance later gradually decreased to 204 ± 17 dynes·s·cm⁻⁵ over the initial 6 postoperative h, a value similar to that observed in the patients given nitric oxide (Fig. 1).

Even in patients with relatively lower preoperative pulmonary vascular resistance (Wood units < 4), inhaled nitric oxide produced a more pronounced reduction in pulmonary vascular resistance than the PGE₁ infusion. Immediately after transplantation in this subgroup, pulmonary vascular resistance was nearly normal (152 ± 23 dynes·s·cm⁻⁵) in patients receiving nitric oxide inhalation compared with a pulmonary vascular resistance (240 ± 43 dynes·s·cm⁻⁵) in patients treated with the PGE₁ infusion.

Immediately after the weaning from CPB, mean pulmonary arterial pressure in the nitric oxide group decreased approximately 30% (from 34 ± 2 to 23 ± 1 mm Hg, \( P < 0.0001 \)); pressure then remained essentially unchanged until 6 h after surgery. In contrast, mean pulmonary arterial pressure in the PGE₁ group decreased only approximately 16%, from 32 ± 2 to 26 ± 1 mm Hg and remained near that value for an hour. Six hours after surgery, though, pressures were nearly identical in the two groups (Fig. 2).

The pulmonary-to-systemic vascular resistance ratio decreased approximately 20% from 0.23 ± 0.02 to 0.19 ± 0.01 in the nitric oxide group. In contrast the pulmonary-to-systemic vascular resistance ratio in the patients given PGE₁ increased approximately 30% from 0.22 ± 0.02 to 0.29 ± 0.02. The ratio between pulmonary vascular resistance and systemic vascular resistance was significantly less in the nitric oxide patients at all postbypass times (Fig. 3).

After transplantation, cardiac output increased incrementally in both groups and was almost doubled 6 h postoperatively (\( P > 0.05 \) versus baseline for each group). However, there were no statistically significant differences between the groups at any time. Heart
rate, mean arterial pressure, right atrial pressure, and pulmonary wedge pressure did not differ significantly in the two study groups (Table 2). Posttransplantation base excess and pH remained stable in the nitric oxide group and decreased slightly in the PGE\(_1\) group, a difference that was not statistically significant. Isoproterenol was administered at comparable doses in all patients of both groups. Eight of 34 patients given nitric oxide required additional epinephrine or norepinephrine, compared with 12 of 28 patients in the PGE\(_1\) group. This difference did not reach statistically significance (8 of 34 versus 12 of 28, \(P = 0.06\)).

Table 1. Patient Characteristics and Potential Confounding Variables

|                      | PGE\(_1\)  
|----------------------|----------
| Male/female          | 31/3     
| Age (yr)             | 55 ± 9   
| Height (cm)          | 172 ± 5  
| Weight (kg)          | 73 ± 8   
| Ischemic cardiomyopathy/idiopathic cardiomyopathy/others | 14/20/1 16/18/1  
| Preoperative PGE\(_1\) infusion | 7/27     
| Cold ischemia time (min) | 169 ± 45  
| Total bypass time (min) | 184 ± 35  
| Preoperative pulmonary vascular resistance (Wood units)\(^a\) | 2.6 ± 1.1 2.8 ± 1.9  

Data are presented as mean ± sd. There were no statistically significant differences among the patients given PGE\(_1\) and nitric oxide. PGE\(_1\) = prostaglandin E\(_1\). \(^a\) Measured when placed on transplant waiting list.

Figure 1. Just after the induction of anesthesia, pulmonary vascular resistance was increased in patients assigned to prostaglandin E\(_1\) (PGE\(_1\)) (\(n = 28\), ■) and nitric oxide (\(n = 34\), ●). The administration of PGE\(_1\) and nitric oxide, starting just before the weaning from CPB, reduced resistance in both groups. However, the decrease in pulmonary vascular resistance was significantly greater in the patients assigned to nitric oxide. Data from six patients who were switched from PGE\(_1\) to nitric oxide are not shown. Results presented as mean ± sem. *Statistically significant differences between the groups.

Figure 2. Just after the induction of anesthesia, mean pulmonary arterial pressure was increased in patients assigned to prostaglandin E\(_1\) (PGE\(_1\)) (\(n = 28\), ■) and nitric oxide (\(n = 34\), ●). The administration of PGE\(_1\) and nitric oxide, starting just before the weaning from CPB, reduced pressure in both groups. However, the decrease in mean pulmonary arterial pressure was significantly greater in the patients assigned to nitric oxide. Data from six patients who were switched from PGE\(_1\) to nitric oxide are not shown. Results presented as mean ± sem. *Statistically significant differences between the groups.

Figure 3. The pulmonary-to-systemic vascular resistance ratio in patients assigned to prostaglandin E\(_1\) (PGE\(_1\)) (\(n = 28\), ■) and nitric oxide (\(n = 34\), ●). The administration of PGE\(_1\) and nitric oxide, starting just before the weaning from CPB, reduced the ratio in patients assigned to nitric oxide but increased the ratio in those given PGE\(_1\). Data from six patients who were switched from PGE\(_1\) to nitric oxide are not shown. Results presented as mean ± sem. *Statistically significant differences between the groups.

Weaning from CPB was successful in all patients assigned to nitric oxide inhalation. In contrast, high pulmonary vascular resistance and right ventricular failure precluded weaning from CPB in six patients.
Table 2. Hemodynamic Responses

<table>
<thead>
<tr>
<th></th>
<th>Pretransplantation</th>
<th>Posttransplantation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(after the induction of anesthesia)</td>
<td>(10 min after CPB)</td>
</tr>
<tr>
<td></td>
<td>PGE$_1$</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>91 ± 3</td>
<td>89 ± 3</td>
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<tr>
<td>CO (L/min)$^1$</td>
<td>3.9 ± 1.1</td>
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<td>MAP (mm Hg)</td>
<td>77 ± 3</td>
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<td>RAP (mm Hg)</td>
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<td>13 ± 1</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>17 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>TPG (mm Hg)</td>
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<td>13 ± 1</td>
</tr>
<tr>
<td>SvO$_2$ (%)</td>
<td>70 ± 2</td>
<td>67 ± 2</td>
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<tr>
<td>pH</td>
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<tr>
<td></td>
<td>127 ± 2$^*$†</td>
<td>130 ± 2$^*$†</td>
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<td>4.8 ± 1.3$^*†$</td>
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<td>60 ± 2$^*†$</td>
<td>65 ± 2$^*†$</td>
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<td>8 ± 0.5$^*†$</td>
<td>7 ± 0.6$^*†$</td>
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<td>11 ± 1$^*†$</td>
<td>11 ± 1$^*†$</td>
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<tr>
<td></td>
<td>15 ± 1</td>
<td>11 ± 1$^*$</td>
</tr>
<tr>
<td></td>
<td>69 ± 2</td>
<td>68 ± 2</td>
</tr>
<tr>
<td></td>
<td>7.33 ± 0.08$^†$</td>
<td>7.35 ± 0.01$†$</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM.

Patients switched to the alternative therapy are not included in this table.

PGE$_1$ = prostaglandin E$_1$, CPB = cardiopulmonary bypass, CO = cardiac output, MAP = mean arterial pressure, RAP = right atrial pressure, PCWP = pulmonary wedge pressure, TPG = transpulmonary gradient, SvO$_2$ = mixed venous oxygen saturation.

$^*$ Statistically significant differences between PGE$_1$ and nitric oxide at each time.

$^†$ Significant differences among pretransplant values.

assigned to PGE$_1$. Baseline hemodynamic characteristics of patients switched from PGE$_1$ to nitric oxide inhalation were similar to those in the remaining patients. The patients who failed to wean with PGE$_1$ had increased mean pulmonary arterial pressures (29 ± 2 mm Hg) at pump flows on CPB between 20% and 30% of normal. Right atrial pressure in the switched patients was 17 ± 2 mm Hg and mixed venous oxygen saturation decreased to 37% ± 3%. These values were sustained for 15 min.

After the switch to CPB with nitric oxide inhalation, mean pulmonary arterial pressure was 25 ± 2 mm Hg, and right atrial pressure was similar to that in the other patients. After the weaning from CPB, pulmonary vascular resistance in these patients decreased from 342 ± 30 dynes · s · cm$^{-5}$ before transplantation to 276 ± 19 dynes · s · cm$^{-5}$. In contrast to all the other patients, cardiac output in switched patients did not increase immediately after heart transplantation. Consequently, pulmonary vascular resistance remained high after heart transplantation, although the values gradually decreased. Six hours after surgery, there was no difference in pulmonary vascular resistance between switched patients and the remaining patients in either study group.

After the weaning from CPB, the switched patients required significantly more inotropic support than those who were able to continue with PGE$_1$. Mixed venous oxygen saturation was significantly lower after transplantation in switched patients (61% ± 5%) than in the others (69% ± 2%). Switched patients were excluded from this statistical analysis and were evaluated separately (Table 3).

Six of 34 patients assigned to nitric oxide inhalation received prostaglandin infusion preoperatively. Seven of 34 patients assigned to PGE$_1$ had prostaglandin infusion before heart transplantation. When evaluated separately, there were no differences in these patients compared with the remaining patients in each treatment group. Only one patient who switched from PGE$_1$ to nitric oxide inhalation had prostaglandin infusion before heart transplantation.

Most patients in our study were weaned from nitric oxide inhalation after 6 h postoperatively. In seven patients, attempts to terminate nitric oxide therapy abruptly increased pulmonary vascular resistance and reduced mixed-venous oxygen saturation and cardiac output. The concentration of inhaled nitric oxide in these patients was thus gradually reduced over a maximum of 48 h.

None of our patients died within 3 days of transplantation. Two patients from the nitric oxide group and one patient given PGE$_1$ developed systemic infections and died within the first month.

Discussion

Major predictors of unsuccessful heart transplantation are preexisting pulmonary hypertension and elevated pulmonary vascular resistance. The prognosis is so poor that patients with pulmonary vascular resistance exceeding 5 Wood units are often precluded from orthotopic heart transplantation. Even transplant patients with relatively lower preexisting pulmonary arterial pressures are at high risk for right ventricular failure, especially during the weaning from CPB. After transplantation, right ventricular function of the donor heart may be impaired by effects of ischemia, preservation, denervation, and surgical manipulations. Myocardial dysfunction after heart transplantation is therefore predominantly caused by right ventricular failure immediately after termination of CPB or in the early postoperative period.

CPB is associated with release of vasoactive substances that alter vascular smooth muscle and endothelial cell function and lead to vasoconstriction of the
pulmonary vasculature. These effects may increase preexisting elevated pulmonary vascular resistance in heart transplant recipients and increase the risk for acute right ventricular failure. An acute increase in right ventricular afterload of the donor heart during and immediately after weaning is associated with a decrease in right ventricular function of the donor right ventricle. However, Chen et al. (8,27) found that, after heart transplantation, the right ventricle adapts acutely with a significant increase in contractility and power. A significant decrease in transpulmonary efficiency was also observed, which presumably improves over time as the right ventricle adapts to increased afterload. It has been shown by Bhatia et al. (28) that the right ventricle after heart transplantation is enlarged and that tricuspid regurgitation is present in most of the patients on the first day after transplantation. Similarly, Bizouarn et al. (7) found a dilated right ventricle throughout the first two days after heart transplantation.

Weaning from CPB after heart transplantation thus may be an extremely difficult facet of heart transplantation and needs special caution. We therefore normally wean patients from CPB with stepwise reductions in pump flow and concomitant administration of inotropic and pulmonary vasodilating drugs.

The ideal drug for treatment of increased pulmonary vascular resistance and consequent right ventricular failure would be a vasodilator acting specifically on the pulmonary vasculature. In contrast, nonselective vasodilators typically induce systemic hypotension, which ultimately aggravates right ventricular dysfunction (7,8,29,30). Girard et al. (21) and Snow et al. (20) have shown that inhaled nitric oxide produced selective reduction in pulmonary vascular resistance after mitral valve replacement in patients with preoperative pulmonary hypertension. After heart transplantation the beneficial effects of nitric oxide inhalation on pulmonary hypertension were demonstrated by Kieler-Jensen et al. (26) and Auler et al. (23). Chen et al. (11,31) evaluated the effects of inhaled nitric oxide after heart transplantation in experimentally induced pulmonary hypertension. They found a reduction in pulmonary vascular resistance with an increase in pulmonary blood flow.

In contrast to all previous reports, our study was designed to directly compare the effects of two pulmonary vasodilators on pulmonary and systemic vascular resistance intraoperatively and immediately after heart transplantation. Our major finding was that immediately after heart transplantation nitric oxide inhalation reduced pulmonary vascular resistance 50%, whereas PGE1 decreased resistance only 10%. The dilatory effect of inhaled nitric oxide on the pulmonary vasculature was thus more pronounced than that of PGE1 infusion. Reduced pulmonary vascular resistance during nitric oxide administration was caused by a significant reduction in mean pulmonary artery pressure, whereas cardiac output and pulmonary capillary wedge pressure were well maintained in both groups.

The more pronounced reduction (more than 1 Wood unit) in pulmonary vascular resistance in the nitric oxide group was thus caused by a larger reduction in pulmonary artery pressure. However, a close relationship between the decrease in pulmonary artery pressure and pulmonary wedge pressure has been demonstrated after heart transplantation (32). Kieler-Jensen et al. (26) found that within 48 hours postoperatively, despite a reduction in pulmonary artery pressure and pulmonary wedge pressure, pulmonary vascular resistance was almost unchanged, remaining at pretransplant values. Furthermore, inhaled nitric oxide reduced pulmonary vascular resistance and pulmonary artery pressure, whereas pulmonary wedge pressure remained stable.

Pulmonary vasodilation resulting from inhaled nitric oxide was selective and was not accompanied by a

### Table 3. Hemodynamic Responses in Patients Switched from PGE1 to Inhaled Nitric Oxide

<table>
<thead>
<tr>
<th></th>
<th>Pretransplant (after the induction of anesthesia)</th>
<th>Posttransplant (10 min after CPB)</th>
<th>Posttransplant (6 h postoperatively)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>83 ± 6</td>
<td>133 ± 5†</td>
<td>128 ± 4†</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.1 ± 0.2</td>
<td>4.1 ± 0.4*</td>
<td>6.4 ± 0.6†</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>69 ± 7</td>
<td>71 ± 4</td>
<td>69 ± 6</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>8 ± 1</td>
<td>10 ± 2</td>
<td>12 ± 2†</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>18 ± 3</td>
<td>11 ± 3†</td>
<td>12 ± 2†</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>35 ± 4</td>
<td>25 ± 2†</td>
<td>27 ± 3†</td>
</tr>
<tr>
<td>PVR (dynes · s · cm⁻⁵)</td>
<td>342 ± 30</td>
<td>276 ± 19†</td>
<td>181 ± 20†</td>
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<td>TPG (mm Hg)</td>
<td>17 ± 2</td>
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<tr>
<td>Sv₀₂ (%)</td>
<td>73 ± 3</td>
<td>61 ± 5†</td>
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<td>pH</td>
<td>7.40 ± 0.02</td>
<td>7.26 ± 0.04†</td>
<td>7.25 ± 0.02†</td>
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</table>

Data are presented as mean ± SEM.

PGE₁ = prostaglandin E₁, CPB = cardiopulmonary bypass, CO = cardiac output, MAP = mean arterial pressure, RAP = right atrial pressure, PCWP = pulmonary wedge pressure, PVR = pulmonary vascular resistance, TPG = transpulmonary gradient, Sv₀₂ = mixed venous oxygen saturation.

*Statistically significant differences between PGE₁ and nitric oxide at each time.

†Significant differences among pretransplant values.
decrease in systemic vascular resistance. Consequently, the pulmonary-to-systemic vascular resistance ratio decreased during nitric oxide administration. Pulmonary vascular resistance also decreased during PGE1 administration. However, systemic resistance decreased even more. Consequently, the pulmonary-to-systemic vascular resistance ratio increased significantly in the patients given PGE1.

The efficacy of nitric oxide was further demonstrated by the fact that all patients given this drug were weaned successfully from bypass, whereas six patients initially given PGE1 were weaned only after being switched to nitric oxide. Six hours after transplantation, pulmonary vascular resistance was comparable in the patients given each vasodilator. This is consistent with the clinical observation that posttransplant pulmonary hypertension, although often severe, usually resolves rapidly (7,8,28,32,33).

Nitric oxide and its reaction with hemoglobin may lead to production of methemoglobin, and on a separate pathway, nitric oxide is oxidized to NO2. Nonetheless, several studies demonstrate that short-term exposure to nitric oxide at concentrations of 35 ppm is associated with minimal methemoglobin production (34). In our study, methemoglobin concentrations never exceeded commonly accepted levels, and NO2 concentrations never exceed 0.5 ppm.

We conclude that inhaled nitric oxide during weaning from CPB after heart transplantation may provide an important reduction in right ventricular afterload without decreasing systemic vascular resistance. This potent and relatively selective pulmonary vasodilator may facilitate weaning from CPB in patients undergoing heart transplantation.

References


