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ORIGINAL

Inhalation of nitric oxide in acute lung injury: results of a European multicentre study

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Abstract *Objective*: To determine whether inhalation of nitric oxide (INO) can increase the frequency of reversal of acute lung injury (ALI) in nitric oxide (NO) responders.
Design: Prospective, open, randomised, multicentre, parallel group phase III trial.
Setting: General ICUs in 43 university and regional hospitals in Europe.
Patients: Two hundred and sixty-eight adult patients with early ALI.
Interventions: NO responders were patients whose PaO_2 increased by more than 20 % when receiving 0, 2, 10 and 40 ppm of INO for 10 min within 96 h of study entry. Responders were randomly allocated to conventional treatment with or without INO. INO, 1–40 ppm, was given at the lowest effective dose for up to 30 days or until an end point was reached. The primary end point was reversal of ALI. Clinical outcome parameters and safety were assessed in all patients.
Results: Two hundred and sixty-eight patients were recruited, of which 180 were randomised NO responders. Frequency of reversal of ALI was no different in INO patients (61 %) and controls (54 %; $p > 0.2$). Development of severe respiratory failure was lower in the INO (2.2 %) than controls (10.3 %; $p < 0.05$). The mortality at 30 days was 44 % for INO patients, 40 % for control patients ($p > 0.2$ vs INO) and 45 % in non-responders.
Conclusions: Improvement of oxygenation by INO did not increase the frequency of reversal of ALI. Use of inhaled NO in early ALI did not alter mortality although it did reduce the frequency of severe respiratory failure in patients developing severe hypoxaemia.

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

Introduction

Inhalation of nitric oxide (INO) causes selective pulmonary vasodilatation without affecting the systemic circulation [1]. It also improves oxygenation and decreases pulmonary hypertension in patients with the acute respiratory distress syndrome (ARDS)[2]. Numerous studies have confirmed these findings and INO is now often used in the treatment of patients with acute lung injury (ALI) and ARDS [3]. Despite its well documented physiological effects, it is important to evaluate whether INO is safe to use and whether it improves outcome in patients with ALI.

We have conducted a prospective, multicentre, randomised, controlled open parallel group study with the primary objective to evaluate whether prolonged INO could increase the frequency of reversal of ALI when therapy with NO was initiated early in the course of acute respiratory failure. Among secondary end points were frequency of severe respiratory failure and mortality. Clinical outcome parameters and safety were assessed in all 268 patients recruited.

Material and methods

This study was approved by the Human Ethics Committees of the 43 participating hospitals in 11 European countries and by appropriate regulatory authorities. Witnessed information to next-of-kin or informed consent was secured in accordance with the individual Institutional Review Board requirements. The study was conducted in accordance with the principles of good clinical practice and supervised by an independent Safety Committee (see Appendix).

Study objectives

The primary objective of the study was to determine whether prolonged INO in addition to conventional treatment could increase the frequency of reversal of ALI when therapy with INO was initiated early.

The secondary objectives were:

1. To determine whether prolonged inhalation of NO in addition to conventional therapy could reduce the frequency of severe respiratory failure (SRF) when treatment with NO was initiated early in ALI.
2. To evaluate whether prolonged INO could reduce the time (days) taken to achieve reversal of ALI compared to the control group.
3. To study the safety of long-term NO inhalation, in particular methaemoglobinaemia and the frequency of organ failure.
4. To monitor 30 day and 90 day mortality and hospitalisation status.

Study patients

Patients with ALI with unilateral or bilateral lung infiltrates, intubated and ventilated for 18–96 h with PaO_2/ FIO_2 less than 22 kPa (< 165 mmHg), PEEP of at least 5 cmH_20, mean airway pressure more than 10 cmH_20, pressure or volume controlled ventilation and I:E ratio between 1:2 and 2:1, were eligible. Blood gases were drawn with the patient in the supine, recumbent position.

Patients with the following problems were excluded from the study: mechanical ventilation for more than 10 days or ventilator treatment for more than 96 h at FIO_2 of at least 0.5; independent lung ventilation; ongoing administration of high dose intravenous vasodilators; SRF as defined below; treatment with extracorporeal lung assist; severe cardiac failure with end-expiratory pulmonary artery occlusion pressure (PAOP) above 18 mmHg or left ventricular ejection fraction below 50 % measured with echocardiography; evidence of a severe ongoing intracranial haemorrhage; ongoing treatment for malignancy, (i.e. cytostatic medication, irradiation or other treatment that had led to leukopenia); AIDS diagnosed prior to admission; previous history of severe chronic kidney (glomerular filtration rate < 10 ml/min/1.73m^2 and/or serum creatinine concentration of 310 μmol/l, i.e. 3.5 mg/ml), liver (serum bilirubin > 40 μmol/l, reduction in serum albumin to < 35 g/l and ascites) or pulmonary disease (PaO_2 < 8 kPa and/or $PaCO_2$ < 6.7 kPa or medical history suggesting severe chronic lung disease); age less than 18 years and pregnancy. Patients with an underlying disease that was clearly irreversible and anticipated to be rapidly fatal were also excluded.

Study design

Nitric oxide delivery system

A primary gas mixture of 50 or 1000 ppm NO in N_2 was used (AGA Gas, Lidingö, Sweden). NO was either added to inspiratory gas before the ventilator [4] or administered after the ventilator (Drägerwerk, Lübeck, Germany). NO and NO_2 levels were continuously monitored with electrochemical cells (City Technology, London, UK or Drägerwerk).

Dose response test

Previous studies have shown that the response to INO may vary between patients, depending on dose and time [5, 6, 7]. We therefore exposed patients to NO in 2, l0 and 40 parts per million (ppm) added to inspired gas for l0 min to search for a positive response to INO. The dose titration was started and ended with a 0 ppm dose. If arterial oxygen tension (PaO_2) increased by 25 % on any dose of NO for the first 140 patients, and by 20 % for the remaining patients (protocol amendment), the patient was defined as a "responder". Responders were randomised, providing that they still fulfilled the inclusion/exclusion criteria.

If PaO_2 did not increase to the threshold value, the dose response test was performed daily for up to 3 days if they still fulfilled criteria for inclusion in the study. A patient who still failed to respond to INO was defined as a "non-responder".

Randomisation

The patients were randomly assigned by telephone to receive either conventional ventilator treatment alone or conventional ventilator treatment with the addition of INO according to a block design by the co-ordinating centre (Danderyd Hospital, Sweden). The responders were stratified according to study centre and to high or low APACHE II score for the first 140 patients, then high or low PaO_2/FIO_2 ratio for the remaining patients (protocol amendment).

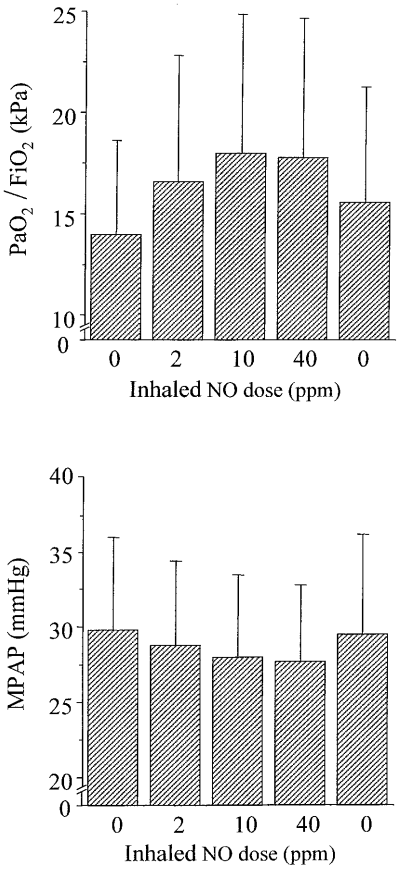

Fig. 1 Changes in mean ± standard deviation of pulmonary artery pressure (mmHg) and arterial oxygenation (kPa) obtained during the first dose-titration test with increasing doses of inhaled NO (0, 2, 10, 40 and 0 ppm) each lasting 10 min in all patients ($n = 268$). NO inhalation produced a clear reduction in mean pulmonary artery pressure ($p < 0.001$) with the maximal response obtained at 10–40 ppm. Arterial oxygenation improved ($p < 0.001$) with the maximal response occurring at 10 and 40 ppm of inhaled NO

Management of patients and treatment strategy of nitric oxide

Both groups were treated in accordance with the clinical practice at each centre. In addition, patients randomised to treatment with INO received 1–40 ppm INO at the lowest effective dose for up to 30 days or until an end point was reached. Changes in INO dose, inspired NO_2 level, ventilator settings, arterial blood gases and methaemoglobin levels were recorded according to clinical practice, but at least once daily.

Guidelines were given to the investigator to reduce the INO dose when FIO_2 was reduced to below 0.5 and to reduce the INO dose to the lowest possible level, with the dosage system used, at a FIO_2 of 0.35 and to wean the patient from NO before end point definition. All end points in the study were determined within 30 days of randomisation.

Patients in the control group could be given NO treatment after they had reached the end point of severe respiratory failure. Follow up of all 268 patients was carried out at days 30 and 90 after inclusion.

Definitions of end points

Reversal of ALI. A patient could be on the ventilator with PEEP ≤ 5 cmH_2O or on a mask CPAP system, with PEEP ≤ 5 cmH_2O but maintaining adequate gas exchange defined as: PaO_2/FIO_2 greater than 31 kPa for patients aged 60 years and PaO_2/FIO_2 greater than 29 kPa for patients over 60 confirmed with two arterial blood gases at least 20 h apart. For the first 140 patients a threshold value for PaO_2 of more than 26 kPa for patients over 70 years old was also used. Alternatively, the patient was extubated and received less than 5 l/min of oxygen via nasal catheter and PaO_2 maintained above 11 kPa for patients younger than 60 years, PaO_2 above 10 kPa for patients over 60 years, confirmed by two arterial blood gases at least 20 h apart. In the INO group the NO therapy was withdrawn prior to the end point definition.

Severe respiratory failure. Gas exchange criteria were: FIO_2 above 0.9 with PaO_2 lower than 8 kPa in three blood gas analyses each 4 h apart, with pressure controlled/limited ventilation, respiratory frequency between 5 and 30, a PEEP of at least 10 cmH_2O and mean airway pressure of at least 20 cmH_2O. SRF could also be defined as two arterial blood gases 2 h apart at a FIO_2 of at least 0.90 resulting in a PaO_2 below 6 kPa (modified slow and fast ECMO criteria [8]).

Monitoring of safety

Blood methaemoglobin levels were measured daily and if they exceeded 5%, the NO concentration was reduced. Organ failure was defined as (a) kidney failure ; serum creatinine above 300 μmol/l and/or institution of renal replacement therapy(RRT) defined as haemofiltration or dialysis, (b) hepatic failure; serum bilirubin higher than 70 μmol/l (c) haemodynamic instability; requirement of inotropic support. All patients recruited were monitored for adverse events until day 90.

Statistical analysis

To demonstrate an increase in the frequency of reversal of ALI from an estimated 50% in the control group to 65% in the INO group with a power of 0.90 and a significance level of 0.05, 600 patients would have been required to be included in the study. The projected time span was 3 years. Inclusion started in June 1994. After inclusion of the first 140 patients the study protocol was amended in February 1996 (see above) to facilitate recruitment. After including another 128 patients, the study was stopped by the sponsor in October 1996, the main reason given being slow recruitment.

Data are presented as means and standard deviations. The primary analysis was an intention-to-treat analysis on all randomised patients. Depending on type and distribution of variables, parametric and non-parametric statistical tests were applied. For variables of categorical type, including the primary efficacy variable, the Mantel-Haenszel chi-square test was used. The variables time to success and time to failure were analysed applying life tables and Cox regression models. A post hoc analysis of reversal ALI, expressed in terms of number of patients that were alive and off the ventilator over time, was also performed using an overall (treatment) analysis of covariance. A p value less than 0.05 was defined as statistical significance. Confidence limits are given for major end point analyses.

Table 1 Shows patient characteristics at randomisation. Mean ± SD are given

Characteristic	Nitric oxide group (n= 93)	Conventional therapy group (n = 87)	Non responder group (n = 88)
Age (years)	58 ± 15	56 ± 17	54 ± 16
Height (cm)	176 ± 9	172 ± 10	174 ± 8
Weight (kg)	82 ± 18	75 ± 16	80 ± 17
Sex (M/F %)	75/25	62/38	73/27
Smoker (last 2 Ys %)	38	41	42
Referral from other hospital %	18	25	16
PaO_2/FIO_2 (kPa)	13.7 ± 4.3	13.4 ± 4.4	15.0 ± 4.6
APACHE II	18.0 ± 6.1	18.7 ± 6.1	not determined
Murray score	2.61 ± 0.53[1]	2.79 ± 0.52	not determined
PEEP ($cm H_2O$)	8.4 ± 2.5	8.9 ± 2.7	8.1 ± 2.3
$PaCO_2$	5.6 ± 1.2	5.6 ± 1.2	6.1 ± 1.7
Serum creatinine	155 ± 97	163 ± 123	147 ± 102
Serum bilirubin	38 ± 36	39 ± 39	45 ± 72
Reasons for ALI (%)			
Direct lung injury:			
Aspiration	18	6	13
Pulm infection	33[2]	46	43
Near drowning	0	1	0
Toxic inhalation	0	0	1
Lung contusion	8	7	13
Other	2	0	2
Indirect lung injury			
Sepsis syndrome	12	16	14
Severe non thoracic trauma	4	0	2
Hypertransfusion	1	1	2
Cardiopulm bypass	1	1	0
Other	11	10	10
Combined lung injury	11	13	3

[1] $p < 0.05$ and [2] $p = 0.01$ versus conventional group

Results

Two hundred and sixty-eight patients fulfilling the inclusion and exclusion criteria entered the study and were subjected to at least a one-dose titration test. Seventy-seven received two-dose titration tests while nine and three patients received three- and four-dose titration tests, respectively. During the first dose titration test INO produced a marked increase ($p < 0.001$) in arterial oxygenation (PaO_2 ; see Fig. 1). There was a significant decrease ($p < 0.001$) in mean pulmonary artery pressure (MPAP) with increasing doses of INO. The maximal vasodilating effect occurred at 10 and 40 ppm (Fig. 1). Hundred eighty (67 %) of the 268 patients were classified as responders to inhaled nitric oxide and 88 patients were non-responders. Responders were randomised to NO inhalation in addition to conventional therapy (93 patients) or conventional therapy only (87 patients).

Patient demographics, laboratory results and reasons for ALI at randomisation are given in Table 1. The three groups were well balanced with respect to age, smoking history, PaO_2/FIO_2 ratio, APACHE II score, serum bilirubin, serum creatinine and number of patients with renal failure at baseline (see also Table 2), while Murray score [9] was slightly higher in the conventional therapy group. The reasons for ALI are presented in Table 1. The distribution of patients with direct versus indirect lung injury were similarly distributed in the three groups, while the number of patients with pulmonary infections was higher in the conventional, compared to the INO, group ($p = 0.01$) and the proportion of patients with aspiration were correspondingly lower.

Patients in the NO group were treated with an average dose of 9 ± 8 ppm for an average length of 9 ± 6 days. Sixty-five patients received a NO dose of between 1 and 10 ppm for less than 10 days. Twenty-one patients received a NO dose of 1–10 ppm for 11–20 days and four patients received 1–10 ppm NO for between 21 and 30 days. Forty-two patients received a NO dose of 10–20 ppm for less than 10 days, nine patients received

Table 2 Renal failure before and during the study

	Nitric oxide group (n = 93)	Conventional therapy group (n = 87)
Patients with renal failure[1] at randomisation	13 (14.0)	13 (14.9)
Patients without renal failure at randomisation given RRT through day 30	23 (24.7)[2]	10 (11.5)
Patient without renal failure at randomisation developing creatinine > 300 μmol/l but not given RRT through day 30	5 (5.4)	2 (2.3)

Data are given as number of patients (%). [1] Renal failure was defined as creatinine > 300 μmol/l and/or renal replacement therapy (RRT). [2] $p < 0.025$ vs conventional group

between 20 and 30 ppm for less than 10 days and 15 patients received between 30 and 40 ppm NO for less than 10 days.

Efficacy

The number of patients reaching reversal of ALI within 30 days after randomisation (primary end point) was 57 of 93 patients (61.3%) in the INO group compared to 47 of 87 patients (54.0%) in the control group (not significantly different; difference between groups 7.3%, 95% confidence interval being 22 to –7.5%). There was no significant difference in time to reversal of ALI between the two groups (Fig. 2). The number of patients that were alive and off the ventilator in relation to time after randomisation is shown in Fig. 3. This post hoc analysis revealed a higher percentage ($p < 0.01$) of patients in the conventional group that were alive and off the ventilator over time as compared to the INO group.

Fewer patients reached SRF in the NO group (2 patients; 2.2%) versus the conventionally treated group (9 patients; 10.3%; $p < 0.05$; differences between groups 8.2%, 95% confidence interval being 1.1% to 15.3%). Six of the nine patients crossed over to INO at the time when SRF was defined by the investigators. They received INO for between 5 and 22 days. Two patients in the conventional, but none in the INO group were given extracorporeal lung assist.

Outcome

The outcome for patients assessed at day 30 and 90 after randomisation is presented in Table 3. There was no significant difference ($p > 0.2$) in outcome between the INO and the conventional groups, also shown as a Kaplan-Meier life table plot of survival over time (Fig. 4).

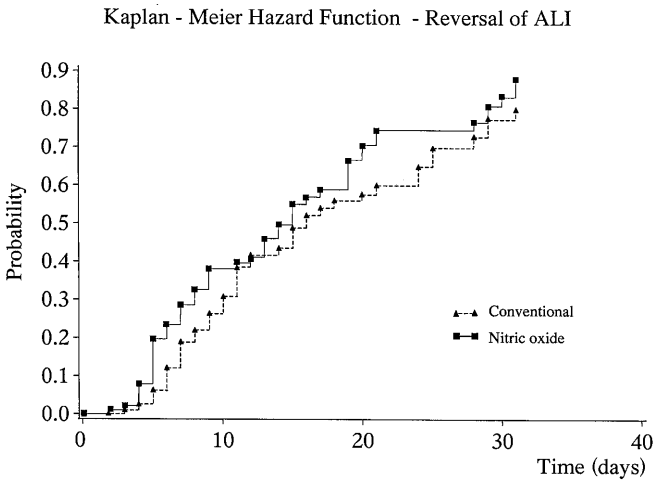

Fig. 2 Kaplan-Meier hazard curve plot of the probability/proportion of the patients reaching reversal of ALI over time. There was no significant difference between time to reversal of ALI in the two study groups. Proportion/probability was calculated taking into account censoring with the patient's dying censored at the time of death

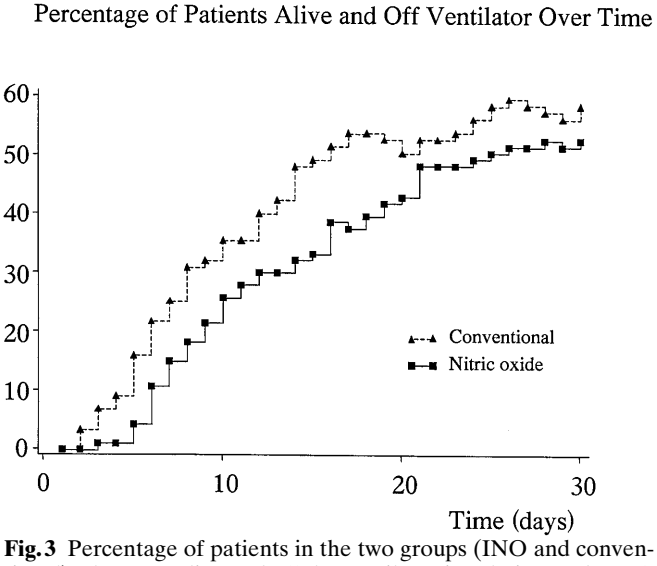

Fig. 3 Percentage of patients in the two groups (INO and conventional) who were alive and off the ventilator in relation to days after randomisation. $p < 0.01$ NO vs conventional group

Safety

Serious adverse events in this open study, that were reported more frequently in the INO group compared to the conventional and non-responder groups and occurred in a significant number, i.e. with a frequency of at least 3%, were circulatory failure (31, 20 and 28%, respectively), encephalopathy (3, 0 and 0%, respectively), sepsis (8, 3 and 7%, respectively) and abnormal renal function (13, 5 and 9%, respectively).

Table 3 Day 30 and 90 assessment

Day 30	Nitric oxide group (n = 93)	Conventional therapy group (n = 87)	Non responder group (n = 88)
	no of patients (%)		
Still in ICU	17 (18.3)	12 (13.8)	6 (6.8)
Still in hospital	12 (13.0)	14 (16.1)	8 (9.1)
Discharged	23 (24.7)	26 (29.9)	34 (38.6)
Dead	41 (44.1)	35 (40.2)	40 (45.5)
Day 90			
	no of patients (%)		
Unknown	0 (0%)	0 (0%)	1 (1.1)
Still in ICU	1 (1.1)	1 (1.1)	0 (0)
Still in hospital	6 (6.5)	4 (4.5)	3 (3.4)
Discharged	38 (40.9)	44 (50.6)	42 (47.7)
Dead	48 (51.6)	38 (43.7)	42 (47.7)

Ten patients in the INO group and three patients in the conventional group experienced adverse events that the investigator described as related to study medication. The most significant events were methaemoglobinaemia (≥ 5%) in one INO, and one conventionally, treated patient, GI haemorrhage in one INO-treated patient, coagulation disorder in one conventionally treated patient and intracranial haemorrhage in one conventionally treated patient. There was no accumulation of methaemoglobin during the study period in the INO group. Median methaemoglobin values varied between 0.5 and 1.2% in the INO group over the 30 study days compared to 0.2–1.0% in the conventional group, but the overall levels were lower than in the INO-treated patients. There was no significant difference in the number of patients with reported platelet, bleeding and clotting disorders between the INO, conventional and non-responder groups (8, 9 and 3%, respectively). Extracardiac vascular disorders including cerebral and gastrointestinal haemorrhage were reported in 3, 7 and 2% in the INO, conventional and non-responder groups, respectively.

Pneumothorax was reported in 8% of the patients in the INO group as compared to 9% in the conventional group and 1% in the non-responder group. Thirteen patients in each group had kidney failure defined as serum creatinine more than 300 μmol/l (3.4 mg/dl) and/or RRT prior to randomisation (see Table 2). Of these, nine patients in the INO and eight in the control group were on RRT prior to randomisation. An additional 23 patients in the INO group and 10 patients in the conventional group were given RRT until day 30 ($p < 0.025$). The creatinine values in these two groups were not significantly different when measured the day before institution of RRT (306 ± 111 and 289 ± 72 μmol/l, respectively). Another five patients in the INO group and two in the control group also developed an increase in serum creatinine levels above 300 μmol/l, but they were not given RRT until day 30. There was no significant difference in the number of patients that developed an elevated bilirubin by day 30 between the two groups. At day 1 following randomisation 67 patients in the INO group (72%) had haemodynamic failure, which was comparable to the 71 patients (82%) in the conventional group. Few patients subsequently developed haemodynamic failure before day 30 (four patients in the INO group and three in the conventional group).

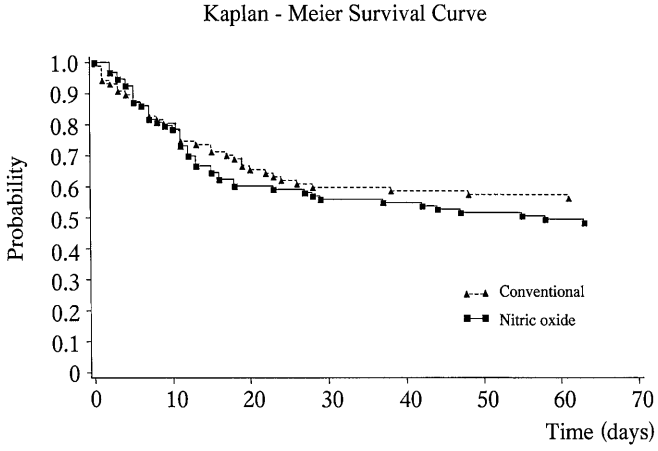

Fig. 4 Kaplan-Meier survival curves after randomisation in the conventional and INO groups. There was no significant difference between the two groups ($0.2 < p < 0.5$)

Discussion

This study evaluated the safety and efficacy of long-term inhalation of NO in patients with ALI. The study did not show that INO increased the frequency of, or shortened time to, the reversal of ALI. A post hoc analysis showed a higher percentage of patients alive and off the ventilator over time in the conventional, as compared to the INO, group partly due to a somewhat (n.s.) higher mortality in the INO group. Patients that received INO exhibited a decreased frequency of severe

respiratory failure. Patients receiving INO developed renal impairment more frequently than patients in the control group.

The study confirms [7, 10, 11, 12] that short-term exposure to INO produces an increase in arterial oxygenation and a decrease in mean pulmonary artery pressure in groups of ALI patients as a whole, while there is a large variation in the optimal dose of NO and the degree of response, in terms of improvement in arterial oxygenation, in individual patients[7]. The positive effect of inhaled NO on arterial oxygenation has probably been the most important reason for the widespread use [3] of INO in ARDS patients in Europe during the last years.

The rationale of this study was to determine whether improvement in arterial oxygenation induced by inhaled NO had a positive effect on outcome in terms of reversal of ALI. Only patients with a clinically meaningful improvement in oxygenation during the NO dose titration test ("responders") were therefore randomised in the present study. In this way we were able to select patients who were considered most likely to benefit from long-term INO therapy. A previous study [12] evaluated the effect of INO on arterial oxygenation over a longer time period (4 h) as compared to the shorter period used in this study (10 min). In that study, changes in oxygenation were also followed over time in a placebo group. Although arterial oxygenation did not improve in the placebo group as a whole, 24 % of the placebo patients were considered as responders as compared to 60 % of the patients in the INO group in that study [12]. These changes in oxygenation in the placebo group were interpreted as being due to rapid changes in respiratory status, suggesting an advantage to evaluating the effect of INO on oxygenation during a shorter time period such as in the present study.

Randomisation of patients to the conventionally treated group and the group receiving INO in addition to conventional therapy was achieved through central block randomisation by telephone. Since the blocks were large and unknown to the hospitals, allocation was well balanced. The patients in the two treatment groups were reasonably balanced in terms of severity of illness at baseline (see Table 1). It has previously been suggested that the PaO_2/FIO_2 ratio 24–48 h after onset of ARDS is an important prognostic factor [13]. This ratio was similar in the INO and conventional groups at randomisation. The APACHE II score should preferably be obtained on the patient's admission to the ICU [14, 15]. For this study we considered it more appropriate to determine the APACHE II score at randomisation when it was important that the two groups were balanced. The distribution of patients with direct versus indirect lung injury were similarly distributed in the INO group versus the control group, although there were differences concerning the proportion of aspiration and pneumonia between groups. Further analyses of prognosis and survival rates in these subgroups of patients did not suggest that these moderate differences between the two groups concerning reasons for ALI had an impact on the result of this study.

There are several potential weaknesses in the present study. Firstly, we initially aimed at recruiting 600 patients within 3 years, a goal which was not reached. Secondly, the study was amended after inclusion of 140 patients, as occurred in other similar studies [12]. Even though entry criteria differed somewhat, all 180 randomised patients (including patients with protocol violations; 26 and 22 in the INO and control group, respectively) were included in the intention-to-treat analysis. Excluding patients with major protocol violations did not change the conclusion of the study (data not shown). It could be argued that the study should have been blinded in terms of treatment gas; however the oxygenation response [12] to INO would have compromised subsequent treatment allocation in which only clear responders to INO were randomised.

In a randomised phase II trial Dellinger and co-workers [12] evaluated the effect of placebo and five different doses (8–57 patients in each group; a total of 177 patients) of INO (1.25–80 ppm) on reversal of ALI, determined as the number of days alive and off the ventilator, and on survival. These workers, as we have also observed, saw no improvement in survival in INO-treated patients. Dellinger and co-workers [12] found no significant difference in the reversal of ALI between the placebo group and the five NO groups, although a subsequent post hoc analysis (not adjusted for multiple comparisons [16]), suggested beneficial effects in the group given 5 ppm of inhaled NO.

Safety aspects were also focused upon in our study. Marked methaemoglobinaemia, bleeding complications or increased frequency of pneumothorax were not observed in the INO, compared to the conventionally, treated group. The development of organ failure was studied over 30 days following randomisation, and we found that more ($p < 0.025$) patients receiving INO, compared to the conventional group, developed increased serum creatinine values (> 300 μmol/l, 3.5 mg/dl) and/or were given RRT (see Table 2). The reason for this is unclear. The decision to initiate RRT was not protocolised, a possible bias in an open study; however, the degree of renal impairment in the two groups given RRT appears to have been similar as judged from serum creatinine levels the day before starting RRT (see Results). An association between INO and acute renal failure in ALI has not been previously suggested. Since we did not exclude patients requiring inotropic support or with non-pulmonary organ failure, our study population could be expected to be at higher risk of developing acute renal failure than those previously reported. But our study does not reveal how INO might influence renal function in these patients. Uptake [17] and metabo-

lism [18] of INO needs to be further studied in patients with ALI, sepsis and multi-organ failure. Additional studies could help us identify patient subgroups in which NO inhalation should be avoided, to minimise unwanted side effects.

This study failed to show that INO administered to adult patients with moderate and early ALI increased the frequency of reversal of ALI, or shortened the time to such reversal. One reason for this lack of long-term effect of inhaled NO might be that the initial improvement in arterial oxygenation may subside over time [19]. Although mortality at days 30 and 90 after randomisation was unchanged, a significantly lower portion of patients randomised to INO developed severe respiratory failure, suggesting that INO may prolong the period for the treatment of other underlying problems in the most severely hypoxic patients. When further studies are performed on the use of inhaled NO in ALI they will have to address whether the observed increase in the use of RRT in patients treated with INO was due to an adverse effect of INO on renal function, or indicates a bias in this open study.

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Appendix I

Members of the Safety Committee were Professor Göran Hedenstierna, Uppsala, Sweden (Chairman), Professor Francoise Lemaire, Creteil, France, Professor Hilmar Burchardi, Göttingen, Germany and Professor Antonio Artigas, Sabadell, Spain.

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