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Response to nitric oxide inhalation in early acute lung injury

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Abstract *Objective:* To evaluate the dose response of inhaled nitric oxide (NO) on gas exchange and central haemodynamics in patients with early acute lung injury (ALI).
Design: Prospective, multicentre clinical study.
Setting: General ICUs in university and regional hospitals.
Patients: 18 patients with early ALI according to specified criteria.
Interventions: During controlled ventilation an inhalation system was used to deliver NO (1000 ppm in N_2) and O_2/air to the low pressure fresh gas inlet of a Siemens 900C ventilator. Haemodynamics and pulmonary gas exchange variables were measured at baseline and at stepwise increased inspiratory NO concentrations of 0.1, 0.3, 1, 3, 10, 30 and 100 ppm, each dose being maintained for 15 min. Dose testing was repeated the next day, and the response to prolonged (2 h) NO inhalation at 1 and 10 ppm was also tested.
Measurements and results: Inhalation of NO produced a significant increase in PaO_2 ($P<0.0025$). The degree of response, as well as the optimal NO dose varied in individual patients and between different days. Venous admixture (Q_{VA}/Q_T) was reduced ($P<0.02$) from 38% (31–46%) to 33% (26–41%). In our patients with early acute lung injury and only a moderate elevation in pulmonary arterial pressure NO inhalation did not reduce mean pulmonary artery pressure significantly, being 27.0 (21–30) mmHg at baseline and 26.0 (21–30) mm Hg at 100 ppm.
Conclusions: This study shows that improvements in arterial oxygenation in response to inhaled NO may show great inter- as well as intraindividual variability, and that improvements in arterial oxygenation occur without any measurable lowering of the pulmonary artery pressure.

Key words Acute respiratory failure · Mechanical ventilation · Nitric oxide · Inhaled · Pulmonary artery pressure

Introduction

Acute lung injury (ALI) is characterised by an increase in venous admixture resulting in arterial hypoxaemia.[1] Nitric oxide (NO) is a mediator produced by vascular endothelium, macrophages and nerve cells, and is believed to be identical with the endothelium-derived relaxing factor [2, 3]. NO has marked vasodilator properties [3]. Previous experience in animals and humans has shown that inhalation of NO in concentrations of 5–80 parts per million (ppm) can induce a selective dilation of the pulmonary vascular bed, without effects on the systemic vasculature [4]. In adults with severe acute lung injury, for example acute respiratory distress syndrome (ARDS), studies have shown that inhalation of NO can selectively improve per-

fusion of ventilated regions, thus reducing intrapulmonary shunt and improving arterial oxygenation [5–8]. Rossaint et al. [5] reported positive effects on gas exchange and a reduction in pulmonary arterial pressure in ARDS patients who inhaled 5–20 ppm NO for 3–53 days.

The present study evaluated the dose-response effect of inhaled NO (0.1–100 ppm) on gas exchange and pulmonary haemodynamics in patients with early ALI of varied aetiology, less severely ill than those previously studied [5, 6, 9]. The consistency of response to inhalating NO was also confirmed by repeated dose testing on consecutive days and by evaluating the response to prolonged inhalation of NO for up to 2 h at 1 and 10 ppm.

Materials and methods

The study was approved by the Human Ethics Committees of the five participating hospitals in Sweden. Eighteen patients with early ALI were included after informed consent from each patient's next of kin. Inclusion criteria were: (a) acute respiratory insufficiency requiring intubation and mechanical ventilation with an inspired oxygen fraction (FIO_2) of at least 0.5; (b) an arterial oxygen tension (PaO_2) to FIO_2 ratio (PaO_2/FIO_2) of less than 20 kPa (< 150 mmHg) for at least 24 h but not more than 72 h with positive end-expiratory pressure at or above 5 cm H_2O; and (c) uni- or bilateral lung infiltrates. Exclusion criteria were: (a) mechanical ventilation more than 7 days before the study; (b) left ventricular dysfunction and/or fluid overload, defined as a pulmonary capillary wedge pressure (PCWP) greater than 18 mmHg; and (c) inhalation of NO. The presence of organ failure was recorded using criteria modified from Knaus et al. [11] and Bernard et al. [12] as: (a) hepatic failure (serum bilirubin >100 μmol/l); (b) kidney failure (serum creatinine >300 μmol/l). The patients received pressure- or volume-controlled ventilation according to each patient's attending physician. Ventilatory settings were unchanged during each dose response testing.

Patients (Table 1)

The median age of the 18 patients was 56 (44–73) years (Table 1). Acute lung injury was secondary to sepsis[16] (4 patients), infectious pneumonia (diagnosed on patient's history, sputum Gram stain and culture, and chest radiograph; 7 patients), trauma and/or pulmonary contusion (3 patients), aspiration (2 patients). Time on ventilator before inclusion was 1–5 days. Thirteen patients received intravenous infusions of vasoactive drugs at the start of study. Additional organ failures were noted in four patients. Thirty days after inclusion nine patients had died (50% mortality). At inclusion the average PaO_2/FIO_2 ratio was 15.2 (10.8–18.4) kPa, calculated intrapulmonary shunt (Q_{VA}/Q_T) 38% (31–46%) and compliance 32 (18–38) ml/cm H_2O. The severity of lung injury according to the schema of Murray et al. [10] was 2.8 (2.5–3.0) .

NO administration and monitoring

A system for delivering NO [13] to the breathing gas was used, consisting of two mass flow regulators (Bronkhorst Hightech, Ruurlo, Netherlands) controlling the flow of NO (50 or 1000 ppm in N_2; AGA Gas, Solna, Sweden), and oxygen/air mixture, respectively, to the low pressure fresh gas inlet to the ventilator. NO dosages were set using mass flow regulators, (deviation from set flow <0.5%). A soda lime absorber placed on the inspiratory tubing was used for scavenging of nitrogen dioxide (NO_2) at NO doses ≥10 ppm. NO concentration was measured on-line by electrochemical cells (City Technology, London, UK). The bias and precision of the electrochemical fuel cells have been evaluated previously [14].The NO cell underestimates the true value by 10% in the interval from 2–50 ppm and overestimates the true value by 0.25 ppm at concentrations below 2 ppm, thus at a set level of 0.1 ppm NO readings were around 0.35 ppm. The error in NO_2 measurements was an underestimate of 0.1 ppm at all levels. The fuel cells were calibrated prior to the dose response tests with a gas containing 75.6 ppm NO and 6.2 ppm NO_2 (AGA Gas).

In evaluating the delivery system [13], NO_2 levels were less than 2 ppm in gas sampled downstream the absorber with a minute ventilation of 9 l/min, FIO_2 0.9 and a NO dose of 100 ppm. In five patients NO_2 levels after the absorber were checked during the dose-response tests, NO_2 being 0.2 (0.17–0.23) ppm at 10 ppm NO, 0.4 (0.3–0.6) ppm at 30 ppm and 1.7 (1.5–1.9) ppm at 100 ppm NO.

Dose-response trials

All 18 patients were subjected to short-term dose testing (15 min of each dose). Short-term testing was repeated in 15 of the patients the next day. Fourteen of the patients were also subjected to prolonged dose testing (120 min on 1 and 10 ppm) on the second or third day.

Short-term dose testing

The experimental procedure started with a control period when baseline haemodynamics and blood sampling were obtained. Stepwise increased concentrations of NO (0.1, 0.3, 1, 3, 10, 30 and 100 ppm) were administered during subsequent 15-min periods followed by a last control period at the end. FIO_2 was measured by side-stream spirometry and kept constant during the test. Haemodynamic measurements and blood samples were obtained at the end of each 15-min period. The following variables were measured both at baseline and at each inspired NO concentration: heart rate, systolic and diastolic systemic and pulmonary artery pressure, central venous pressure (CVP), PCWP, cardiac output (CO). Measurements of intravascular pressures were performed at end expiration. CO was measured in triplicate by thermodilution at random during the respiratory cycle. Mean systemic (MAP) and pulmonary artery pressure (MPAP) were calculated by standard formulas. Systemic vascular resistance was calculated as (MAP-CVP)/CO, and pulmonary vascular resistance (PVR) was calculated as (MPAP–PCWP)/CO. Transpulmonary pressure gradient in the pulmonary circulation (TPG) was calculated from the difference between MPAP and PCWP. Pulmonary compliance (C) was calculated as $V_T/(IPP-EEP)$. Arterial and mixed venous oxygen saturation (SaO_2 and SVO_2) and arterial and mixed venous oxygen tension (PaO_2 and PVO_2) were measured. Intrapulmonary shunt-fraction was calculated using standard formulas [15].

Prolonged dose testing

Measurements of central haemodynamics and gas-exchange were obtained prior to and after 15 and 120 min at 1 and 10 ppm. Thirty

Table 1 Patients characteristics (*L* liver, *K* kidney, *R* responder, *NR* nonresponder, *NT* not tested, d_1 day 1, d_2 day 2)

Pat. no.	Diagnosis	Age (years)	Sex	PaO_2/FIO_2 (kPa)	Q_s/Q_t (%)	Compliance (ml/cmH_2O)	ARDS (severity score)	MPAP (mmHg)	PVR (dyne s cm^{-5})	Inotropic support ($\mu g\ kg^{-1}\ min^{-1}$)	Organ failure	Survival	NO response (d_1/d_2)
1	Fungal sepsis	41	F	18.4	46	17	2.5	31	112	Dopamine 2	L	D	R/R
2	Fungal sepsis	54	F	8.6	39	17	3	30	236	Dopamine 3.5		D	R/NT
3	Aspiration	73	F	11.3	47	37	3.25	27	124	Dopamine 3		D	NR/R
4	Meningococceal sepsis	20	M	10.8	38	77	2	26	54	Dopamine 3 Dopexamine 2.2		S	R/NT
5	Oesophageal carcinoma	53	F	10.2	48	37	3.25	27	119	Dopamine 10 Dobutamine 12		S	R/NR
6	Pneumonia	80	F	19	25	30	2.75	27	170	Dopamine 5 Dobutamine 7		S	R/NR
7	Multiple blood transfusion	81	M	19.4	19	36	2.25	22	178	Dobutamine 11 Norapinefrine 0.3	K, L	D	R/R
8	Pneumonia	79	F	9	41	16	3	38	548	Dopamine 2.5		D	NR/R
9	Multitrauma	22	M	11	38	40	2.75	40	187	Dopamine 2 Dobutamine 2.3		S	NR/R
10	Bacterial infection	65	F	17	28	34	2.75	30	294		L	S	R/NR
11	Trauma	49	F	16.2	33	75	1.75	18	124			S	NR/NR
12	Pneumonia	73	F	15.8	47	16	3	18	102	Dopamine 10 Dobutamine 13		D	NR/NR
13	Trauma	48	M	19	31	39	2.75	17	81			S	R/NR
14	Postoperative infection	49	F	18.4	27	18	2.75	27	286			S	NR/R
15	Trauma	79	M	16.3	31	24	2	17	40			D	NR/R
16	Aspiration	44	F	9.7	40	21	3	32	111	Dopamine 2.5		S	NR/NR
17	Oesophageal carcinoma	70	M	12	53	38	2.75	21	188	Dopamine 2 Dobutamine 4		D	R/NR
18	Pneumonia	81	F	14.5		29	2.50	27	143	Dopamine 4 Dobutamine 7	K	D	NR/NT

minutes after cessation of NO the measurements were again performed. Methemoglobin concentration were measured in an ABL-520 oxygen saturation analyser (Radiometer, Copenhagen, Denmark) prior to and after 2 h exposure to NO 10 ppm.

Statistical analysis

Data are presented as median and interquartile range and evaluated using one-way analysis of variance for repeated measurements. The relation between the PaO_2/FIO_2 ratio at baseline and the maximum improvement in PaO_2 (%) during NO inhalation on day 1 was evaluated using Spearman's rank order analysis. A P value <0.05 was considered to indicate statistical significance.

Results

Short-term dose testing

Changes in central haemodynamics during short-term inhalation of NO at 100 ppm, are shown in Table 2. Patients studied had moderately elevated MPAP, TPG and PVR at baseline. There was no significant decrease in MPAP or TPG even at the highest dose of inhaled NO (100 ppm). No change in MAP or CO was observed. There was no significant correlation between the initial level of PVR and the change in PVR at 100 ppm NO either on day 1 or 2.

Figure 1 shows changes in arterial oxygenation (PaO_2) at constant FIO_2 during short-term NO inhalation on two consecutive days. NO inhalation produced a significant increase in PaO_2 (analysis of variance; $P<0.0025$). Similar response curves were obtained in the 15 patients tested on day 2. Fig. 2 shows the changes in PaO_2, MPAP and PVR in the responding group (patients with increased PaO_2 above 25% on the optimal dose). NO inhalation also produced a significant ($P<0.02$) decrease in venous admixture (Q_{VA}/Q_T; Fig 3).

Figure 4 presents the change in PaO_2 at the "optimal" dose (the dose producing the greatest increase in PaO_2) of NO for each patient on days 1 and 2. There was a large variation in the optimal dose of NO and in the effect on arterial oxygenation on two consecutive days in the same patient. There was no significant correlation ($R=0.10$) between the PaO_2/FIO_2 ratio at baseline and the maximal degree of improvement in PaO_2 during NO.

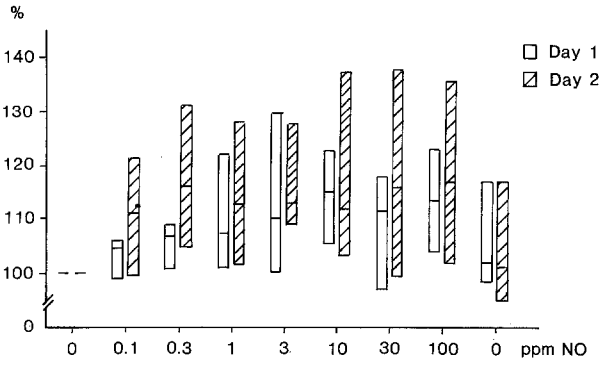

Fig. 1 Inhalation of NO produced a significant increase in arterial oxygen tension PaO_2 ($P<0.0025$). Values are percentages of baseline median and interquartile range for patients on day 1 (□; $n=18$) and day 2 (▨; $n=15$)

Tidal volume, peak airway pressure, $PaCO_2$ 5.0 (4.6–5.7) to 4.9 (4.6–5.9) and PVO_2 4.7 (4.5–5.3) to 5.0 (4.5–5.7) at baseline and at 100 ppm respectively, did not change significantly during NO administration.

Prolonged dose testing

The effect of prolonged (2 h) of inhalation of NO at 1 and 10 ppm, on arterial oxygenation is shown in Fig 5. The improvement in arterial oxygenation observed after 15 min of NO was sustained throughout the 120 min period, at both 1 and 10 ppm of NO, with a return towards control values after cessation of NO.

There was no significant change in methemoglobin concentration, which was 0.9% (0.5–1.0%) during control measurements and 1.0% (0.7–1.3%) after 2 h inhalation of 10 ppm NO.

Discussion

The major findings of this study are that (a) inhaled nitric oxide may improve oxygen exchange in patients with early ALI, the average optimum response being obtained at about 10 ppm; and (b) in the individual patient both the magnitude of the response and the optimum dose varied on two consecutive days. In addition, we observed that

Table 2 Central haemodynamic during NO inhalation (day 1)

	0 ppm	100 ppm	0 ppm
MAP (mmHg)	68 (61–80)	68 (58–80)	68 (58–81)
MPAP (mmHg)	27 (21–31)	26 (21–30)	27 (21–30)
PCWP (mmHg)	13 (11–14)	12 (10–16)	12 (10–16)
TPG (mmHg)	14 (9–21)	12 (8–16)	12 (7–16)
CO (l/min)	6.9 (5.7–9.4)	6.4 (5.1–8.2)	6.5 (5.0–9.1)
PVR (dyne s cm^{-5})	144 (102–198)	157 (82–218)	143 (94–209)

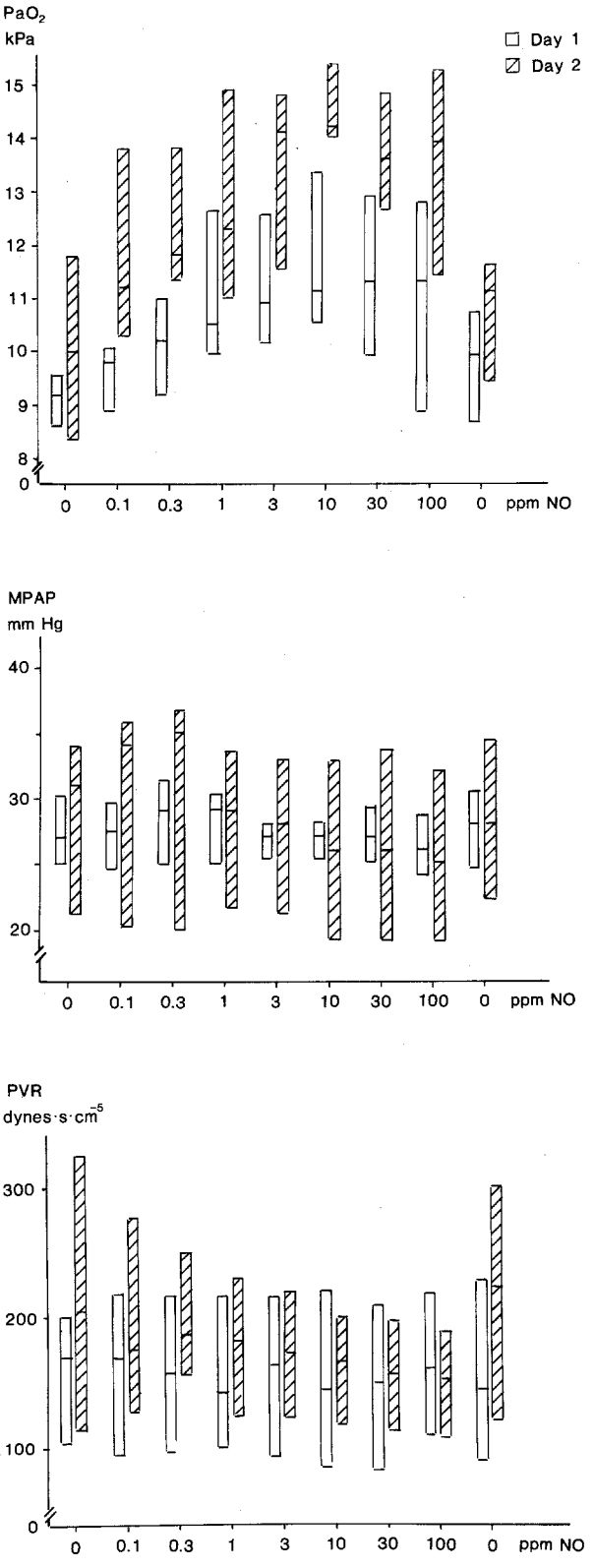

Fig. 2 The effect of inhalation of NO on PaO_2, MPAP and PVR in the responder group, i.e., patients with improved PaO_2 > 25% on the optimum dose of inhaled NO. Values are median and interquartile range for patients on day 1 (□; $n=9$) and day 2 (▨; $n=7$)

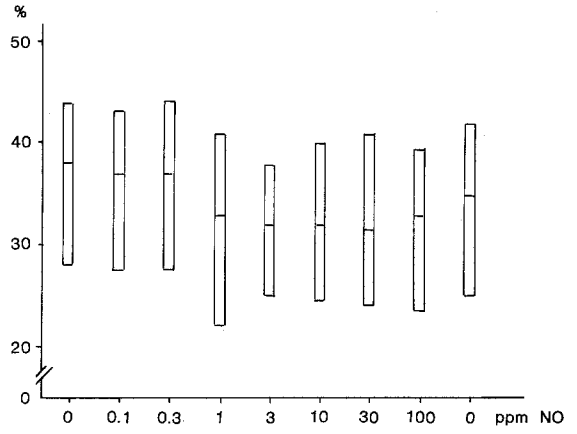

Fig. 3 Reduction ($P<0.02$) in calculated venous admixture (Q_{VA}/Q_T) on day 1. Values are median and interquartile range ($n=18$)

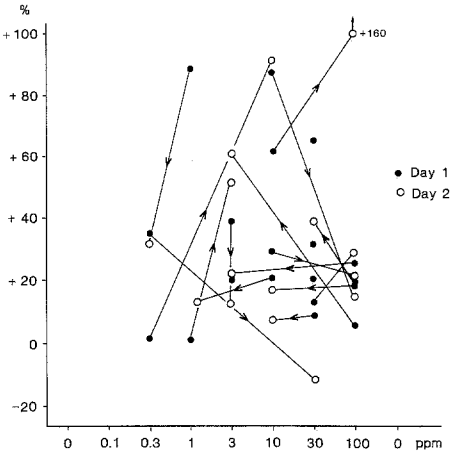

Fig. 4 Fig. 4 Changes in arterial oxygen tension (PaO_2) at the "optimum dose" compared to NO baseline level with inhaled NO for each patient on days 1 (●; $n=18$) and 2 (○; $n=15$), respectively. Note the variability in the optimum dose of NO and magnitude of the response at two consecutive days. The optimum dose was defined as the NO dose giving the highest PaO_2 value in percentage of baseline value of PaO_2 prior to NO

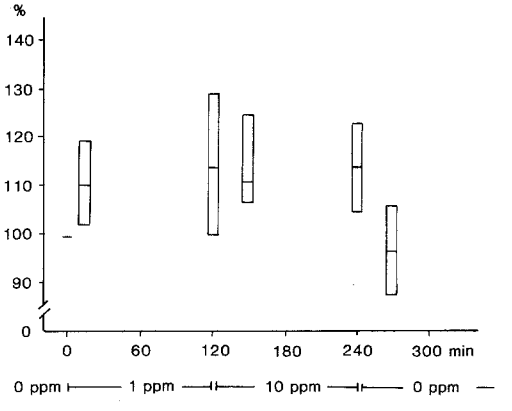

Fig. 5 The effect of prolonged (2 h) exposure to NO, 1 and 10 ppm, on arterial oxygen tension (PaO_2). Values are given as median and interquartile range ($n=14$)

the response to inhaled NO established within the first 15 min of exposure was sustained for at least 2 h. The improvement in oxygen exchange was not accompanied by a significant reduction in MPAP or PVR. This is in contrast to previous studies [9] in which improvement in oxygenation was generally accompanied by a decrease in MPAP and PVR. In other studies in ARDS patients it does appear that improvement in oxygenation can be obtained at low doses of NO (around 0.1 ppm) with only small changes in PVR [6]. Our patients had normal or only modestly elevated MPAP and PVR in combination with an increased venous admixture. This probably reflects an early stage of the disease. It was possible to improve the perfusion/ventilation mismatch without lowering MAP and PVR to any measurable extent.

Dose response studies of short-term inhalation of NO have previously been performed in patients with severe ALI, i.e. in ARDS [6]. Patients in that study had a lung injury severity score according to Murray et al [10] of 3–4 compared to 1.75–3.25 in the patients of the present study. In agreement with the present study, the maximum effect in severe ARDS was obtained at a dose around 10 ppm, although the improvement in arterial oxygenation response was more pronounced than in our study. Most patients in that study were, however, treated with veno-venous extracorporeal membrane oxygenation, which might affect the response to inhaled NO. The dose-response of inhaled NO has also been evaluated in a group of ARDS patients selected on the basis of a documented clear improvement in oxygenation as a result of inhaling NO [9]. In that study the maximum effect of inhaled NO on arterial oxygenation was observed even at doses of less than 1 ppm, with no further improvement at 5 ppm. It was also reported there that the dose of inhaled NO was measured in the trachea actually giving values of mixed inspiratory and expiratory NO concentrations. In reality, the true inspiratory NO levels given to these patients may have been higher than the values presented, since measurements were performed both during inspiration and expiration and much of the inspired NO is taken up by the lungs [17].

In the present study the individual response to inhaled NO was variable. If a responder is defined as a patient with improved PaO_2 above 25% from baseline level on an optimum dose of inhaled NO, 12 patients (67%) were responders on one of the two days tested, two patients on both days, and four were nonresponders on both days. In severe ARDS Bigatello et al. [8] reported individual responses to a dose of 20 ppm inhaled NO and showed that only 38% of the patients improved in terms of oxygenation more than 25%. A similarly variable effect of inhalation of NO was observed in another study of patients with severe ARDS, in which only a subgroup responded to NO with a clinically significant improvement in oxygenation [18].

It is interesting that the response to inhaled NO can differ in the same patient on two consecutive days. In our patients there did not appear to be a relationship between a change in vasopressor and other pharmacological therapy on different study days and altered response to NO in terms of oxygenation. Instead, it appears that an altered response to inhalation of NO reflects changes in the course of the disease. The variable response to inhaled NO suggests that a dose-response test should be performed in each individual patient on at least two consecutive days to determine whether a patient is a responder or nonresponder and to define the optimum dose of NO for that patient prior to the start of prolonged inhalation of NO in clinical trials. The optimum dose for improving oxygenation and reduction in pulmonary arterial pressure may also differ widely between patients because of different diagnoses, the degree of increase in pulmonary vascular resistance, concomitant therapy such as veno-venous extracorporeal carbon dioxide removal, and the presence of vasoactive drugs such as almitrine [18, 19].

It is beyond the scope of this paper to discuss the legal and safety issues of inhaled NO. The toxicity of nitrogen oxides has recently been reviewed [20]. Among known side effects of inhaled NO are methemoglobinemia, exposure to NO_2 and other higher oxides of nitrogen, reports of increased bleeding time, increased pulmonary vasoconstriction and hypoxaemia when NO is suddenly withdrawn, and reports of mutagenicity.

We conclude that remaining issues concerning the safety and efficacy of inhaled NO make it difficult to state what should be an optimum dose during therapy in ALI. The danger of significant NO_2 formation in inspired gas even with scavenging makes it difficult to justify prolonged therapy with inhaled NO at high doses, i.e., above 30 ppm. However, if the purpose of NO therapy is only a maximum improvement in O_2 exchange, then our data confirm (a) that much lower doses are often sufficient, and (b) that the optimum dose varies over time during the ALI process and between individuals. It is our opinion that a future randomised trial of inhaled NO in early ALI should first identify individual benefits in terms of an improvement in oxygen exchange and then allow treatment at the dose of NO found to be the best compromise between reduction of the lung vascular constriction and improved gas exchange.

In conclusion, this study shows that inhalation of NO improves oxygenation even in early ALI. In the individual patient, however, both the degree of response and the optimal NO dose may, however, vary. This indicates that careful evaluation of the acute effect of different doses of inhaled NO on gas exchange should be performed in the individual patient prior to the start of long-term NO inhalation therapy in clinical trials.

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References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet II:319–323
2. Moncada S, Palmer RMJ, Higgs EA (1991) Nitric oxide: physiology, pathophysiology and pharmacology. Pharmacol Rev 43:109–142
3. Moncada S, Higgs A (1993) The L-arginine – nitric oxide pathway. N Engl J Med 329:2002–2012
4. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM (1991) Inhaled nitric oxide: A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83: 2038–2047
5. Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM (1993) Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 328: 399–405
6. Gerlach H, Rossaint R, Pappert D, Falke KJ (1993) Time-course and dose-response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Eur J Clin Invest 23:499–502
7. Gerlach H, Pappert D, Lewandowski K, Rossaint R, Falke KJ (1993) Long-term inhalation with evaluated low doses of nitric oxide for selective improvement of oxygenation in patients with adult respiratory distress syndrome. Intensive Care Med 19:443–449
8. Bigatello LM, Hurford WE, Kacmarek RM, Roberts JD, Zapol WM (1994) Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome. Effects on pulmonary hemodynamics and oxygenation. Anesthesiology 80:761–770
9. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Arthaud M, Poète P, Bodin L, Korinek AM, Viars P (1994) Inhaled nitric oxide in acute respiratory failure: dose-response curves. Intensive Care Med 20:319–327
10. Murray JF, Matthay M, Luce J, Flick M (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Resp Dis 138:720–723
11. Knaus WA, Draper EA, Wagner DI, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
12. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ (1987) High dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 317: 1565–1570
13. Stenqvist O, Kjelltoft B, Lundin S (1993) Evaluation of a new system for ventilatory administration of nitric oxide. Acta Anaesth Scand 37:687–691
14. Nathorst Westfelt U, Lundin S, Stenqvist O (1995) Safety aspects on delivery and monitoring of nitric oxide during mechanical ventilation. Acta Anaesthesiol Scand 40:302–310
15. Nunn JF (1993) Nunn's applied respiratory physiology, 4th edn. Butterworth-Heinemann, London, pp 178–179
16. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA (1987) A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:653–658
17. Nathorst Westfelt U, Benthin G, Lundin S, Stenqvist O, Wennmalm Å (1995) Conversion of inhaled nitric oxide to nitrate in man. Br J Pharmacol 114: 1621–1624
18. Wysocki M, Delclaux C, Roupie E, Langeron O, Liu N, Herman B, Lemaire F, Brochard L (1994) Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome. Intensive Care Med 20:254–259
19. Payen DM, Gatecel C, Plaisance P (1993) Almitrine effect on nitric oxide inhalation in adult respiratory distress syndrome. Lancet 341:1664
20. Gaston B, Drazen JM, Loscalzo J, Stamler JS (1994) The biology of nitrogen oxides in the airways. Am J Respir Crit Care Med 149:538–551