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Inhaled nitric oxide (NO) for the treatment of early allograft failure after lung transplantation

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Abstract *Objective*: Inhalation of high concentrations of nitric oxide (NO) has been shown to improve gas exchange and to reduce pulmonary vascular resistance in individuals with ischemia-reperfusion injury following orthotopic lung transplantation. We assessed the cardiopulmonary effects of low doses of NO in early allograft dysfunction following lung transplantion.
Design: Prospective clinical dose-response study.
Setting: Anesthesiological intensive care unit of a university hospital.
Patients and participants: 8 patients following a single or double lung transplantation who had a mean pulmonary arterial pressure (PAP) in excess of 4.7 kPa (35 mmHg) or an arterial oxygen tension/fractional inspired oxygen ratio (PaO_2/FIO_2) of less than 13.3 kPa (100 mmHg).
Interventions: Gaseous NO was inhaled in increasing concentrations (1, 4 and 8 parts per million, each for 15 min) via a Siemens Servo 300 ventilator.
Measurements and results: Cardiorespiratory parameters were assessed at baseline, after each concentration of NO, and 15 min after withdrawal of the agent [statistics: median (25th/75th percentiles: Q1/Q3), rANOVA, Dunnett's test, $p < 0.05$]. Inhaled NO resulted in a significant, reversible, dose-dependent, selective reduction in PAP from 5.5(5.2/6.0) kPa at control to 5.1(4.7/5.6) kPa at 1 ppm, 4.9(4.3/5.3) kPa at 4 ppm, and to 4.7(4.1/5.1) kPa at 8 ppm. PaO_2 increased from 12.7(10.4/17.1) to 19.2(12.4/26.0) kPa at 1 ppm NO, to 23.9(4.67/26.7) kPa at 4 ppm NO and to 24.5(11.9/28.7) kPa at 8 ppm NO. All patients responded to NO inhalation (either with PAP or PaO_2), all were subject to long-term inhalation (1–19 days). All were successfully weaned from NO and were discharged from the intensive care unit.
Conclusion: The present study demonstrates that low-dose inhaled NO may be an effective drug for symptomatic treatment of hypoxemia and/or pulmonary hypertension due to allograft dysfunction subsequent to lung transplantation.

Key words Lung transplantation · Inhaled vasodilators · Nitric oxide · Pulmonary hypertension · Selective pulmonary vasodilation · Reperfusion injury

Introduction

The early postoperative course of patients following a single or double lung transplantation (sLuTx/dLuTx) is often complicated by ischemia-reperfusion injury of the lung. The latter is characterized by endothelial damage, neutrophil sequestration, and decreased release of endothelial nitric oxide (NO) [1]. As a consequence, a progressive increase in pulmonary vascular resistance (PVR) and a decrease in oxygenation may occur and may contribute significantly to the postoperative morbidity and mortality of these patients [2, 3]. About 25–37 % of the early postoperative deaths following LuTx or heart-lung transplantation are related to early allograft dysfunction due to ischemia-reperfusion injury [2].

The use of an inhaled vasodilator like NO may be beneficial in this situation, because it is assumed that inhaled drugs only reach alveolar areas of the lung that are ventilated, thereby preserving hypoxic pulmonary vasoconstriction in the nonventilated lung. Redistribution of blood flow from the nonventilated to the ventilated lung decreases ventilation-perfusion (V/Q) mismatch, which, together with true intrapulmonary shunt, is the major cause of hypoxemia in reperfusion injury of transplanted lungs. NO causes smooth muscle cells to relax by stimulating intracellular cyclic 3′-5′ guanosine monophosphate formation. After inhalation, the vasodilating effect of NO is restricted to the lung, because any systemically absorbed NO is inactivated within seconds. Inhaled NO (iNO) may improve oxygenation in patients suffering from hypoxemia due to V/Q mismatch and induce selective pulmonary vasodilation in subjects with pulmonary hypertension [4–6].

Besides its pulmonary vasodilatory effects, iNO may exert beneficial effects on early allograft dysfunction via various mechanisms, mainly due to a reduction of endothelial reperfusion injury. Possible mechanisms include an inhibition of xanthine oxidase [7], quenching of superoxide radicals, inhibition of leukocyte-endothelial interaction [8, 9], platelet aggregation [10], and maintaining endothelial homeostasis [11].

While beneficial effects of inhaled NO have been demonstrated in a variety of in vitro and in vivo experimental models of lung transplantation [1, 3, 12–15], no dose-response curves are available and clinical data are limited [16–19] due to the small number of patients receiving allografts in a single center. Up to now, concentrations of up to 80 ppm [19] of iNO have been reported for the treatment of lung allograft dysfunction in humans, whereas much lower doses were shown to exert beneficial effects in patients suffering from the acute respiratory distress syndrome [20, 21]. Furthermore, iNO still has to be regarded as toxic in high concentrations [22], especially in ischemia-reperfusion injury, where highly toxic peroxynitrite is produced from NO and oxygen radicals [23, 24].

The aim of the present study, therefore, was to assess prospectively the effects of low doses of inhaled NO in patients presenting with severely impaired gas exchange and/or pulmonary hypertension following sLuTx or dLuTx.

Materials and methods

Patients

From July 1994 through February 1997, 38 patients underwent sLuTx/dLuTx at our institution (sLuTx: $n = 20$, dLuTx: $n = 18$). After approval by the local ethics committee and after written informed consent had been obtained from relatives, 8 of these 38 patients, who fulfilled the criteria of severe early allograft dysfunction after lung transplantation, as described below, were included in the study according to the principles of the Helsinki Declaration. Inclusion criteria were an arterial oxygen tension/fractional inspired oxygen (PaO_2/FIO_2) ratio of less than 13.3 kPa (100 mmHg), despite optimizing ventilator settings, and/or a pulmonary arterial pressure (PAP) in excess of 4.7 kPa (35 mmHg). All patients were studied in the intensive care unit (ICU) within 12 h postoperatively.

In 5 patients, sLuTx was performed, 3 received sequential dLuTx. All grafts were flushed with 4 l of precooled Euro-Collins or low potassium dextrane solution (Perfadex) (Table 1). Hypothermic storage was carried out by topical cooling. Allograft dysfunction was associated with other organ dysfunction in 7 patients (Table 1). Immunosuppression was achieved by intravenous administration of a combination of the following drugs: tacrolimus (Prograf) or cyclosporin (Sandimmun) alternatively, prednisolone (Solu-Decortin), azathioprine (Imurek), ATG-Fresenius (Table 1). All patients were intubated and mechanically ventilated using a Siemens-Servo 300 ventilator and pressure-controlled ventilation (respiratory rate 12–20 breaths/min). Peak inspiratory pressures of up to 4.9 kPa (37 mmHg) were allowed, resulting in tidal volumes between 371 and 1004 ml and a median (25th/75th percentiles: Q1/Q3) arterial carbon dioxide tension of 6.0(5.5/6.7) kPa [45(41/50) mmHg] before and 5.7(4.5/6.7) kPa [43(34/50) mmHg] after administration of iNO. Peak end expiratory pressure did not exceed 0.8 kPa (8 cmH_2O). At the time of enrollment, 4 patients were ventilated with an FIO_2 of 1.0. Three patients were on an FIO_2 of 0.5 and one on 0.9. Patients were sedated and paralyzed with fentanyl (0.04–0.09 μg/kg per min), midazolam (2.1–6.1 μg/kg per min), and pancuronium bromide (0–1.2 μg/kg per min). All patients except 1 received dopamine at doses of 2.2–15.4 μg/kg per min; 5 received additional cardiotonic or vasoactive drugs (Table 1).

Administration of NO

For administration of NO (1000 ppm, Pulmomix), we used a modified Servo ventilator (Servo 300B – NO/A) with a flow-controlled NO gas module, producing a defined inspiratory NO jet [max. NO peak flow 30 ml/s, max. gas peak flow NO 3 l/s, max. set (NO) 10 ppm, max. FIO_2 at max. set NO 0.99, mixing error < 5 %] of 1/100th of the patient gas flow. Using Pulmomix, ventilator specifications allowed for NO concentrations from 0 to 10 ppm. Inspiratory and expiratory concentrations of NO and NO_2 were assessed and

Table 1 Clinical characteristics of patients

	Patient no./sex							
	1/M	2/M	3/M	4/M	5/F	6/M	7/F	8/F
Age (years)	47	21	61	56	51	44	16	44
Height (m)/weight (kg)	1.68/65	1.70/55	1.78/88	1.82/72	1.58/48	1.74/87	1.65/50	1.62/62
Surgery	sLuTx	dLuTx	sLuTx	sLuTx	sLuTx	sLuTx	dLuTx	dLuTx
Cardiopulmonary bypass	No	Yes	No	No	No	Yes	Yes	Yes
Graft preservation solution	Euro-Collins	Euro-Collins	Euro-Collins	Euro-Collins	Euro-Collins	LPD	LPD	LPD
Immunosupression	CyA/Aza/P	FK/Aza/P	FK/Aza/ P/ATG	FK/Aza/P	FK/Aza/ P/ATG	FK/Aza/ P/ATG	FK/Aza/P	FK/Aza/P
Underlying disease	Pulmonary fibrosis	Cystic fibrosis	Pneumo-coniosis	Antitrypsin deficiency	Pulmonary emphysema	Pulmonary fibrosis	Cystic fibrosis	Honeycomb lung
LIS/APACHE II score post-LuTx	3/18	2.7/22	0.7/22	1.7/20	2.5/34	2.8/30	0.8/16	2.5/20
PaO_2 pre-LuTx	65 (9 l O_2/min)	40 ambient air	63 ambient air	28 ambient air	47 ambient air	28 ambient air		66 (1.5 l O_2/min)
PaO_2/FIO_2 post-LuTx	72.3	93	339	145	67.1	193.6	264.8	84
NO response	PaO_2	PaO_2/PAP	PaO_2	PaO_2	PaO_2	PAP	PaO_2/PAP	PaO_2/PAP
Mechanical ventilation (days)	52	23	5	57	3	45	4	55
NO therapy (days)	5	2	4	3	2	19	3	1
Organ failure[a]	Kidney	Kidney, liver	Kidney	Kidney	Kidney	Kidney	–	Kidney, heart
Epinephrine (μg/kg per min)	–	–	–	0.76	–	0.40	0.20	–
Norepinephrine (μg/kg per min)	–	1.06	–	–	0.21	–	–	–
Dopexamine (μg/kg per min)	–	2.03	–	–	1.0	0.4	–	–

[a] Data reported for accompanying organ failure were those at the time of the study. Definition of organ failure according to Fisher et al. [37]
(*LIS* lung injury score according to Murray et al. [38], *APACHE II* Acute Physiology and Chronic Health Evaluation, *sLuTx single* lung transplantation, *dLuTx* double lung transplantation, *LPD* low potassium dextrane solution, *Aza* azathioprine, *CyA* cyclosporin, *P* prednisolone, *FK* tacrolimus, PaO_2 arterial O_2 tension, PaO_2/FIO_2 PaO_2/fractional inspired oxygen ratio, *PAP* pulmonary artery pressure)

monitored continuously throughout the study by chemiluminescence (CLD 700 Al, ECO-Physics, latency 40 s) and NO/NO_2-sensitive electrochemical cells, respectively. Methemoglobin levels were monitored by CO oximetry (Radiometer) with every blood gas determination in all patients and at least three times daily during long term inhalation.

Measurements

For continuous pressure recording, a fast-response thermodilution pulmonary artery catheter (Swan-Ganz TD cath. 93A-431–7.5F G, Baxter) and radial or femoral artery catheters (Leadercath, Vygon) were inserted. Central venous pressure, mean PAP, pulmonary artery occlusion pressure, and mean arterial pressure were documented via a Siemens Sirecust 1281 Monitoring unit. Cardiac index, right ventricular ejection fraction, and right ventricular end-diastolic volume were assessed by the thermodilution technique using four injections of iced saline (10 ml) at end-expiration (REF-1, Ejection Fraction/Cardiac Output Computer, Baxter). pH, and partial pressure of oxygen (PO_2) and carbon dioxide were determined and oxygen saturation directly measured by oximetry using a blood gas analyzer/hemoxymeter (ABL 520, Radiometer). PVR, systemic vascular resistance, oxygen delivery, oxygen uptake, and intrapulmonary shunt (Qs/Qt) were calculated using standard formulae. For calculation of Qs/Qt, ideal capillary O_2 content (CcO_2) is required, which was calculated as $CcO_2 = Hb \cdot 1.34 + 0.0031 \cdot PalvO_2$, assuming an O_2 saturation of 100 %, where Hb is hemoglobin concentration and $PalvO_2$ is alveolar PO_2. $PalvO_2$ was assessed as $PalvO_2 = FIO_2 \cdot (Pbar - 6.3\ kPa\ (47\ mmHg)) - PaCO_2/0.8$, where FIO_2 is fractional inspired oxygen, Pbar is barometric pressure, $PaCO_2$ is partial pressure of carbon dioxide in arterial blood, and 0.8 is an assumed respiratory quotient.

Protocol

FIO_2 was held constant throughout the study period. NO was administered at concentrations of 1, 4, and 8 ppm for 15 min each, and measurements taken thereafter; 15 min after withdrawal of 8 ppm of NO a control measurement was performed. After termination of the study protocol, the decision on further treatment with NO and the timepoint of weaning patients from NO was up to the attending physician of the ICU. The dose of choice was the

minimal effective NO concentration. Stepwise daily reduction of NO was initiated if gas exchange allowed for an $FIO_2 < 0.8$. NO administration was stopped at FIO_2 0.4. The total number of days on iNO treatment was recorded.

Statistical analysis

Most data were not normally distributed. Therefore, all values are given as median and quartiles. Statistical analysis was performed using a Friedmann repeated measures analysis of variance on ranks. If the F value was significant ($p < 0.05$), the following time points were compared to their respective control values before treatment according to Dunnett's procedure [25]: NO 1 ppm, NO 4 ppm, and NO 8 ppm, and control post-NO versus control before NO. Differences were considered significant at $p < 0.05$.

Results

A significant decrease in PAP and PVR was observed at each of three concentrations of iNO (1, 4, and 8 ppm) (Fig. 1). No other hemodynamic or ventilatory variables were affected by inhaled NO (Fig. 2, Table 2). Carbon dioxide pressure varied by ± 5 % (Table 2).

Inhaled NO resulted in a significant increase in PaO_2 with all concentrations tested (Fig. 3). A decrease in Qs/Qt was observed with all concentrations of iNO, but reached statistical significance with 4 and 8 ppm only. Changes in PaO_2 were more pronounced at 4 and 8 ppm of NO (+ 88/ + 93 % vs. control) than at 1 ppm NO (+ 52 %). The effects of iNO on gas exchange were reversible after withdrawal of the agent.

Prolonged iNO therapy was considered beneficial in all patients. NO application was maintained over a period of 1 to 19 days at minimal effective concentrations. Most patients fulfilled both inclusion criteria. Those, in whom impaired gas exchange was the leading problem were treated effectively with 1 to 4 ppm NO and those in whom the main problem was pulmonary hypertension with 4 to 8 ppm NO. As with the patients' response to therapy, the subsequent weaning process was individual. The inspiratory NO concentration remained unchanged until the FIO_2 could be reduced to 0.8 or the PAP had fallen below 30 mmHg. The NO concentration then was reduced stepwise if PAP did not increase following dose reduction. NO was switched off at an FIO_2 below 0.4 and/or a PAP below 25 mmHg. All patients were successfully weaned from NO and discharged from the ICU.

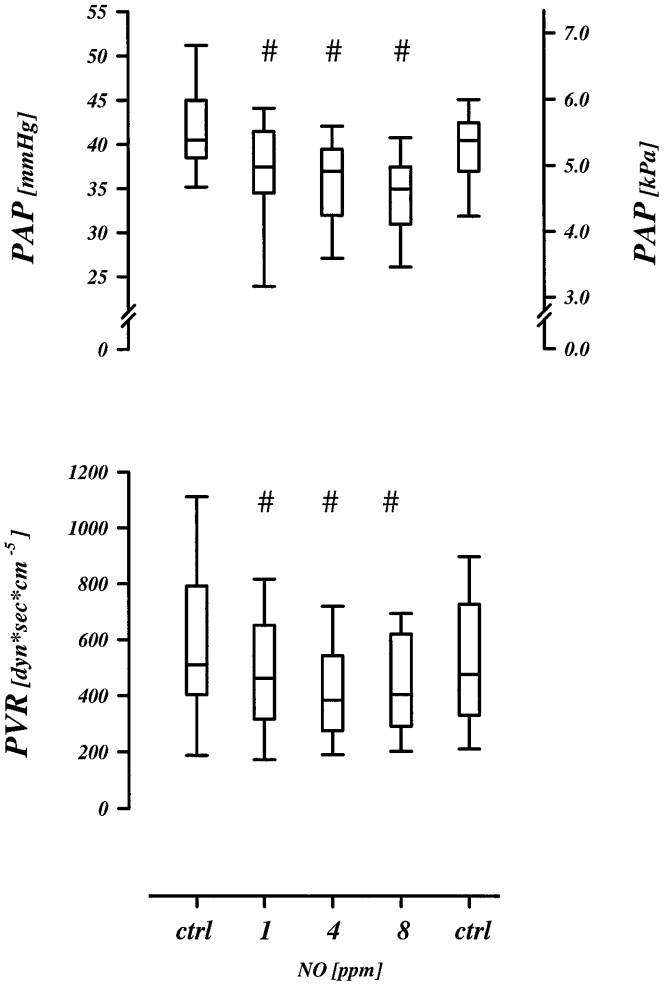

Fig. 1 Effects of inhaled NO on pulmonary hemodynamics. The boxes show dose-response relationships for three concentrations of inhaled NO (1, 4, and 8 ppm) as compared to control *ctrl* values. Changes in pulmonary artery pressure *PAP* and pulmonary vascular resistance *PVR* are indicated. The boxes contain the central 50 % of data (median), i. e., from the 25th to the 75th percentile (Q1/Q3), the error bars depict the 5th and 95th percentiles; $n = 8$. $p < 0.05$ (vs control value before administration of NO). For further explanation see text

Discussion

The main result of the present study is that inhaled NO effectively improves oxygenation and reduces PVR in patients with early allograft failure following lung transplantation. Beneficial effects were seen with doses of NO as low as 1 ppm. All patients received prolonged iNO therapy and were successfully weaned.

Recently, Date et al. [18] investigated the effects of 20–60 ppm NO in 15 patients with early allograft dysfunction and found a significant decrease in PAP from 4.0 to 3.5 kPa (30 to 26 mmHg) and an increase in PaO_2/FIO_2 from 11.7 to 20.4 kPa (88 to 153 mmHg) [18]. Adatia et al. [19] reported a drop in PAP and an increase in PaO_2 in 5 of 6 patients after lung transplantation following 80 ppm of NO [19]. Very similar changes in PAP and PaO_2 were observed in the present study (Fig. 1–3) using tenfold lower concentrations of NO (1–8 ppm). This suggests that effective treatment of re-

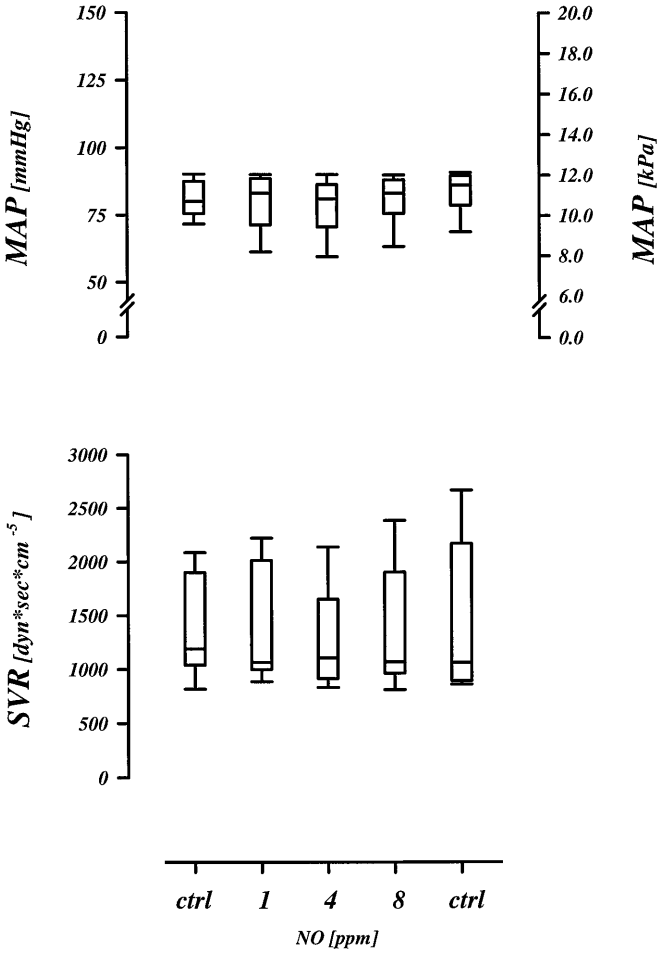

Fig. 2 Effects of inhaled NO on systemic hemodynamics. The boxes show dose-response relationships for three concentrations of inhaled NO (1, 4, and 8 ppm) as compared to control *ctrl* values. Changes in measured mean arterial pressure *MAP* and calculated systemic vascular resistance *SVR* are indicated. The boxes contain the central 50% of data (median), i.e., from the 25th to the 75th percentile (Q1/Q3), the error bars depict the 5th and 95th percentiles; $n = 8$. No significant changes were detected

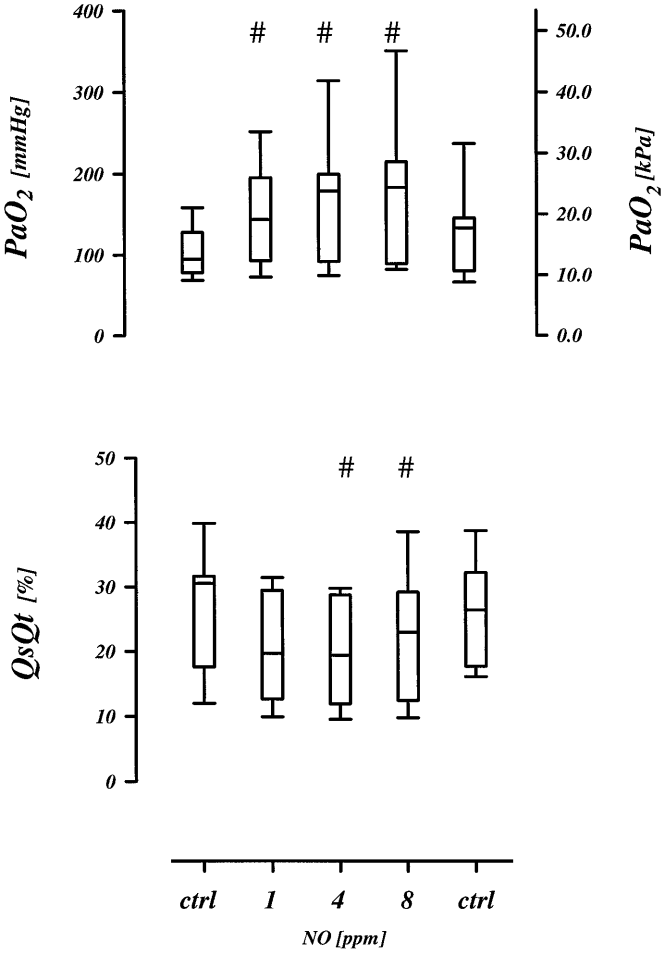

Fig. 3 Effects of inhaled NO on gas exchange. The boxes show dose-response relationships for three concentrations of inhaled NO (1, 4, and 8 ppm) as compared to control *ctrl* values. Changes in measured PaO_2 and calculated intrapulmonary shunt *Qs/Qt* are indicated. The boxes contain the central 50% of data (median), i.e., from the 25th to the 75th percentile (Q1/Q3), the error bars depict the 5th and 95th percentiles; $n = 8$. $p < 0.05$ (vs control value before administration of NO). For further explanation see text

perfusion injury following lung transplantation, as in the adult respiratory distress syndrome (ARDS) [20, 21, 26] is possible by administering low concentrations of iNO.

The use of "low-dose NO" might be especially attractive following lung transplantation because it is well known that NO may contribute to the production of highly toxic peroxynitrite in the presence of superoxide anions [23, 24], that are abundantly generated during reperfusion of ischemic tissue. Increased peroxynitrite generation might explain the absence of efficacy in reducing reperfusion injury [13, 27] or even the deleterious effects of high NO concentrations (80 ppm) [28, 29] reported recently in connection with reperfusion injury.

Beneficial effects of iNO, apart from pulmonary vasodilation, are reported from various experimental models of ischemia/reperfusion of the lung. A reduction in myeloperoxidase activity [12] and alveolar leukocyte count after sLuTx [1], and a reduction of thiobarbituric acid-reactive materials [12] in graft samples during storage after reperfusion are indicative of a reduction of pulmonary sequestration of leukocytes and reduced oxidative injury in the presence of NO. In experimental sLuTx, a reduction in blood flow shift toward single lung grafts [14] reduced graft edema.

A crucial point about NO inhalation in ischemia/reperfusion injury of the lung seems to be timing. Data from recent publications suggest that NO can exert divergent effects on graft function and reperfusion injury depending on the time of application [3, 12, 28, 30, 31]. We did not administer NO as a prophylactic measure

Table 2 Cardiorespiratory effects of inhaled NO. Values are medians (25th; 75th percentiles) (n = 8)

	Control	NO (1 ppm)	NO (4 ppm)	NO (8 ppm)	Control
HR (l/min)	121 (113; 134)	122 (112; 129)	114 (112; 131)	119 (109; 129)	118 (116; 128)
CI (l/min per m^2)	2.3 (1.8; 2.9)	2.2 (1.7; 2.9)	2.4 (1.9; 3.2)	2.4 (1.9; 3.2)	2.5 (1.9; 2.9)
PAOP (kPa)	1.6 (1.3; 2.9)	1.6 (1.3; 3.3)	1.7 (1.3; 3.1)	1.7 (1.3; 2.5)	1.7 (11.5; 3.2)
CVP (kPa)	1.6 (0.9; 2.4)	1.6 (0.8; 2.4)	1.7 (1.1; 2.5)	1.7 (1.1; 2.4)	1.7 (1.1; 2.4)
RVEF (%)	30 (24; 33)	28 (22; 33)	25 (23; 35)	31 (24; 37)	25 (21; 33)
RVEDV (ml)	117 (77; 167)	143 (91; 180)	151 (95; 199)	120 (90; 193)	132 (115; 188)
Hb (g/l)	124 (109; 135)	125 (110; 135)	123 (109; 132)	120 (109; 132)	124 (113; 134)
metHb (% Hb)	0.50 (0.45; 0.65)	0.55 (0.50; 0.70)	0.60 (0.50; 0.75)	0.70* (0.65; 0.90)	0.65* (0.55; 0.85)
DO_2 (ml/min)	693 (448; 753)	625 (405; 819)	631 (444; 889)	672 (465; 865)	647 (436; 830)
VO_2 (ml/min)	225 (186; 293)	253 (166; 276)	271 (176; 300)	218 (183; 289)	202 (167; 279)
MV (l/min)	8.3 (7.2; 9.7)	8.7 (7.1; 9.8)	8.5 (7.3; 9.7)	8.4 (7.6; 9.7)	8.7 (8.1; 9.7)
$PaCO_2$ (kPa)	6.0 (5.4; 6.6)	6.0 (5.1; 6.8)	6.2* (5.0; 6.6)	5.8* (5.0; 6.4)	5.7* (4.5; 6.7)

* $p < 0.05$ (vs control value before NO administration) (*HR* heart rate, *CI* cardiac index, *PAOP* pulmonary artery occlusion pressure, *CVP* central venous pressure, *RVEF* right ventricular ejection fraction, *RVEDV* right ventricular end-diastolic volume, *Hb* hemoglobin concentration in arterial blood, *metHb* methemoglobin concentration as percentage of hemoglobin, DO_2 oxygen delivery, VO_2 oxygen consumption, *MV* minute ventilation, $PaCO_2$ partial pressure of carbon dioxide in arterial blood)

(donor pretreatment), but only in cases of severe allograft failure in the postoperative course. Therefore, we are not able to define whether the administration of NO prior to reperfusion of the transplanted lung may be beneficial. A significant deterioration of graft function reported with iNO application prior to perfusion of grafts [28] is probably attributable to the route of administration of iNO. In the presence of microatelectasis iNO leads to a redistribution of pulmonary blood flow with macroscopically visible inhomogeneous perfusion of the grafts. Insufficient washout of blood cells in hypoperfused areas may locally aggravate ischemia reperfusion injury. Thus, a positive effect of NO preinhalation, reported in other studies [30, 31] might be dependent on sufficient recruitment of alveoli.

Concerns about potential NO toxicity were raised in a multicenter study in patients with acute lung injury [32], where preliminary analyses showed evidence for an increased incidence of renal failure in patients receiving NO therapy (*Personal communication: "Initial report from the AGA clinical trial, NO-93–002/002 A, on inhaled nitric oxide (iNO) in acute lung injury (ALI), AGA, Healthcare, Stockholm, October 1997*). In contrast, a phase II clinical investigation in 177 patients demonstrated no significant differences in incidence or type of adverse events in the NO and placebo group [33]. In the present study, 7 of 8 patients developed acute renal failure (ARF) during their clinical course. This was present on admission to the ICU in most of our patients. The high incidence of renal failure in this group, therefore, partly reflects the severity of disease (APACHE II score, Murray Score). In addition, intraoperative fluid restriction or the use of cardiopulmonary bypass may have contributed to the initiation of ARF. Other patients developed ARF later during ICU treatment. In those allograft recipients, many therapeutic interventions apart fom iNO are known to impair renal function severely (e.g., immunosuppression, antibiotics). Due to the lack of a control group, the contribution of iNO to the incidence of ARF in our patients remains questionable, and no conclusion can be drawn.

Rebound pulmonary hypertension after withdrawal of NO has been demonstrated under a variety of clinical conditions including ARDS [34]. A recent animal study suggests that rebound phenomena may also occur after acute termination of NO in lung transplant patients [15].

In the present study, no rebound phenomena were observed after short-term administation of NO for 1 h. In those patients in whom long-term therapy with NO seemed warranted, NO was slowly tapered off after cardiopulmonary stabilization. Thereby rebound pulmonary hypertension could be avoided in all patients. Unlike in ARDS patients, in whom iNO therapy is often required for many days or weeks, iNO was successfully withdrawn within 5 days or less in 7 of 8 patients in our study.

In the present study no control group was investigated. Because most of our patients had severely impaired gas exchange and hemodynamics, intervention was mandatory. We therefore refrained from evaluating a control group in these critically ill patients because of ethical considerations. To ensure that the observed effects were not due to random variability or time-dependent drifts, baseline values after withdrawal of NO served as internal controls. The heterogeneity of our patients' underlying diseases and therapies is obvious. This is due to the nature of underlying disease and therapy and thus is present in any clinical investigation on iNO in allograft failure published so far [17–19]. The use of different preservation solutions does not appear to influence the patient's clinical course once allograft failure has occurred. Inclusion of single and double lung procedures, as performed in our study, probably does not notably influence results, for it has been shown recently that ischemia and reperfusion of single lung grafts cause endothelial injury in both lungs of the recipient [35]. Thus, heterogeneity of procedures probably does not alter the investigated effects of iNO therapy. Lastly, only concentrations in the range below 10 ppm were studied. We refrained from investigating high NO concentrations because of concerns of toxicity and knowledge of the efficacy of low concentrations of iNO in human ARDS [20, 21].

In summary, the present study demonstrates that iNO at low doses improves gas exchange and lowers mean pulmonary arterial pressure (PAP) without any obvious adverse effects in patients suffering from early allograft dysfunction following lung transplantation. However, although increased survival due to inhalation of NO in experimental warm ischemia and reperfusion has been reported [36], it remains to be elucidated whether inhaled NO actually decreases mortality from early allograft failure in patients following lung transplantation.

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