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Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hypertension Before Transplantation

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Objectives. **We investigated the effect of inhaled nitric oxide and infused acetylcholine in patients with pulmonary hypertension undergoing cardiac catheterization before cardiopulmonary transplantation.**

Background. **The fate of patients under consideration for transplantation of the heart or lungs, or both, is influenced by the evaluation of their pulmonary vascular reactivity.**

Methods. **We evaluated 11 patients who were classified into two groups on the basis of mean left atrial pressure >15 mm Hg (group I, n = 6) or ≤15 mm Hg (group II, n = 5). All patients inhaled nitric oxide at 80 ppm. This was preceded by an infusion of 10^{-6} mol/liter of acetylcholine in seven consecutive patients (n = 3 in group I, n = 4 in group II).**

Results. **In group I, inhaled nitric oxide decreased pulmonary artery pressure from (mean ± SE) 71 ± 13 to 59 ± 10 mm Hg ($p < 0.05$), pulmonary vascular resistance from 14.9 ± 3.8 to 7.6 ± 1.7 Um^2 ($p < 0.05$) and intrapulmonary shunt fraction from 17.8 ± 3.6% to 12.7 ± 2.1% ($p < 0.05$). Left atrial pressure tended to increase from 27 ± 4 to 32 ± 5 mm Hg ($p = 0.07$). In group II pulmonary vascular resistance decreased in response to nitric oxide from 36.4 ± 9.0 to 31.1 ± 7.9 Um^2 ($p < 0.05$). Cardiac index, systemic pressure and resistance did not change in either group. Seven patients who received acetylcholine had no significant alteration in pulmonary hemodynamic variables.**

Conclusions. **These preliminary observations suggest that nitric oxide is a potent pulmonary vasodilator with minimal systemic effects. It may be useful in discriminating patients needing combined heart and lung transplantation from those requiring exchange of the heart alone.**

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The fate of patients under consideration for transplantation of the heart or lungs, or both, is influenced by the evaluation of their pulmonary vascular reactivity. Successful reduction of an elevated pulmonary vascular resistance may delay the need for transplantation or permit exchange of the heart alone (1–3). Pulmonary hypertension was established as an adverse prognostic factor for cardiac transplantation in early reports (4) and remains a significant risk factor for early death despite continued improvement in survival of high risk patients (5,6). Current pulmonary vascular assessment often relies on intravenously infused vasodilators. Their administration is not without hazard, and the hemodynamic results may be confounded by changes in cardiac output, systemic hypotension and hypoxemia secondary to increased intrapulmonary shunting (7). In contrast, the inhalation of nitric oxide has been shown to vasodilate the human pulmonary vascular bed with minimal systemic effects and without increasing intrapulmonary shunting (8–14). The systemic effects of inhaled nitric oxide are limited by its avid affinity for, and subsequent inactivation by, hemoglobin (15). Evidence is accumulating that the production of nitric oxide from L-arginine by the endothelial cell mediates vessel tone through a cyclic guanosine monophosphate (cGMP)-dependent mechanism in both the systemic and pulmonary circulations (16–19).

The vascular response to acetylcholine, an endothelium-dependent vasodilator (20), is regarded as a measure of endothelial cell integrity and has been documented to be abnormal in a number of vascular diseases (21,22). The pulmonary vascular response to acetylcholine may be abnormal after cardiopulmonary bypass (9) and in patients with congestive heart failure and secondary pulmonary hypertension (23). If decreased production of endogenous nitric oxide is responsible for vasoconstriction in patients with pulmonary hypertension rather than obliteration of the pulmonary vasculature, then administration of nitric oxide might achieve pulmonary vasodilation. Therefore, we investigated the effects of nitric oxide inhalation and acetylcholine infusion on the hemodynamic variables and gas exchange in patients with pulmonary hypertension undergoing cardiac catheterization as part of their assessment before consideration for cardiopulmonary transplantation.

Methods

Patients. We evaluated 11 patients (median age 13 years, range 0.7 to 27) with pulmonary hypertension (mean [±SE]

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Table 1. Pretransplantation Diagnoses of Patients

Pt No./Gender	Age (yr)	Diagnosis
1/M	2	Shone syndrome variant
2/F	8	Shone syndrome variant
3/F	9	Idiopathic restrictive cardiomyopathy
4/F	13	Ventricular failure after Senning procedure for TGA and VSD
5/M	20	Adriamycin-induced cardiotoxicity
6/F	26	Shone syndrome variant; severe MR
7/M	0.7	Primary pulmonary hypertension (right to left atrial shunt)
8/F	11	Cystic fibrosis
9/F	14	Eisenmenger complex with small VSD
10/F	23	Eisenmenger complex with ASD
11/M	27	Eisenmenger complex with VSD and pulmonary artery band

ASD (VSD) = atrial (ventricular) septal defect; F = female; M = male; MR = mitral regurgitation; Pt = patient; TGA = transposition of the great arteries.

pulmonary artery pressure 71.6 ± 8.4 mm Hg) who underwent cardiac catheterization to assess their pulmonary vascular resistance and reactivity as part of their pretransplant management (Table 1). The patients were classified into two groups on the basis of a mean left atrial pressure >15 mm Hg (group I) or ≤15 mm Hg (group II) and coinciding with whether they were combined heart and lung or lung transplant candidates, respectively. Thus, group I had an elevated mean left atrial pressure (27.0 ± 4.2 mm Hg) and treatment options potentially restricted to combined heart and lung transplantation. In contrast, group II had a low mean atrial pressure (7.2 ± 1.3 mm Hg), and these patients were considered candidates for lung transplantation. The difference in left atrial pressure was significant ($p < 0.05$). The only other difference in the measured baseline variables between the groups was a higher right atrial pressure in group I. There was a tendency for group I to have a higher partial pressure of arterial oxygen (Pao_2) ($p = 0.05$) and lower pulmonary vascular resistance (Table 2).

Group I: high left atrial pressure. Group I included six patients (Patients 1 to 6) with an elevated pulmonary vascular resistance (mean 14.9 ± 3.8 Um^2) and transpulmonary gradient (mean 44.7 ± 12.2 mm Hg) in the setting of severe left ventricular failure despite optimal medical management with digoxin, diuretic drugs and, when appropriate, maximal afterload reduction therapy.

Patients 1, 2, and 6 were diagnosed as having Shone syndrome variants. Patients 1 and 2 had an elevated enddiastolic pressure, mild mitral stenosis (previous mitral valve replacement in Patient 1) and moderate left ventricular outflow tract obstruction. Patient 6 had undergone mitral valve replacement (twice) and aortic valve replacement. In addition, a ventricular septal defect and aortic coarctation were repaired in infancy. Her predominant lesion was severe perivalvar mitral regurgitation not amenable to surgical correction. Two other patients had acquired cardiomyopathies (idiopathic in Patient 3 and secondary to adriamycin treatment for leukemia 12 years earlier in Patient 5). Patient 4 had right ventricular (systemic ventricular) failure after a Senning procedure with ventricular septal defect closure for transposition of the great arteries in infancy. Subsequently, she had undergone tricuspid valve (systemic atrioventricular valve) replacement.

Group II: low left atrial pressure. Group II included five patients (Patients 7 to 11) who had pulmonary hypertension with an elevated pulmonary vascular resistance (mean 36.4 ± 9.0 Um^2) but with preserved ventricular function. Two patients had primary lung pathology (Patient 7 had primary pulmonary hypertension; Patient 8 had cystic fibrosis). Three patients had pulmonary hypertension associated with congenital intracardiac shunts and had developed the Eisenmenger complex. Patient 9 had a large ventricular septal defect in infancy but had developed progressive elevation of pulmonary vascular resistance despite spontaneous reduction in the size of the defect. Patient 10 had an atrial septal defect with reversed shunting, and Patient 11 had a large ventricular septal defect and developed pulmonary vascular disease after an inadequate pulmonary artery band placed in infancy. These three patients were considered for lung transplantation with primary cardiac repair (24).

Hemodynamic assessment. Seven consecutive patients were investigated with both acetylcholine and nitric oxide (Patients 1, 3, 4, 7, 8, 10 and 11), and four patients received nitric oxide gas alone (Patients 2, 5, 6 and 9) because we had discontinued the use of acetylcholine as a pulmonary vasodilator at the time of their assessment. During cardiac catheterization but before angiography, hemodynamic measurements were recorded at baseline, during a 2-min infusion of acetylcholine, 15 min after return to a steady baseline and after 15 min of nitric oxide inhalation (80 ppm). In two patients we recorded hemodynamic variables at 40 as well as 80 ppm. In addition to receiving nitric oxide preoperatively, Patient 4 was studied after heart transplantation.

The hemodynamic variables recorded were heart rate, systemic and pulmonary arterial pressures, right and left atrial pressures, arterial and venous blood gases and oxygen saturation. In six patients (Patients 1 to 3, 5, 6 and 8) without tricuspid or pulmonary regurgitation or intracardiac shunting, cardiac output was measured by thermodilution, and left atrial pressure from pulmonary artery wedge pressures. In four patients with intracardiac shunts (Patients 7 and 9 to 11) and one with pulmonary regurgitation (Patient 4), the systemic and pulmonary blood flows were estimated using the Fick principle. Oxygen consumption was measured (Waters Inc., model MM20). Oxygen saturation was measured by co-oximetry in blood drawn from systemic artery, pulmonary artery, systemic vein and pulmonary vein or left atrium. All preoperative studies were conducted with the patients awake and breathing spontaneously but sedated with midazolam and morphine. The postoperative study in Patient 4 was conducted during mechanical ventilation.

Delivery and monitoring of nitric oxide. The details of nitric oxide gas preparation, delivery and monitoring have

Table 2. Hemodynamic Response to Inhaled Nitric Oxide

Group I: Patients With High Left Atrial Pressure

Pt No.		BP (mm Hg)	PAp (mm Hg)	CI (liters/min per m^2)	PAWp/LAp (mm Hg)	RAp (mm Hg)	SVRI (Um^2)	PVRI (Um^2)	HR (beats/min)	Pao_2 (mm Hg)	TPG (mm Hg)	Q_s/Q_t (%)
1	Baseline	69	92	3.4	16	10	17.4	22.4	148	65	76	26.8
	NO 80 ppm	72	84	4.7	26	10	13.2	12.3	148	76	58	19.7
2	Baseline	80	120	2.9	32	18	21.4	30.3	130	53	88	25.6
	NO 80 ppm	100	90	3.4	45	18	24.1	13.2	100	84	45	17.5
3	Baseline	74	56	3.1	26	10	20.6	9.7	85	96	30	10.7
	NO 80 ppm	66	40	3.1	26	10	18.1	4.5	80	89	14	8.2
4	Baseline	67	45	2.6	22	8	22.7	8.8	61	90	23	13.5
	NO 40 ppm	70	37	2.4	22	5	27.1	6.3	73	NA	15	NA
	NO 80 ppm	67	35	2.4	22	5	25.8	5.4	73	96	13	12.2
5	Baseline	75	37	2.0	21	14	30.5	8.0	75	102	16	6.2
	NO 80 ppm	75	34	2.1	24	14	29.0	4.8	70	100	10	6.1
6	Baseline	65	80	3.4	45	40	7.4	10.3	83	107	35	23.8
	NO 80 ppm	70	70	4.0	50	40	7.5	5.0	111	327	20	12.7
Mean ± SE	Baseline	72 ± 2	72 ± 13	2.9 ± 0.2	27 ± 4	17 ± 5	20.0 ± 3.1	14.9 ± 3.8	97 ± 14	86 ± 9	45 ± 12	17.8 ± 3.6
	NO 80 ppm	75 ± 5	59 ± 10	3.3 ± 0.4	32 ± 5	16 ± 5	19.6 ± 8.2	7.6 ± 1.7	97 ± 12	129 ± 40	27 ± 8	12.7 ± 2.1

Group II: Patients With Low Left Atrial Pressure

Pt No.		BP (mm Hg)	PAp (mm Hg)	CI (liters/min per m^2)	PBFI (liters/min per m^2)	PAWp/LAp (mm Hg)	RAp (mm Hg)	SVRI (Um^2)	PVRI (Um^2)	HR (beats/min)	Pao_2 (mm Hg)	TPG (mm Hg)
7	Baseline	56	80	2.7	1.9	7	6	18.5	38.4	152	46	73
	NO 80 ppm	57	82	3.0	2.1	7	6	17.0	35.7	153	48	75
8	Baseline	100	30	3.5	3.5	12	7	26.6	5.1	80	NA	18
	NO 80 ppm	95	27	3.5	3.5	13	7	25.1	4.0	80	NA	14
9	Baseline	75	80	2.3	1.6	6	6	30.0	46.3	79	58	74
	NO 40 ppm	75	80	2.1	1.7	7	6	32.9	42.9	80	NA	73
	NO 80 ppm	75	74	2.3	1.8	6	6	30.0	37.8	83	62	68
10	Baseline	116	66	2.4	1.9	4	4	46.7	32.6	142	57.0	62
	NO 80 ppm	116	66	3.2	2.3	6	5	34.7	26.1	156	57.0	60
11	Baseline	107	102	2.7	1.6	7	7	37.0	59.4	75	41	95
	NO 80 ppm	105	100	2.9	1.8	7	7	33.8	51.7	75	42	93
Mean ± SE	Baseline	91 ± 11	72 ± 12	2.7 ± 0.2	2.1 ± 0.4	7 ± 2	6 ± 1	31.8 ± 4.8	36.4 ± 9.0	106 ± 17	51 ± 4	64 ± 13
	NO 80 ppm	90 ± 11	70 ± 12	3.0 ± 0.2	2.3 ± 0.3	8 ± 1	6 ± 1	28.1 ± 3.3	31.1 ± 7.9	109 ± 18	52 ± 4	62 ± 13

Baseline = before nitric oxide (NO); BP = mean systemic arterial pressure; CI = cardiac index; HR = heart rate; LAp = left atrial pressure; NA = not available; Pao_2 = systemic arterial oxygen tension; PAp = mean pulmonary artery pressure; PAWp = pulmonary artery wedge pressure; PBFI = pulmonary blood flow index; Pt = patient; PVRI = pulmonary vascular resistance index; Q_s/Q_t = intrapulmonary shunt fraction; RAp = right atrial pressure; SVRI = systemic vascular resistance index; TPG = transpulmonary gradient.

been reported elsewhere (9,25). In brief, nitric oxide gas (Scott Specialty Gases) of medical grade quality and conforming to Food and Drug Administration guidelines was supplied in tanks in a concentration of 800 ppm. Pure nitrogen and nitric oxide were fed separately into a Bird (Bird Products Corporation) low flow blender at 50 psi. This blender controlled the proportion of nitric oxide and nitrogen mixture that flowed into a second Bird blender, where it was blended with oxygen. The fraction of inspired oxygen delivered to the patient could thus be adjusted (between 0.21 and 0.97) independently of the nitric oxide. The gas flow distal to the oxygen blender was controlled by a standard oxygen flowmeter. This gas mixture was delivered to the patient through a one-way inspiratory valve to a face mask. An in-line oxygen analyzer was positioned between the flowmeter and the face mask. The mask was hand held by an investigator to fit snugly over the patient's face. The expiratory gases from the patient circuit were scavenged by a reservoir bag and regulated wall suction. Nitric oxide and nitrogen dioxide levels were monitored by chemiluminescence. A sampling port at the airway permitted a volume of inspiratory gas mixture to flow to the analyzer (Thermoenvironmental Instruments Chemiluminescence, model 42H).

Methemoglobin levels were measured after nitric oxide inhalation with a co-oximeter (CIBA-Corning, model 2500) using a multiwavelength spectrophotometric method.

Acetylcholine. Acetylcholine was diluted in 5% dextrose to yield a concentration of 10^{-6} mol/ml and infused into the pulmonary artery at a rate (in ml/min) equal to the baseline pulmonary blood flow (in liters/min), to achieve a final concentration in the pulmonary circulation of 10^{-6} mol/liter for all

Table 3. Hemodynamic Response to 10^{-6} mol/liter of Acetylcholine Infused Over 2 min

Pt No.		BP (mm Hg)	PAp (mm Hg)	CI (liters/min per m^2)	PAWp/LAp (mm Hg)	RAp (mm Hg)	SVRI (Um^2)	PVRI (Um^2)	HR (beats/min)	Pao_2 (mm Hg)	TPG (mm Hg)	Q_s/Q_t (%)
Group I: Patients With High Left Atrial Pressure												
1	Baseline	65	91	4.0	15	10	13.8	19.0	146	65	76	NA
	ACh	60	91	4.3	15	10	11.6	17.7	146	67	76	NA
3	Baseline	62	52	3.1	19	10	16.8	10.6	85	92	33	11.0
	ACh	66	52	3.0	18	10	18.7	11.3	90	83	34	18.0
4	Baseline	58	36	2.2	16	7	23.2	9.1	61	94	20	11.7
	ACh	55	33	2.2	16	6	22.3	7.7	60	90	17	11.8
Mean ± SE	Baseline	62 ± 2	60 ± 16	3.1 ± 0.5	17 ± 1	9 ± 9	17.9 ± 2.8	12.9 ± 3.1	97 ± 25	84 ± 9	43 ± 17	11.4 ± 0.4
	ACh	60 ± 3	59 ± 17	3.2 ± 0.6	16 ± 1	9 ± 1	17.5 ± 3.1	12.2 ± 2.9	99 ± 25	80 ± 7	42 ± 18	14.9 ± 3.1

Pt No.		BP (mm Hg)	PAp (mm Hg)	CI (liters/min per m^2)	PBFI (liters/min per m^2)	PAWp/LAp (mm Hg)	RAp (mm Hg)	SVRI (Um^2)	PVRI (Um^2)	HR (beats/min)	Pao_2 (mm Hg)	TPG (mm Hg)
Group II: Patients With Low Left Atrial Pressure												
7	Baseline	58	86	2.3	1.4	6	6	22.6	57.1	165	42	80
	ACh	58	88	2.8	1.5	6	6	18.4	54.7	165	41	82
8	Baseline	104	31	4.2	4.2	13	7	23.1	4.3	101	NA	18
	ACh	103	27	4.0	4.0	12	7	24.0	3.8	90	NA	15
10	Baseline	118	70	3.2	2.1	6	4	35.6	30.5	146	60	64
	ACh	116	66	2.9	2.1	7	4	38.6	28.1	146	61	59
11	Baseline	105	101	2.7	2.3	7	8	35.9	40.9	75	43	94
	ACh	105	101	2.6	2.2	7	7	37.7	42.7	75	43	94
Mean ± SE	Baseline	96 ± 13	72 ± 15	3.1 ± 0.4	2.5 ± 0.6	8 ± 2	6 ± 1	28.7 ± 4.1	33.2 ± 11.1	122 ± 21	48 ± 5	64 ± 17
	ACh	96 ± 13	71 ± 16	3.1 ± 0.4	2.5 ± 0.5	8 ± 1	6 ± 1	29.2 ± 5.4	32.3 ± 11.0	119 ± 22	48 ± 6	63 ± 17

ACh = after acetylcholine infusion; Baseline = before acetylcholine; BP = mean systemic arterial pressure; CI = cardiac index; HR = heart rate; LAp = left atrial pressure; NA = not available; Pao_2 = systemic arterial oxygen tension; PAp = mean pulmonary artery pressure; PAWp = pulmonary artery wedge pressure; PBFI = pulmonary blood flow index; Pt = patient; PVRI = pulmonary vascular resistance index; Q_s/Q_t = intrapulmonary shunt fraction; RAp = right atrial pressure; SVRI = systemic vascular resistance index; TPG = transpulmonary gradient.

patients, independent of differences in pulmonary blood flow. In earlier studies this dose of acetylcholine had reliably caused pulmonary vasodilation with minimal systemic effects in children with congenital heart disease undergoing preoperative cardiac catheterization (9).

Statistical analysis and calculations. The change in the hemodynamic variables between baseline and in response to acetylcholine and nitric oxide was compared with a nonparametric test for repeated measures (Friedman), and when differences were found, a Wilcoxon signed-rank test was used. A p value <0.05 was considered significant. The differences between groups I and II were analyzed using a Mann-Whitney *U* Test.

Standard equations were used to calculate systemic and pulmonary vascular resistances and were indexed to body surface area. To calculate the intrapulmonary shunt fraction (Q_s/Q_t) in patients with high left atrial pressure, we applied the equation as described by Riley and Cournand (26).

Ethical approval and informed consent. The investigation was approved by the Children's Hospital Investigational Review Board and reported to the Food and Drug Administration. Written informed consent was obtained from the patients or their parents.

Results

Individual patient responses to inhaled nitric oxide and acetylcholine are displayed in Tables 2 and 3, respectively.

Effect of nitric oxide. *Nitric oxide in group I (patients with an elevated left atrial pressure).* Group I patients displayed marked pulmonary vascular reactivity in response to nitric oxide. Pulmonary artery pressure decreased from 71.7 ± 12.9 to 58.8 ± 10.4 mm Hg ($p < 0.05$); pulmonary vascular resistance decreased from 14.9 ± 3.8 to 7.6 ± 1.7 Um^2 ($p < 0.05$); and transpulmonary gradient was reduced from 44.7 ± 12.2 to 26.7 ± 8.1 mm Hg ($p < 0.05$) (Table 2). The intrapulmonary shunt fraction decreased from 17.8 ± 3.6% to 12.7 ± 2.1% ($p < 0.05$). There was a tendency for left atrial pressure to increase (27.0 ± 4.2 to 32.2 ± 4.9 mm Hg, $p = 0.07$). Cardiac index was 2.9 ± 0.2 liters/min per m^2 at baseline and 3.3 ± 0.4 liters/min per m^2 with nitric oxide. Systemic vascular resistance index and blood pressure did not change with nitric oxide. All six patients had a baseline pulmonary vascular resistance ≥8 Um^2, thereby potentially eliminating transplantation of the heart alone. However, four patients responded to inhaled nitric oxide with a reduction in pulmonary artery pressure that reduced pulmonary vascular resistance <6.0 Um^2 and in three

patients transpulmonary gradient <15 mm Hg such that their transplantation status was altered from combined heart and lung transplantation to heart transplantation alone. Two of these patients (Patients 3 and 4) underwent successful cardiac transplantation with a low pulmonary vascular resistance in the postoperative period. Three days after cardiac transplantation, Patient 4 had a pulmonary artery pressure of 41 mm Hg and pulmonary vascular resistance of 5.5 Um^2, identical to that predicted by the preoperative assessment with nitric oxide. There was a further reduction in pulmonary artery pressure to 36 mm Hg and in pulmonary vascular resistance to 4.2 Um^2 in response to inhaling nitric oxide for 15 min.

Patient 3 had a mean pulmonary artery pressure in the immediate postoperative period of 25 mm Hg, with a pulmonary vascular resistance of 3.5 Um^2. One month after transplantation, mean pulmonary artery pressure was 26 mm Hg and pulmonary vascular resistance 6.2 Um^2. Patient 3 died 2 months after cardiac transplantation and after hospital discharge of acute graft rejection.

There were three additional deaths. Patient 1 died after heart and lung transplantation, Patient 2 during an intercurrent pneumonia while awaiting a heart and lung donation and Patient 6 while awaiting a donor heart. Patient 5 is awaiting cardiac transplantation.

Important increases in left atrial pressure and cardiac index were confined to Patients 1, 2, and 6, who carried the diagnosis of Shone syndrome variants. All three patients had a suprasystemic pulmonary artery pressure but no intracardiac shunt.

In patients 1 and 2, left atrial pressure returned toward baseline at 18 and 33 mm Hg, respectively, 15 min after discontinuing the inhalation of nitric oxide.

Nitric oxide in group II (patients with a low left atrial pressure). Although there was a statistically significant decrease in pulmonary vascular resistance from 36.4 ± 9.0 to 31.1 ± 7.9 Um^2 ($p < 0.05$), the changes in pulmonary hemodynamic variables were not clinically important (Table 2). There was a tendency for pulmonary artery pressure to decrease and for pulmonary blood flow to increase. Only Patient 8 with cystic fibrosis responded to nitric oxide with a 10% decline in pulmonary artery pressure and a 21% decline in pulmonary vascular resistance. Patient 8 underwent lung transplantation, and the four other group II patients are awaiting transplantation.

Effect of acetylcholine. In the seven patients who received acetylcholine, there was no overall significant alteration in pulmonary hemodynamic variables. The decrease in pulmonary vascular resistance was significantly less than that with nitric oxide ($p < 0.05$) (Table 3).

Acetylcholine in group I (patients with a high left atrial pressure). Three of six patients received acetylcholine. No patient responded with a larger decrease in pulmonary artery pressure or pulmonary vascular resistance than that with nitric oxide. Acetylcholine did not change pulmonary artery pressure in two patients (Patients 1 and 3), but pulmonary vascular resistance increased by 6.5% in Patient 3 and decreased by 7% in Patient 1, associated with changes in cardiac index. Patient 4 responded with an 8% decrease in pulmonary artery pressure and a 15% decrease in pulmonary vascular resistance without a change in cardiac index.

Acetylcholine in group II (patients with a low left atrial pressure). Four of five patients received acetylcholine. Patient 8 with cystic fibrosis responded with a 13% decrease in pulmonary artery pressure and a 12% decrease in pulmonary vascular resistance. Patient 11 responded with a small increase in pulmonary vascular resistance (4.5%) accompanied by a small decrease in pulmonary blood flow (4.5%).

Differences between groups I and II. The difference in the responses of patients with a high versus low left atrial pressure is evident from Table 2. The percent change in pulmonary artery pressure ($p < 0.05$), pulmonary vascular resistance ($p < 0.01$) and transpulmonary gradient ($p < 0.01$) were significantly greater with nitric oxide in group I than group II.

Pathologic findings. Pathologic examination of the heart in three of the patients who died (Patients 1, 2, and 6) confirmed the clinical diagnosis and demonstrated very hypertrophied left atrial and ventricular walls with extensive endocardial fibroelastosis. Vascular histologic examination of the lungs in Patients 1 and 2 demonstrated changes of grades 3 to 4 and grade 2 in Patient 6 according to the classification of Heath and Edwards (27). Left ventricular cavity size was reduced in Patients 1 and 2.

Nitrogen dioxide and methemoglobin. Nitrogen dioxide levels remained <1 ppm throughout exposure to nitric oxide in all patients. Methemoglobin levels ranged from 0% to 0.9% (mean 0.4 ± 0.1%, normal reference range 0% to 5%).

Discussion

General findings. This preliminary evaluation suggests that nitric oxide was effective in lowering pulmonary artery pressure and pulmonary vascular resistance without important systemic effects in a small group of patients undergoing assessment of pulmonary vascular reactivity as a prelude to cardiopulmonary transplantation. The response was most clinically important in the group of patients with ventricular failure and left atrial hypertension. On the basis of the response to nitric oxide, four patients were reclassified to receive heart transplantation alone, and two did so with low pulmonary vascular resistance in the postoperative period. In the two patients in whom the challenge with inhaled nitric oxide failed to lower pulmonary vascular resistance adequately, histologic examination of the explanted lungs confirmed severe pulmonary vascular disease. We suggest that nitric oxide may be useful in further discriminating between those patients needing combined cardiopulmonary transplantation and those for whom cardiac replacement alone is sufficient. In contrast to assessment of pulmonary vascular reactivity with intravenous vasodilators, use of inhaled nitric oxide minimizes confounding variables, such as systemic vasodilation and concomitant changes in cardiac output, and simplifies the interpretation of changes in pulmonary vascular resistance (11,28,29). However, because we did not compare endothelium-independent intravenous vasodilators, such as

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