Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure

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Objective. 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. Nonselective 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 ± SEM 256 ± 41 to 139 ± 14 dynes - cm⁻²) than with the maximally tolerated dose of nitroprusside (264 ± 49 to 169 ± 30 dynes - cm⁻², p < 0.05, nitric oxide vs. nitroprusside). Pulmonary capillary wedge pressure increased with 80 ppm nitric oxide (26 ± 2 to 32 ± 2 mmHg, 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 perioperative 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 E₁ (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.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Diagn</th>
<th>NYHA Class</th>
<th>LVEF</th>
<th>Outcome</th>
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<td>1</td>
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<td>DCM</td>
<td>IV</td>
<td>0.17</td>
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<td>Died, not listed for transplantation</td>
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<td>0.23</td>
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<td>Died 4 weeks after transplantation (renal, hepatic failure)</td>
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<tr>
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<tr>
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<tr>
<td>15</td>
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<td>DCM</td>
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<tr>
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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 ± SEM 51 ± 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 ± 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 MR-2 oxygen consumption monitor (Waters Associates). Derived hemodynamic variables were calculated using the following formulas:

Cardiac index (liters/min per m²) = Cardiac output/Body surface area; Transpulmonary pressure gradient (mm Hg) = Mean pulmonary artery pressure - Pulmonary capillary wedge pressure; Stroke volume index (ml/m²) = Cardiac index/Heart rate; Right ventricular stroke work index (g-m/m²) = (0.0136)(Mean pulmonary artery pressure - Right atrial pressure)(Stroke volume index); Left ventricular stroke work index (g-m/m²) = (0.0136)(Mean systemic arterial pressure - Pulmonary capillary wedge pressure)(Stroke volume index); Systemic vascular resistance (dynes·sec·cm⁻⁵) = 80(Mean systemic arterial pressure - Right atrial pressure)/Cardiac output; Pulmonary vascular resistance (dynes·sec·cm⁻⁵) = 80(Transpulmonary pressure gradient)/Cardiac output.

Nitric oxide delivery. Nitric oxide gas (800 ppm in nitrogen [N₂]) (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 N₂. 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,
of Nitric Oxide Administration to Each Patient was -40

The dosage of nitroprusside was titrated upward until a systolic

duration to the inhalation of 20, 40 and 80 ppm nitric oxide.

We administered >90% oxygen throughout the study protocol.

Nitrogen dioxide was not measurable in the expired gas at any
doze 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. Transpulmonary pressure gradient decreased from 14 ± 2 to 11 ± 1 mm Hg (p < 0.05), and pulmonary vascular resistance decreased from 264 ± 49 to 169 ± 30 dynes cm⁻¹ (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.

Results

Baseline Measurements. Right atrial pressure was elevated 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 m². Pulmonary vascular resistance was elevated at 323 ± 64 dynes cm⁻¹.

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 cm⁻¹ (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 cm⁻¹ (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
2. The relation between dose of nitric oxide and pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP) is 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 ± 43 μg/min) to >90% oxygen, mean pulmonary artery pressure decreased from 38 ± 4 to 19 ± 3 mm Hg (p < 0.01), and pulmonary capillary wedge pressure decreased from 26 ± 3 to 9 ± 2 mm Hg (p < 0.01) (Table 2). Transpulmonary pressure gradient did not change, but cardiac index increased from 2.2 ± 0.2 to 2.9 ± 0.3 liters/min per m² (p < 0.05), and pulmonary vascular resistance decreased from 264 ± 49 to 169 ± 30 dyn/cm² cm⁻¹ (p < 0.05) (Fig. 1B). Mean systemic arterial pressure decreased from 90 ± 2 to 68 ± 1 mm Hg (p < 0.01). The dosage of nitroprusside was limited to <500 μg/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
because of concomitant administration of >90% oxygen. Met-hemoglobin levels did not increase to >1.5% in any patient during nitric oxide administration.

Clinical outcome. In 13 of the 16 patients studied, pulmo-nary vascular resistance decreased to <200 dynes-cm⁻² with both nitroprusside and nitric oxide. In Patients 1 and 14, neither agent lowered pulmonary vascular resistance to <200 dynes-cm⁻². 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 pulmo-nary vascular resistance decreased to 240 dynes-cm⁻² with nitroprusside and to 200 dynes-cm⁻² with nitric oxide, underwent successful transplantation; his pulmonary vascular resistance was 146 dynes-cm⁻² 1 week postoperatively.

In all, seven study patients have undergone transplanta-tion. Pulmonary vascular resistance decreased from 328 ± 104 dynes-cm⁻² preoperatively to 157 ± 18 dynes-cm⁻² 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 E₁ 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 presence of pulmonary hypertension is of importance to pa-tients 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

![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 (△) and SEM are also shown.](image-url)

![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.](image-url)
pulmonary venous pressure or arteriolar vasoconstriction may reverse with normalization of left atrial pressure after heart transplantation (21). This observation has led to efforts to utilize vasodilators such as nitroprusside (20) to identify patients with heart failure whose pulmonary hypertension is reversible and can therefore undergo heart transplantation. Costard-Jäckle et al. (22) reported that patients whose pulmonary vascular resistance decreased to ≥200 dynes·cm⁻² during nitroprusside infusion before transplantation had a mortality rate of only 4% at 3 months after transplantation. In contrast, those whose pulmonary vascular resistance could not be reduced to ≥200 dynes·cm⁻² or could be so reduced only at the expense of systemic hypotension had a 3-month mortality rate of 41% and 28%, respectively. Other vasodilators have been utilized in attempts to evaluate pulmonary vasoreactivity without incurring systemic hypotension. Prostaglandin E1 also caused limiting systemic hypotension at dosages required for adequate pulmonary vasodilation in patients with heart failure (6). Adenosine decreased pulmonary vascular resistance without decreasing systemic arterial pressure in patients undergoing evaluation for heart transplantation, but the degree of baseline pulmonary vasoconstriction of patients in this study was not in the range considered to be a contraindication to transplantation (23).

**Effects of nitric oxide on the pulmonary and systemic circulations.** Nitric oxide, an endothelium-derived relaxation factor, causes vascular smooth muscle cell relaxation by activating guanylate cyclase, leading to an increase in intracellular cyclic guanosine monophosphate (GMP) and reduction of intracellular calcium concentration (24,25). Because nitric oxide is rapidly bound to (26) and inactivated by (27) hemoglobin, inhaled nitric oxide might be expected to be a selective pulmonary vasodilator. Previous studies in hypoxic sheep (10), patients with primary pulmonary vascular disease (15) and patients with pulmonary hypertension that was secondary to congenital heart disease (11) or chronic obstructive lung disease (28) or that persisted after cardiopulmonary bypass (29,30) have shown significant reductions in pulmonary vascular resistance, without alterations in systemic arterial pressure, in response to nitric oxide at dosages ranging from 20 to 80 ppm.

The results of the present study extend to patients with chronic left heart failure the observation that nitric oxide decreases pulmonary vascular resistance without reducing systemic vascular resistance or mean systemic arterial pressure. The major effect of nitric oxide was a decrease in transpulmonary pressure gradient associated with an increase in pulmonary capillary wedge pressure without an equivalent increase in pulmonary artery pressure. In contrast, nitroprusside, a nitric oxide donor (31), caused a decrease in pulmonary vascular resistance associated with an increase in cardiac output without a change in transpulmonary pressure gradient; although pulmonary artery pressure decreased with nitroprusside, there was a corresponding decrease in pulmonary capillary wedge pressure.

Furthermore, nitroprusside had, as expected, systemic hemodynamic effects, reducing mean systemic arterial pressure by 24% and systemic vascular resistance by 34%. This systemic arterial vasodilation, while having a beneficial effect on ventricular performance through afterload reduction of the left ventricle, may have limited the dose of nitroprusside administered to the pulmonary circulation. Thus, the ratio of pulmonary vascular resistance to systemic vascular resistance did not change with nitroprusside, whereas it decreased by 40% with nitric oxide, demonstrating the selectivity of inhaled nitric oxide for the pulmonary circulation.

**Effect of nitric oxide on left heart filling pressure.** The increase in pulmonary capillary wedge pressure observed with nitric oxide was unexpected and undoubtedly reflects an increase in left ventricular end-diastolic pressure. Similarly, Haywood et al. (23) observed an increase in pulmonary capillary wedge pressure associated with a decrease in pulmonary vascular resistance during infusion of adenosine in patients with heart failure. There are several possible mechanisms for our observation: 1) There may have been increases in left ventricular end-systolic and end-diastolic volumes due to a negative inotropic effect of nitric oxide. The demonstration by Finkel et al. (32) that inhibitors of nitric oxide synthase reverse the ability of pro-inflammatory cytokines to decrease contractility in hamster papillary muscle supports such a negative inotropic effect. 2) Left ventricular preload may have increased in response to improved right ventricular pump function. These changes would be associated with an increase in left ventricular end-diastolic volume and pressure. Because stroke volume was unaltered by nitric oxide in our study, this explanation is unlikely. 3) Left ventricular diastolic function may have been impaired without a change in left ventricular end-diastolic volume. It seems unlikely that an agent that increases intracellular cyclic GMP and decreases intracellular calcium would have a direct adverse effect on myocardial relaxation. However, if inhalation of nitric oxide causes dilation and increased turgor of the coronary circulation, it could impair left ventricular compliance by this mechanism (33). Because nitric oxide is rapidly inactivated by hemoglobin (27), any effect of nitric oxide on the left ventricular myocardium or the coronary circulation must be mediated by a metabolite or carrier molecule that preserves its biologic effect: Evidence has been presented for the existence of such molecules (34). Whatever the mechanism, the increase in left ventricular filling pressure seen during nitric oxide administration may limit its role to that of a diagnostic rather than a therapeutic agent in patients with severe heart failure.

**Clinical implications.** Although controversy remains with regard to the level of pretransplantation pulmonary vasoconstriction beyond which the risk of right heart failure after transplantation is excessive, the study of Costard-Jäckle and Fowler (4) has established an acceptably low risk in patients whose pulmonary vascular resistance is ≤200 dynes·cm⁻² either at baseline or during administration of a dose of nitroprusside that does not induce systemic hypotension. In our study, 13 of 16 patients had this level of pulmonary vasodilation without systemic hypotension with either nitric...
oxide or nitroprusside; 2 patients had pulmonary vasoconstriction that was not reversed by these agents; 1 patient (Patient 9) did not achieve the specified degree of pulmonary vasodilation with nitroprusside because administration of this agent was limited by systemic hypotension. His pulmonary vascular resistance did decrease satisfactorily with nitric oxide; he underwent heart transplantation without postoperative right heart failure and had a subsequent early decrease in pulmonary vascular resistance. Nitric oxide may thus have an important role in identifying potential heart transplant recipients in whom reversal of pulmonary vasoconstriction by nonselective vasodilators such as nitroprusside is limited by systemic hypotension. Further studies enrolling greater numbers of patients with pulmonary vasoconstriction that reverses with nitric oxide who ultimately undergo heart transplantation are necessary to test this hypothesis. In the seven patients who have thus far received a heart transplant, the decrease in pulmonary vascular resistance observed with inhaled nitric oxide during their initial evaluation did predict the decrease observed after transplantation.

Summary. Inhaled nitric oxide is a selective pulmonary vasodilator in patients with severe chronic heart failure. The selectivity of inhaled nitric oxide for the pulmonary circulation offers a potential advantage over nonselective vasodilators such as nitroprusside in the identification of reversible pulmonary vasoconstriction in potential heart transplant recipients. Nitric oxide increases left ventricular filling pressure in patients with severe heart failure by an unknown mechanism.

References