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CARDIAC AND PULMONARY REPLACEMENT

INHALED NITRIC OXIDE REDUCES HUMAN LUNG ALLOGRAFT DYSFUNCTION

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Objective: Early severe graft dysfunction, as manifested by hypoxia and pulmonary hypertension, occurs in 10% to 20% of lung transplant recipients. We retrospectively investigated whether inhaled nitric oxide would reduce human lung allograft dysfunction by comparing postoperative hemodynamic data, gas exchange, and outcome in lung transplant recipients with early graft dysfunction treated with or without nitric oxide. **Method:** Among 243 adult lung transplant procedures, there were 32 patients (13.2%) in whom immediate severe allograft dysfunction developed (arterial oxygen tension/inspired oxygen concentration ratio <150). Group 1 ($n = 17$) included patients who underwent transplantation before nitric oxide became available in our center and were treated conventionally. Group 2 ($n = 15$) included those treated with nitric oxide as soon as severe allograft dysfunction was diagnosed. Duration of nitric oxide therapy (20 to 60 ppm) was 15 to 217 hours (average 84 hours). **Results:** In group 2, nitric oxide lowered mean pulmonary artery pressure from 30 ± 2 to 26 ± 2 mm Hg ($p < 0.05$), improved the ratio of arterial oxygen tension to inspired oxygen fraction from 88 ± 10 to 153 ± 30 ($p < 0.05$) within 1 hour, and caused a sustained improvement in these parameters during extended therapy. Mean arterial pressure and cardiac index were unchanged during nitric oxide therapy. Transient methemoglobinemia (>6%) developed in two patients. However, no complications were associated with nitric oxide use. Duration of mechanical ventilation was 17 ± 5 days in group 1 and 12 ± 3 days

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in group 2. Four patients had airway complications in group 1, whereas no airway complication was encountered in group 2. Mortality was 24% (4/17) in group 1 and 7% (1/15) in group 2. Conclusion: Nitric oxide improves oxygenation and decreases pulmonary artery pressure without systemic circulatory effects in patients with severe allograft dysfunction. Furthermore, in these patients, nitric oxide may shorten postoperative mechanical ventilation time and reduce airway complications and mortality. (J Thorac Cardiovasc Surg 1996;111:913-9)

Despite improved preservation methods and perioperative management, severe allograft dysfunction occurs in 10% to 20% of lung transplant recipients.^{1,2} Its associated severe hypoxia, pulmonary hypertension, and lung edema complicate postoperative management. Nitric oxide was reported to be an important endothelium-derived relaxing factor in 1987.³ Rossaint and colleagues⁴ reported in 1993 that extended treatment with inhaled nitric oxide for patients with severe adult respiratory distress syndrome reduces the pulmonary artery pressure without producing systemic vasodilatation and increases arterial oxygenation by improving ventilation-perfusion matching. We⁵ recently tested the effect of short periods of nitric oxide inhalation on hemodynamics and arterial oxygenation in patients after bilateral lung transplantation. Nitric oxide dramatically improved the arterial oxygen tension/inspired oxygen fraction ($\text{PaO}_2/\text{Fio}_2$) ratio and lowered the mean pulmonary artery pressure in patients with impaired oxygenation. We⁶ recently demonstrated that nitric oxide markedly improved posttransplantation gas exchange in canine lung allografts stored for 18 hours. The purpose of this report was to compare the effects of inhaled nitric oxide with conventional therapy in a group of lung transplant recipients with severe allograft dysfunction.

Patients and methods

Between September 1988 and December 1994, 243 consecutive single ($n = 111$) and bilateral sequential single ($n = 132$) lung transplants were performed at Barnes Hospital. En bloc double lung transplants ($n = 8$) performed in our early experience were not included in this study. Thirty-two patients (13.2%) had immediate severe allograft dysfunction, as manifested by a $\text{PaO}_2/\text{Fio}_2$ ratio less than 150. These 32 patients were divided into two groups. Group 1 ($n = 17$) included patients having lung transplantation before January 1993 (when inhaled nitric oxide became available in our institution) and treated conventionally. Group 2 ($n = 15$) included those patients having lung transplantation after February 1993 and treated with inhaled nitric oxide as soon as severe

allograft dysfunction was diagnosed. These two groups were compared in regard to requirement for extracorporeal membrane oxygenation (ECMO), days requiring mechanical ventilation, airway complications, and mortality. In group 2, the effect of inhaled nitric oxide was evaluated by the changes of systemic and pulmonary hemodynamics and arterial blood gases measured before and during nitric oxide treatment.

Donor lungs were harvested by the technique we⁷ have previously described. All donors were pretreated with systemic heparin and the pulmonary artery bed was flushed with modified Euro-Collins solution after prostaglandin E_1 (500 μg) administration. All transplant operations were performed by means of previously described techniques.⁸ Cardiopulmonary bypass was used in all patients with pulmonary hypertension and in other patients as dictated by inadequate gas exchange or hemodynamics during transplantation.⁹

Routine clinical monitoring of the patients included a radial arterial line and a 7.5F Swan-Ganz catheter (Baxter Healthcare Corp., Irvine, Calif.) positioned into the pulmonary artery through the internal jugular vein. Systemic, pulmonary artery, pulmonary wedge, and central venous pressures were recorded. Cardiac output was determined by the thermodilution method.

Postoperative sedation included intravenous fentanyl citrate and midazolam. Vecuronium bromide was given when indicated. Inotropic support, vasodilators, and diuretics were used as necessary to maximize hemodynamic stability and graft function. Prostaglandin E_1 (0.01 to 0.03 $\mu\text{g}/\text{kg}$ per minute) was administered routinely from 1989 unless significant hypotension was encountered. All patients received mechanical ventilation in the volume-controlled mode with the application of positive end-expiratory pressure (5 to 15 cm H_2O). Ventilator settings were adjusted to provide adequate oxygenation as measured by PaO_2 and adequate ventilation as measured by arterial pH and carbon dioxide tension. Standard immunosuppression consisted of cyclosporine, azathioprine, steroid, and antilymphocyte antibody as reported previously.¹⁰

Nitric oxide was supplied from Scott Specialty Gases (Plumsteadville, Pa.) in cylinders containing nitric oxide in nitrogen in a concentration of 2200 ppm. The delivery system consisted of a reducing valve and a flowmeter. The nitric oxide gas mixture (1/8 to 1/4 L/min) was delivered into the inspiratory port of the ventilator. The concentration of nitric oxide was continuously measured from a sampling line at the Y connector attached to the endotracheal tube; a chemiluminescence device (model 42A,

Table I. Characteristics of patients

	Group 1 (n = 17): without NO	Group 2 (n = 15): with NO	Probability
Recipient age (yr)	40.7 ± 3.5	44.3 ± 2.8	NS
Recipient sex (M/F)	4/13	5/9	NS
Donor age (yr)	22.3 ± 1.5	25.6 ± 2.8	NS
Donor PaO ₂ (mm Hg)	455 ± 16	452 ± 16	NS
Diagnosis			NS
Obstructive	4	4	
Restrictive	4	3	
Septic	5	3	
PVD	4	5	
Procedure			NS
Single	8	3	
Bilateral	9	12	
Total ischemic time (min)	380 ± 26	369 ± 24	NS
CPB (yes/no)	8/9	8/7	NS
Initial PaO ₂ (mm Hg)	80.8 ± 7.4	82.6 ± 8.1	NS

NO, nitric oxide; PVD, primary pulmonary hypertension and Eisenmenger's syndrome; CPB, cardiopulmonary bypass; NS, not significant. Donor PaO₂ and initial PaO₂ were measured with Fio₂ 100%.

Thermoenvironmental Instruments, Franklin, Mass.) that was calibrated before each use with a calibration gas of known 25 ± 1 ppm nitric oxide in nitrogen (Scott Specialty Gases) was used to obtain these measurements. The flow was adjusted according to the concentration measured by the analyzer. The starting dose of inhaled nitric oxide was 40 to 60 ppm and the gas was gradually weaned to 20 ppm. It was continued until its cessation did not cause deterioration in oxygenation or pulmonary artery pressure. Methemoglobin levels were measured every 2 to 6 hours with a Co-Oximometer (model 2500, Ciba-Corning, Medfield, Mass.) by means of a multiple wave-length spectrophotometric method. When methemoglobinemia (>6%) was noticed, 1 gm of ascorbic acid was given intravenously and the dose of nitric oxide was reduced.

Informed consent was obtained from all patients for nitric oxide administration and the protocol for nitric oxide use was approved by the Human Studies Committee of Washington University.

All data are presented as the mean ± the standard error of the mean. Significance was sought between the two groups with use of a χ^2 test for nonparametric data and Student's *t* test for parametric data. Repeated-measures analysis of variance was used to test the effect of nitric oxide on systemic and pulmonary hemodynamics and also on arterial blood gas analysis. Statistical significance was determined at a *p* value of 0.05.

Results

Demographic results (Table I). Recipient age, recipient sex, donor age, donor PaO₂, procedure, total ischemic time, use of cardiopulmonary bypass during transplant procedures, and initial PaO₂ (Fio₂ =

Table II. Comparison of outcome between the two groups

	Group 1 (n = 17) without NO	Group 2 (n = 15) with NO
ECMO	3/17 = 18%	3/15 = 20%
Days ventilated	17 ± 5	12 ± 3
Airway complication	4/17 = 24%	0/15 = 0%
Hospital mortality	4/17 = 24%	1/15 = 7%

NO, Nitric oxide; ECMO, extracorporeal membrane oxygenation.

1.0) after reperfusion were not significantly different between the two groups.

Comparison of outcome between the two groups. (Table II). Three patients in each group required ECMO. Five of them, all three patients in group 1 and two patients in group 2, required ECMO immediately after transplantation because they could not be weaned from cardiopulmonary bypass owing to severe allograft dysfunction. In one group 2 patient ECMO was begun 24 hours after transplantation because of progressive allograft dysfunction despite nitric oxide treatment. Two patients requiring ECMO in each group ultimately recovered and one patient requiring ECMO in each group died of severe allograft dysfunction.

Duration of mechanical ventilation required was 17 ± 5 days in group 1 and 12 ± 3 days in group 2.

Four patients in group 1 had airway complications. Early fatal bronchial dehiscence occurred in two patients, one of whom underwent retransplantation without success, and late bronchial stenosis occurred in two patients. In contrast, no airway complication was encountered in group 2.

Hospital mortality was four of 17 (24%) in group 1 and one of 15 (7%) in group 2. Causes of death in group 1 were airway dehiscence in two patients, severe allograft dysfunction in one, and sepsis in one patient. One patient in group 2 died of severe allograft dysfunction.

Requirement of ECMO, duration of mechanical ventilation, airway complication, and hospital mortality did not reach statistical significance between the two groups.

Effect of inhaled nitric oxide. Nitric oxide treatment was initiated in the operating room in four patients and on arrival at the intensive care unit in five patients. In the remaining six patients, nitric oxide was initiated 1 to 10 hours after they arrived in the intensive care unit because of progressive allograft dysfunction. Duration of nitric oxide therapy was 15 to 217 hours (average 84 hours).

Fig. 1. $\text{PaO}_2/\text{FiO}_2$ ratio before (BL, baseline) and after nitric oxide treatment. Statistical analysis was performed on the data obtained during the first 8 hours because of the different durations of nitric oxide (NO) therapy in each case. * $p < 0.05$, ** $p < 0.01$ (versus baseline).

The effect of nitric oxide on hemodynamics and arterial blood gases was evaluated by comparing the data obtained during nitric oxide therapy and those obtained immediately before nitric oxide therapy was initiated (baseline value). Data were obtained from 13 patients treated with inhaled nitric oxide, excluding two patients who required ECMO immediately after transplantation. Because the duration of nitric oxide therapy was different in each case, statistical analysis was performed on the data obtained during the first 8 hours (Table III). Nitric oxide administration resulted in rapid improvement of arterial oxygenation and pulmonary artery pressure without affecting systemic pressure or cardiac index and caused a sustained improvement in these parameters during extended therapy (Figs. 1 and 2).

Transient methemoglobinemia ($>6\%$) developed in two patients, 10.5% after 24 hours and 6.7% after 8 hours, respectively, on a nitric oxide concentration of 40 ppm. Both patients were successfully treated with ascorbic acid administration and reduction of nitric oxide dose. No complications were associated with nitric oxide administration.

Discussion

Early severe allograft dysfunction, as manifested by allograft edema, pulmonary hypertension, and decreased arterial oxygenation, develops in 10% to 20% of lung transplant recipients.^{1,2} This dysfunction has been known as pulmonary reimplantation response.¹¹ Ischemia-reperfusion injury is thought to be the major cause of this phenomena.¹² A

Fig. 2. Mean pulmonary artery (PA) pressure before (BL, baseline) and after nitric oxide (NO) treatment. Statistical analysis was performed on the data obtained during the first 8 hours because of the different durations of nitric oxide therapy in each case. * $p < 0.05$ (versus baseline).

number of strategies have been developed in an attempt to reduce early allograft dysfunction, for example, use of oxygen-derived radical scavengers,¹³ pentoxifylline,¹⁴ and prostaglandin E₁.¹⁵ However, 13% of deaths occurred within 90 days after transplantation and were still attributable to severe allograft dysfunction at the moment according to the St. Louis International Lung Transplant Registry (Pohl MS, personal communication).

Endothelial dysfunction may play a central role in pulmonary hypertension. Acetylcholine relaxes pre-constricted vascular smooth muscle by binding to muscarinic receptors on the endothelial cell, causing the release of a potent vasodilating substance called endothelium-derived relaxing factor.¹⁶ In 1987, nitric oxide was reported to be an important endothelium-derived relaxing factor.³ Nitric oxide is thought to diffuse from the endothelium to adjacent smooth muscle and produce relaxation through a cyclic guanosine monophosphate-dependent pathway. The vascular response to acetylcholine is altered in a number of conditions, such as chronic obstructive lung disease,¹⁷ pulmonary hypertension after cardiopulmonary bypass,¹⁸ and lung transplantation^{19,20} wherein significant endothelial nitric oxide production is inadequate. However, vasodilatation may be elicited by inhaled nitric oxide, an endothelium-independent smooth muscle relaxant.

We previously tested the effects of short periods of nitric oxide inhalation (40 to 60 ppm) and systemic prostaglandin E₁ (0.03 to 0.06 mg/kg per minute) on hemodynamics and arterial oxygenation

Table III. Effect of nitric oxide on hemodynamics and arterial blood gas

	Baseline	One hour	Two hours	Four hours	Eight hours
PaO ₂ /Fio ₂	88 ± 10	153 ± 30*	153 ± 27*	175 ± 32*	188 ± 25†
PaCO ₂ (mm Hg)	48 ± 3	47 ± 4	42 ± 2	41 ± 2	41 ± 2
mAP (mm Hg)	75 ± 4	77 ± 2	74 ± 2	78 ± 3	70 ± 2
mPAP (mm Hg)	30 ± 2	26 ± 2*	26 ± 2*	27 ± 2*	26 ± 1*
mPCWP (mm Hg)	15 ± 2	14 ± 2	14 ± 2	13 ± 2	13 ± 2
mCVP (mm Hg)	10 ± 1	10 ± 1	9 ± 1	8 ± 1	9 ± 1
CI (L/min/m ²)	2.9 ± 0.2	2.6 ± 0.2	2.4 ± 0.1	2.5 ± 0.2	2.6 ± 0.2

mAP, Mean arterial pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; mCVP, mean central venous pressure; CI, cardiac index. Data were obtained from 13 patients treated with inhaled nitric oxide excluding two patients who required ECMO immediately after transplantation. mPCWP was obtained from only nine patients.

**p* < 0.05 versus baseline value.

†*p* < 0.01 versus baseline value.

in patients after bilateral lung transplantation.⁵ In patients with impaired oxygenation, nitric oxide improved PaO₂/Fio₂ ratio and lowered mean pulmonary artery pressure without systemic circulatory effects. In contrast, prostaglandin E₁ did not improve oxygenation and lowered systemic arterial pressure. Interestingly, in patients without impaired oxygenation, nitric oxide was of no benefit and paradoxically worsened oxygenation. We have also demonstrated the beneficial effects of inhaled nitric oxide on allograft dysfunction owing to reperfusion injury in a canine single lung transplant model.⁶

On the basis of this experience and several reports on nitric oxide treatment for pulmonary hypertension²¹⁻²³ and adult respiratory distress syndrome,⁴ extended inhaled nitric oxide treatment has been given to the 15 lung transplant recipients with severe allograft dysfunction since February 1993. Inhaled nitric oxide rapidly improved oxygenation and decreased pulmonary artery pressure without systemic circulatory effects. It should also be noted that inhaled nitric oxide does not cause tachyphylaxis. Because nitric oxide, an endothelium-independent smooth muscle relaxant, is delivered via the airway, pulmonary blood flow is redistributed away from nonventilated regions of the lungs and toward ventilated regions, thereby improving the matching of ventilation and perfusion. Another beneficial effect may be derived from a potential antineutrophil effect of nitric oxide. Our previous canine study demonstrated that preserved lung allografts treated with inhaled nitric oxide had decreased myeloperoxidase activity, indicating decreased neutrophil sequestration in comparison with that of untreated allografts.

Patients with severe lung allograft dysfunction usually require prolonged mechanical ventilation. We²⁴ have recently reported that prolonged mechanical ventilation is associated with an increased incidence of airway complications. Whether this increase is due to mechanical ventilation itself or to the parenchymal injury necessitating mechanical ventilation is not known. Our observations suggest that inhaled nitric oxide may shorten the time required for mechanical ventilation in patients with severe allograft dysfunction. Interestingly, four patients treated without nitric oxide had airway complications, two of which proved fatal. In contrast, no airway complications were noted when nitric oxide was used.

ECMO has been used when conventional measures for treatment of severe allograft dysfunction proved unsuccessful.²⁵ In our entire experience of 243 patients undergoing lung transplantation, only six patients required ECMO. Four of them survived and were discharged from the hospital. We have avoided the use of ECMO as much as possible because of the potential complications of bleeding, infection, and renal insufficiency. We speculate that at least two more patients would have required ECMO had nitric oxide not been available. On the other hand, one patient required ECMO 24 hours after transplantation because of progressive allograft dysfunction despite nitric oxide therapy. This patient's lung never recovered. Our current strategy is to use nitric oxide as the first therapeutic intervention in the presence of severe allograft dysfunction and to reserve ECMO for subsequent treatment failures or for circumstances in which euvoletic hemodynamic instability proves refractory to management with standard pressor and inotropic agents.

The absence of systemic vasodilatation with inhaled nitric oxide was confirmed in this study. The lack of systemic effects results from the rapid inactivation of nitric oxide by hemoglobin in red blood cells.¹⁸ The reaction of hemoglobin and nitric oxide forms nitrosyl hemoglobin and subsequently methemoglobin.²⁶ Intravenously infused vasodilators such as prostaglandin E₁, on the other hand, cause both pulmonary and systemic vasodilatation.^{5,15} The dose of a vasodilator agent is limited by concomitant dilatation of the systemic vasculature, leading to systemic arterial hypotension.

The therapeutic importance of our data on inhaled nitric oxide is evident but must be considered in conjunction with possible toxic effects. Nitric oxide can be converted by oxidation to nitric dioxide and other toxic agents such as peroxyxynitrite, resulting in lung injury.²⁷ Formation of methemoglobin may decrease oxygen delivery. There is indirect evidence that nitric oxide may be directly related to allograft rejection. In a rat left lung allograft model we²⁸ have recently demonstrated that inhibition of nitric oxide synthase by aminoguanidine markedly delayed the onset and decreased the severity of lung allograft rejection. Little evidence for nitric oxide toxicity exists with exposures less than 100 ppm in normal rats²⁷ and rabbits.²⁹ In fact, in our experience we observe no complications associated with extended nitric oxide inhalation for up to 217 hours. Transient mild methemoglobinemia occurred in two patients and was successfully treated with ascorbic acid administration. We did not encounter any episodes of intractable acute rejection.

In summary, this study demonstrates that inhaled nitric oxide improves gas exchange and decreases pulmonary artery pressure in patients with early allograft dysfunction. It also suggests that inhaled nitric oxide may shorten postoperative mechanical ventilation time, reduce airway complications, and reduce mortality in patients with severe lung allograft dysfunction.

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REFERENCES

- Haydock DA, Trulock EP, Kaiser LR, et al. Lung transplantation: analysis of thirty-six consecutive procedures performed over a twelve-month period. *J Thorac Cardiovasc Surg* 1992;103:329-40.
- Davis RD, Trulock EP, Manley J, et al. Differences in early results after single-lung transplantation. *Ann Thorac Surg* 1994;58:1327-1335.
- Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;327:524-6.
- Rossaint R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399-405.
- Triantafyllou AN, Pohl MS, Okabayashi K, et al. Effects of inhaled nitric oxide and prostaglandin E₁ in the early post-operative management of patients following bilateral lung transplantation. *Circulation* 1994;90:3432.
- Okabayashi K, Triantafyllou A, Yamashita M, et al. Inhaled nitric oxide reduces lung allograft reperfusion injury. *Surg Forum* 1994;155:276-8.
- Sundaresan S, Trachiotis GD, Aoe M, et al. Donor lung procurement: assessment and operative technique. *Ann Thorac Surg* 1993;56:1409-13.
- Pasque MK, Cooper JD, Kaiser LR, et al. Improved technique for bilateral lung transplantation: rationale and initial clinical experience. *Ann Thorac Surg* 1990;49:785-91.
- Triantafyllou AN, Pasque MK, Huddleston CB, et al. Predictors, frequency, and indications for cardiopulmonary bypass during lung transplantation in adults. *Ann Thorac Surg* 1994;57:1248-51.
- Trulock EP. Management of lung transplant rejection. *Chest* 1993;103:1566-76.
- Siegelman SS, Sinha SBP, Veith FJ. Pulmonary reimplantation response. *Ann Surg* 1973;177:30-6.
- Kirk AJB, Colquhoun IW, Dark JH. Lung preservation: a review of current practice and future directions. *Ann Thorac Surg* 1993;56:990-1000.
- Lambert CJ, Eagan TM. Optimal timing of administration of a free radical scavenger in lung preservation. *Transplantation* 1992;54:205-9.
- Okabayashi K, Aoe M, DeMeester SR, et al. Pentoxifylline reduced lung allograft reperfusion injury. *Ann Thorac Surg* 1994;58:50-6.
- Aoe M, Trachiotis GD, Okabayashi K, et al. Administration of prostaglandin E₁ after lung transplantation improves early graft function. *Ann Thorac Surg* 1994;58:655-61.
- Furchgott RF, Zawadzki JW. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288:373-6.
- Andot S, Kouyoumdjian C, Defouilloy C, et al. Hemodynamic and gas exchange responses to infusion of acetylcholine and inhalation of nitric oxide in patients with chronic obstructive lung disease and pulmonary hypertension. *Am Rev Respir Dis* 1993;148:310-6.
- Wessell DL, Adatia I, Giglia TM, et al. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation* 1993;88:2128-38.
- Fullerton DA, McIntyre RC, Mitchell MB, et al. Lung transplantation with cardiopulmonary bypass exaggerates pulmonary vasomotor dysfunction in the transplanted lung. *J Thorac Cardiovasc Surg* 1995;109:212-7.
- Adatia I, Lillehei C, Arnold JH, et al. Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. *Ann Thorac Surg* 1994;57:1311-8.
- Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, et al. Inhaled

- nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet* 1991;338:1173-4.
22. Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:818-9.
 23. Kinsella JP, Neish SR, Shaffer E, et al. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:819-20.
 24. Date H, Trulock EP, Arcidi JM, et al. Improved airway healing after lung transplantation: an analysis of 348 bronchial anastomoses. *J Thorac Cardiovasc Surg* 1995;110:1424-33.
 25. Whyte RI, Deeb GM, McCurry KR, et al. Extracorporeal life support after heart and lung transplantation. *Ann Thorac Surg* 1994;58:754-9.
 26. Frostell C, Fratacci MD, Wain JC, et al. Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991;83:2038-47.
 27. Stavert DM, Lehnert BE. Nitrogen oxide and nitrogen dioxide as inducers of acute pulmonary injury when inhaled at relatively high concentrations for brief periods. *Inhal Toxicol* 1990;2:53-67.
 28. Shiraishi T, DeMeester SR, Worrall NK, et al. Inhibition of inducible nitric oxide synthase ameliorates rat lung allograft rejection. *J Thorac Cardiovasc Surg* 1995;110:1449-60.
 29. Hugod C. Effect of exposure to 43 ppm nitric oxide and 3.6 ppm nitrogen dioxide on rabbit lung. *Int Arch Occup Environ Health* 1979;42:159-67.

Discussion

Dr. Paul F. Waters (*Los Angeles, Calif.*). We in our program have also encountered severe early graft dysfunction that leaves us helplessly watching the patient become hypoxemic and hypotensive, with very few therapeutic modalities other than ECMO. We have seen an excellent therapeutic response to nitric oxide in some cases and have found it to be ineffective in others. Have any of your patients been unresponsive to nitric oxide therapy?

Dr. Date. We had one patient who did not respond to nitric oxide treatment. This patient required ECMO 24 hours after the initiation of nitric oxide, but the lung never recovered. This patient probably should have been treated with ECMO earlier. However, we do not know how to distinguish between patients who should be treated with ECMO from the beginning and those who should be treated with nitric oxide when the graft dysfunction is very severe.

Dr. Waters. Is your use of nitric oxide now still a reactive process or are you using it prophylactically in patients in whom the risk is particularly high, for instance, patients with Eisenmenger-type pulmonary vascular disease or those with primary pulmonary hypertension?

Dr. Date. We have actually tested more than 50 patients with a short course of nitric oxide. Only the patients with graft dysfunction as manifested by P_{aO_2}/F_{iO_2} ratios less than 150 responded well, which means oxygenation was improved. However, nitric oxide had an adverse effect in patients who did not have graft dysfunction, which means

oxygenation became worse. Therefore, we use nitric oxide only for the patient with graft dysfunction as manifested by a P_{aO_2}/F_{iO_2} ratio less than 150.

Dr. Waters. I see. I noticed that some of your patients with pulmonary vascular disease had single lung transplants and some had double lung transplants. What were the particular reasons why one patient would receive one operation and another the other?

Dr. Date. Currently, if both lungs are available, we use bilateral lung transplantation for this group of patients. However, donor shortage is a big problem. If single lung transplantation is the only option for that patient, then we use that option. However, the primary choice for us is double lung transplantation at this time.

Dr. Waters. Are you saying that there is no particular stratification, that the type of treatment depends on whether there is a double lung block available?

Dr. Date. The quality of the lung also has an impact. If we do a single lung transplantation, the lung has to be perfect and the lung has to be close to the center. The ischemic time should be shorter than for bilateral lung transplantation, because the patient who receives a single lung transplant for pulmonary hypertension has a difficult course.

Dr. Waters. My final question relates to any thoughts that you might have on the etiology of this severe graft dysfunction. Do you think it is an immunologic process, a reperfusion injury, a combination?

Dr. Date. We have investigated the effect of nitric oxide using a canine left single lung transplant model, and we found that by administering nitric oxide we could reduce myeloperoxidase activity. Therefore, maybe one of the causes of this reimplantation phenomenon is neutrophil activation, and nitric oxide may be working on this phenomenon.

Dr. Waters. Have you used leukocyte depletion at all in reperfusion?

Dr. Date. No, not yet.

Dr. Robert C. Robbins (*Stanford, Calif.*). I agree with Dr. Waters' comments about primary pulmonary hypertension and your comments about the use of double lung transplantation. I think that is the best operation.

In patients with primary pulmonary hypertension, have you observed that if you do the operations without cardiopulmonary bypass dysfunction is worse in the lung that is implanted first, probably related to reperfusion injury?

Dr. Date. We have to use cardiopulmonary bypass for transplant operations in patients with pulmonary hypertension. If we do not, the patient cannot tolerate the pneumonectomy. Therefore, we electively use cardiopulmonary bypass for all patients with pulmonary hypertension. With regard to bilateral lung transplantation in this group of patients, function in the first transplanted lung is usually poorer than that of the second transplanted lung, even though the second lung has a longer ischemic time. The probable reason is hyperperfusion to the first transplanted lung during the second lung implantation, as you mentioned.