# Low-Dose Inhaled Nitric Oxide in Patients With Acute Lung Injury
## A Randomized Controlled Trial

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I NHALED NITRIC OXIDE HAS BEEN shown to be a selective pulmonary vasodilator with minimal systemic effects.[1,2] Nitric oxide has been shown to improve outcome, as measured by the need for extracorporeal membrane oxygenation, in persistent pulmonary hypertension of the newborn.[3,4] Inhaled nitric oxide has also been shown to improve gas exchange both in animal models of acute respiratory distress syndrome (ARDS)[5-8] and in humans.[9-16] Two single-center studies[17,18] demonstrated the ability of inhaled nitric oxide to improve oxygenation in ARDS patients with no difference in clinical outcome. Three multicenter, randomized, placebo-controlled trials[19-21] also failed to demonstrate an impact on mortality. In one of these studies,[19] fixed doses of nitric oxide at 0, 1.25,

**Context** Inhaled nitric oxide has been shown to improve oxygenation in acute lung injury.

**Objective** To evaluate the clinical efficacy of low-dose (5-ppm) inhaled nitric oxide in patients with acute lung injury.

**Design and Setting** Multicenter, randomized, placebo-controlled study, with blinding of patients, caregivers, data collectors, assessors of outcomes, and data analysts (triple blind), conducted in the intensive care units of 46 hospitals in the United States. Patients were enrolled between March 1996 and September 1999.

**Patients** Patients (n=385) with moderately severe acute lung injury, a modification of the American-European Consensus Conference definition of acute respiratory distress syndrome (ARDS) using a ratio of $PaO_2$ to $FiO_2$ of ≤250, were enrolled if the onset was within 72 hours of randomization, sepsis was not the cause of the lung injury, and the patient had no significant nonpulmonary organ system dysfunction at randomization.

**Interventions** Patients were randomly assigned to placebo (nitrogen gas) or inhaled nitric oxide at 5 ppm until 28 days, discontinuation of assisted breathing, or death.

**Main Outcome Measures** The primary end point was days alive and off assisted breathing. Secondary outcomes included mortality, days alive and meeting oxygenation criteria for extubation, and days patients were alive following a successful unassisted ventilation test.

**Results** An intent-to-treat analysis revealed that inhaled nitric oxide at 5 ppm did not increase the number of days patients were alive and off assisted breathing (mean [SD], 10.6 [9.8] days in the placebo group and 10.7 [9.7] days in the inhaled nitric oxide group; P=.97; difference, –0.1 day [95% confidence interval, –2.0 to 1.9 days]). This lack of effect on clinical outcomes was seen despite a statistically significant increase in $PaO_2$ that resolved by 48 hours. Mortality was similar between groups (20% placebo vs 23% nitric oxide; P=.54). Days patients were alive following a successful 2-hour unassisted ventilation trial were a mean (SD) of 11.9 (9.9) for placebo and 11.4 (9.8) for nitric oxide patients (P=.54). Days alive and meeting criteria for extubation were also similar: 17.0 placebo vs 16.7 nitric oxide (P=.89).

**Conclusion** Inhaled nitric oxide at a dose of 5 ppm in patients with acute lung injury not due to sepsis and without evidence of nonpulmonary organ system dysfunction results in short-term oxygenation improvements but has no substantial impact on the duration of ventilatory support or mortality.

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**Box 1. General Entry Criteria**

**Inclusion Criteria**

1. Nonpregnant adults (≥18 years)
2. Developed ALI within the preceding 72 hours as defined as:
    $PaO_2/FiO_2$ ≤250, regardless of the amount of PEEP
    Bilateral infiltrates on frontal chest radiograph
    Pulmonary artery occlusion pressure ≤18 mm Hg when measured or no
    clinical evidence of left atrial hypertension
3. ALI resulting from at least 1 of the following:
    Pneumonia
    Aspiration pneumonitis
    Toxic gas inhalation
    Pulmonary contusion
    Acute pancreatitis
    Massive blood transfusion (including transfusion reactions)
    Multiple trauma
    Elective or emergency major surgery
    Fat emboli
    Postpartum ALI
4. $FiO_2$ of 0.50-0.95 or a set PEEP ≥8 cm $H_2O$

**Exclusion Criteria**

1. History of immunocompromise, including:
    Received chemotherapy or radiation therapy within the last 30 days
    ≥20 mg of prednisone or equivalent for ≥30 days
    ≥50 mg of prednisone or equivalent continually for >10 days within the
    last 30 days
    Received organ transplant
    AIDS (human immunodeficiency virus–positive patients could be entered into
    the study provided they had bronchoalveolar lavage results negative for
    *Pneumocystis carinii*)
2. Persistent systemic hypotension, defined as systolic blood pressure <90
    mm Hg, or a nonpurposeful reduction of systolic pressure by ≥40 mm Hg; pa-
    tients who had severe sepsis or a systolic blood pressure >90 mm Hg but were
    receiving >5 µg/kg per minute of dopamine (or equivalent) and who met
    any of the following conditions within 4 hours before the initiation of treat-
    ment gas:
    Systemic vascular resistance <800 dynes·sec·m³ and an elevated cardiac
    index >4 L/m²/min
    White blood cell count >20 000/µL or <4000/µL
    Urine output <0.5 mL/kg/h for 1 hour
3. Evidence of nonpulmonary organ dysfunction, defined as 1 or more of the fol-
    lowing:
    Creatinine ≥1.5 mg/dL (132.60 µmol/L)
    Total bilirubin ≥4.0 mg/dL (68.40 µmol/L) and aspartate aminotransferase
    or alanine aminotransferase level >2 times the upper limit of normal
    Platelet count ≤50×10³/µL
    Prothrombin time ≥1.5 times the upper limit of normal

Abbreviations: ALI, acute lung injury; $FiO_2$, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

## METHODS

### Patients

Patients in intensive care units were enrolled from 46 academic, teaching, and community hospitals in the United States. The study was approved by the institutional review board at each participating hospital. Written informed consent was obtained from each patient or his or her legal representative before enrollment.

Eligible patients had moderately severe acute lung injury due to causes other than severe sepsis, using a modification of the American-European Consensus Conference definition of ARDS (a ratio of $PaO_2$ to fraction of inspired oxygen [$FiO_2$] of ≤250 instead of ≤200).[22] Because inhaled nitric oxide was expected to affect only the lung, study entry criteria were established to exclude patients in whom poor outcome and duration of mechanical ventilation were unlikely to be altered by improvements in oxygenation. Therefore, patients with evidence of nonpulmonary system failure at the time of randomization and sepsis-induced ARDS were excluded. Patients with sustained hypotension, vasopressor support with evidence of high-output failure, severe head injury, severe burns, or evidence of other organ system dysfunction (renal, hepatic, thrombocytopenia, and disseminated intravascular coagulopathy) were excluded. Entry criteria are presented in BOX 1.

### Treatment Procedures

Patients were randomly assigned to receive either inhaled placebo gas (nitrogen) or 5 ppm of nitric oxide (INO Therapeutics Inc, Port Allen, La) (FIGURE 1). Patients received gas labeled only with a study code and without designation of contents. The trial used concealed allocation, with randomization occurring centrally at the manufacturing plant. Patient numbers were preassigned sequentially by site (ie, site 01, patient 001, 002, etc). Drug cylinders were labeled to identify the patient number without revealing the contents. All drug cylinders were prepared and labeled before shipment to an investigative site by a research pharma-

5, 20, and 40 ppm were given to patients with ARDS from causes other than severe sepsis. In that study, non–statistically significant decreases were noted in both the intensity of mechanical ventilation (oxygenation index) and the duration of mechanical ventilation in the 5-ppm dose group. On the basis of that subgroup analysis, the current multicenter, randomized, blinded, placebo-controlled trial was initiated.

cist at the sponsor's manufacturing facility. No individual at any clinical site had a copy of the randomization code before analysis. All patients, clinicians (physicians, nurses, and respiratory care practitioners), and investigators were blinded to treatment assignment. The monitors on the inhaled nitric oxide delivery system were covered with a locked metal device that was opened only if the high-dose nitric oxide or nitrogen dioxide alarm sounded. Each site had a separate laboratory investigator team not involved in patient care that was responsible for the monitoring and recording of methemoglobin levels and nitric oxide and nitrogen dioxide alarms. Alarm episodes were infrequent (3 episodes reported) during the trial.

The inhaled nitric oxide was delivered through a commercially available delivery system (INOvent; Datex-Ohmeda, Madison, Wis) that blended the treatment gas (nitrogen or nitric oxide at 100-ppm balance nitrogen) 1:20 with the ventilator gases to deliver a target parts per million value into the inspiratory limb of the ventilator. An analysis in the inspiratory circuit immediately before patient treatment ensured that the delivered concentration of gas was accurate. Nitric dioxide was not removed. Continuous monitoring of nitric oxide, nitrogen dioxide, and $FiO_2$ concentrations occurred at the distal inspiratory limb. All patients received ventilatory support while using the inhaled nitric oxide delivery system.

All patients continued treatment with active or placebo gas until the end of the trial (28 days), death, or adequate oxygenation was achieved. Adequate oxygenation was defined as pulse oximetry oxygen saturation of 92% or more or $PaO_2$ of 63 mm Hg or more ($PaO_2$ took precedence when both values were known), without treatment gas at ventilator settings of an $FiO_2$ of 0.4 or less, and a positive end-expiratory pressure (PEEP) of 5 cm $H_2O$ or less. As long as these oxygenation criteria were met, decreases in treatment gas continued in 20% decrements (titrated down by 1 ppm if inhaled nitric oxide was being administered) every 30 minutes until either

the treatment gas concentration was decreased to 0% or the oxygenation criteria were not satisfied. If the latter occurred, the treatment gas was titrated up until oxygenation criteria were reachieved. Clinicians determined increments of upward titration based on degree of desaturation. If 0% treatment gas was tolerated for 24 hours, treatment gas was permanently discontinued. If procedures were required outside the intensive care unit and treatment gas could be reinstituted within 24 hours, patients were continued in the study. If not, they were classified as premature discontinuations.

The investigators participating in the trial agreed to guidelines for prioritizing the mechanical ventilation settings as detailed in BOX 2. No other management guidelines were provided to investigators.

Oxygenation and ventilation parameters were recorded at baseline, 4 hours, and 12 hours after initiation of study gas and then every 12 hours thereafter for the 28-day study period. Methemoglobin levels were measured at baseline, 30 minutes, 4 hours after initiation of the study gas, and then every other day while patients received the treatment gas. Chest radiographs were obtained at baseline and then at days 7, 14, 21, and 28 while the patient was hospitalized. Complete blood cell counts and serum biochemistry values were collected at baseline and then on days 1, 3, 5, 14, 21, and 28.

## Outcome Measures

The prospectively defined primary efficacy end point for this trial was the duration of mechanical ventilation measured by number of days patients were alive and not receiving assisted breathing, defined as the time of extubation (≥72 hours) or the reduction of both pressure support and continuous positive airway pressure to 5 cm $H_2O$ or less in patients with tracheostomies. To avoid the misclassification of patients with short duration of mechanical ventilation due to death, the end point was measured as the number of days alive from the time the patient was both alive and not receiving assisted breathing to
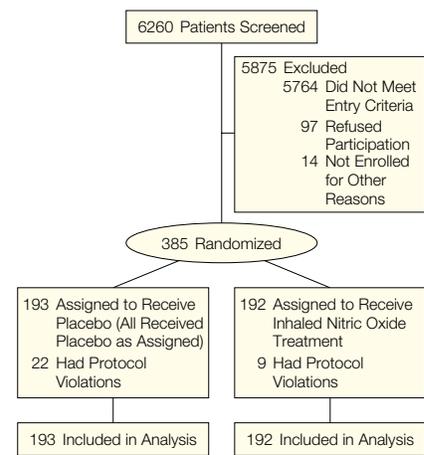
the end of the 28-day study. Secondary end points were mortality, days patients were alive and meeting oxygenation criteria for extubation, and days patients were alive following a successful unassisted ventilation test.

Esteban et al[23] suggested that testing patients who received mechanical ventilation for their ability to maintain spontaneous breathing off the ventilator (2-hour unassisted ventilation test) was associated with a high likelihood of successful extubation. Each patient in this trial who met oxygenation criteria for extubation was assessed daily with an unassisted ventilation test to determine if he or she could breathe without mechanical support. Oxygenation criteria, determined by a panel of critical care clinicians participating in this study, were prospectively established as representing criteria that would make a patient a candidate for extubation. These criteria included an $FiO_2$ of 0.40 or less, a $PaO_2$ of 60 mm Hg or more, and a PEEP of 5 cm $H_2O$ or less in a patient no longer receiving treatment gas. Because inhaled nitric oxide would not be expected to influence ventilatory capability or airway protection, these criteria would be more relative to inhaled nitric oxide effect.

## Definitions

For the purposes of this trial, the following criteria were used to establish a diag-

**Figure 1.** Flow Diagram

**Box 2. Guidelines for Prioritizing Ventilatory Support of Patients With Acute Lung Injury**[*]

1. Initially institute positive end-expiratory pressure (PEEP) to optimize compliance (usually 8-12 cm $H_2O$) and to prevent shear force injury
2. Decrease inspiratory plateau pressure to $\leq$35 cm $H_2O$ (this level achieves total lung capacity in healthy patients)
3. Decrease $FiO_2$ to $\leq$0.60 (to minimize theoretical concern for oxygen toxicity)
4. Decrease $FiO_2$ to $\leq$0.40 and decrease PEEP to 5 cm $H_2O$ (allowing extubation from an oxygenation criteria standpoint, one of the study's secondary end points)

[*]These recommendations are expert opinion as proposed by the clinical advisory committee and refined at the investigator meeting prior to study commencement.

nosis of the etiologies of acute lung injury: (1) pneumonia: pulmonary infiltrates thought to be due to primary lung infection, fever, and/or leukocytosis and a sputum Gram stain with more than 25 white blood cells and less than 10 epithelial cells per low-power field; (2) aspiration: witnessed or clinical history compatible with aspiration of gastric contents; (3) pulmonary contusion: pulmonary infiltrates that appear within 24 hours of blunt trauma to the chest; (4) acute pancreatitis: clinical syndrome consistent with pancreatitis associated with increased serum amylase and lipase concentrations; (5) massive blood transfusion of 10 U or more; (6) postpartum acute lung injury occurring within 72 hours of delivery without evidence of sepsis or cardiac dysfunction; and (7) acute lung injury associated with surgical procedure: patients fitting trial definition of acute lung injury who had undergone a surgical procedure with no other cause of acute lung injury identified.

Nonpulmonary organ system dysfunction was defined by 1 or more of the following: creatinine, 1.5 mg/dL or more ($\geq$132.60 µmol/L); total bilirubin, 4.0 mg/dL or more ($\geq$68.40 µmol/L) with an aspartate aminotransferase or alanine aminotransferase level more than 2 times the upper limit of normal; platelets, $50 \times 10^3/\mu L$ or less; or prothrombin time, at least 1.5 times the upper limit of normal.

### Statistical Methods

An intention-to-treat analysis was performed. Continuous variables were compared using either the $t$ test or, if the distribution of the variable was not normal, the Wilcoxon rank sum test. Categorical variables were compared using the Fisher exact test. Variables are reported as mean (SD). No interim analyses were planned or performed. The level of statistical significance was prospectively set at $P\leq$.05. The statistical software used was SAS version 6.12 (SAS Institute Inc, Cary, NC).

The sample size determination was based on the following assumptions derived from data generated in previous clinical trials: (1) the desired type I error of .05 was the threshold for statistical significance (2-tailed); (2) the difference in the number of days alive without assisted breathing was at least 3.5 days; (3) the standard deviation of the mean number of days alive without assisted breathing was 9.54 days and this was the same in the placebo and treatment arms; and (4) the desired power (1–$\beta$) for the trial was 80%. Using these assumptions, the calculated minimum sample size for each of 2 identical but separate trials was determined to be approximately 258 patients. Before completion of the 2 trials, the decision was made by the clinical advisory committee to recommend prospective merger of the databases and shorten both trials at a combined sample size of 385. If this trial had produced positive results and the US Food and Drug Administration had required a second trial for approval, a second trial would have been performed.

## RESULTS

Between March 1996 and September 1999, 385 patients (193 placebo, 192 inhaled nitric oxide) were enrolled at 46 sites. No patients were lost to follow-up or withdrawn from the study. All patients had complete data collected until death, discharge, or end of study. Total protocol violations were similar between treatment groups. Major protocol violations occurred in 31 patients and more frequently in placebo patients (22 placebo, 9 inhaled nitric oxide). Most frequent violations were a $PaO_2/FiO_2$ ratio greater than 250, intubation for more than 72 hours, and unilateral pulmonary infiltrates. Results are presented for the intent-to-treat group, but findings were similar for evaluable patients.

The primary causes of ARDS and baseline characteristics of patients in the treatment groups are shown in TABLE 1. The groups were well balanced with respect to the primary causes of ARDS and baseline respiratory dysfunction. A statistically significant higher mean pulmonary artery pressure was noted in the inhaled nitric oxide group at baseline ($P$=.02). Glucocorticoids were administered in 15% of placebo and 16% of nitric oxide patients at randomization. A pulmonary artery catheter was used in 54% of placebo patients and 57% of nitric oxide patients. No patients received extracorporeal membrane oxygenation or high-frequency oscillation. During the study, prone positioning was performed in 7.3% of placebo and 5.7% of nitric oxide patients.

### Efficacy Outcomes

The primary outcome variable, days patients were alive and not receiving assisted breathing to day 28, was not different in the placebo and intervention groups (mean [SD], 10.6 [9.8] vs 10.7 [9.7] days; $P$=.97; difference, –0.1 day [95% confidence interval, –2.0 to 1.9]). The results for all of the efficacy variables are presented in TABLE 2. There was no statistically significant difference in mortality between treatment groups: the 28-day mortality rate was 20% (39/193 patients) in the placebo group and 23% (44/192 patients) in the inhaled nitric oxide group ($P$=.54). There were no significant differences in

any other secondary outcome between groups. Changes in PaO₂ and PEEP over time for the 2 groups are shown in **FIGURE 2**. There was a statistically significant increase in the group means during the initial 24 hours that resolved by 48 hours.

### Safety

A total of 1296 adverse events were reported to have occurred in these critically ill patients (630 in the inhaled nitric oxide group and 666 in the placebo group). There was 41 infections reported in the placebo group and 66 in the inhaled nitric oxide group. None of the infections was judged by blinded investigators to have been related to treatment gas administration. The total number of cardiovascular, gastrointestinal, endocrine, hematologic, metabolic and nutritional, and nervous system adverse events were similar in the treatment groups. Respiratory system adverse events were more frequent in the placebo group (61% vs 51% in the nitric oxide group). This difference resulted from an increased number of placebo patients with pneumonia (20% vs 16%), pneumothorax (16% vs 13%), and apnea (7% vs 4%). There was no difference in the percentage of patients developing any elevations of creatinine ($\geq 3.0$ mg/dL [265.2 µmol/L]; 4% placebo vs 6% inhaled nitric oxide) or in patients with markedly elevated creatinine ($\geq 3.5$ mg/dL [309.4 µmol/L]; 3% placebo vs 5% inhaled nitric oxide).

As expected, none of the inhaled nitric oxide patients had clinically relevant levels of methemoglobin. One patient in the placebo group had a methemoglobin level higher than 5%. No nitrogen dioxide levels above 2 ppm were reported. The incidence of air leak syndrome (pneumothorax, pneumomediastinum, pneumopericardium) was 21% in both treatment groups. The hematologic and clinical chemistry values and changes from baseline values were similar between groups.

### COMMENT

This trial assessed the effects of 5 ppm of inhaled nitric oxide in patients with

ARDS and severe acute lung injury, defined as a PaO₂/FiO₂ ratio of less than 250. As seen in previous trials, the addition of inhaled nitric oxide induced a rapid improvement in the oxygenation of these patients, which was maintained for 24

hours. It was not associated with any clinically relevant change in patient outcomes measured by days alive without assisted breathing, the number of patients alive and not using assisted breathing at day 28, the days alive after a suc-

**Table 1.** Baseline Patient Characteristics

|  | Placebo (n = 193) | Inhaled Nitric Oxide (n = 192) |
| --- | --- | --- |
| Age, mean (SD), y | 50 (17) | 50 (17) |
| Men, No. (%) | 104 (54) | 100 (52) |
| Origin of ARDS, No. (%)* |  |  |
|   Pneumonia | 89 (46) | 88 (46) |
|   Surgical procedure | 58 (30) | 71 (37) |
|   Multiple trauma | 50 (26) | 52 (27) |
|   Aspiration pneumonitis | 48 (25) | 42 (22) |
|   Pulmonary contusion | 35 (18) | 35 (18) |
|   Massive transfusion | 19 (10) | 27 (14) |
|   Other | 15 (8) | 13 (7) |
| Pulmonary variables, mean (SD) |  |  |
|   PaO₂/FiO₂ | 138 (43) | 133 (42) |
|   Set PEEP, cm H₂O | 10 (2) | 10 (3) |
|   Inspiratory plateau pressure, cm H₂O | 32 (7) | 33 (8) |
|   Mean tidal volume, mL/kg | 10 (2.6) | 10 (2.6) |
|   MPAP, mm Hg† | 29 (8) | 31 (7) |

Abbreviations: ARDS, acute respiratory distress syndrome; FiO₂, fraction of inspired oxygen; MPAP, mean pulmonary artery pressure; PEEP, positive end-expiratory pressure.
*A patient may have more than 1 origin.
†All differences are nonsignificant except MPAP, for which $P = .02$.

**Table 2.** Efficacy Outcomes

| Outcome | Placebo (n = 193) | Inhaled Nitric Oxide (n = 192) | P Value |
| --- | --- | --- | --- |
| Days alive without assisted breathing, mean (SD) | 10.6 (9.8) | 10.7 (9.7) | .97 |
| Mortality, No. (%) | 39 (20) | 44 (23) | .54 |
| Alive and without assisted breathing by day 28, No. (%) | 127 (66) | 127 (66) | .40 |
| Days alive after successful 2-hour unassisted ventilation trial, mean (SD) | 11.9 (9.9) | 11.4 (9.8) | .54 |
| Days alive after reaching oxygenation criteria, mean (SD) | 17.0 (10.1) | 16.7 (10.3) | .89 |

**Figure 2.** Mean PaO₂ and Positive End-Expiratory Pressure (PEEP) During the First 7 Days of Therapy
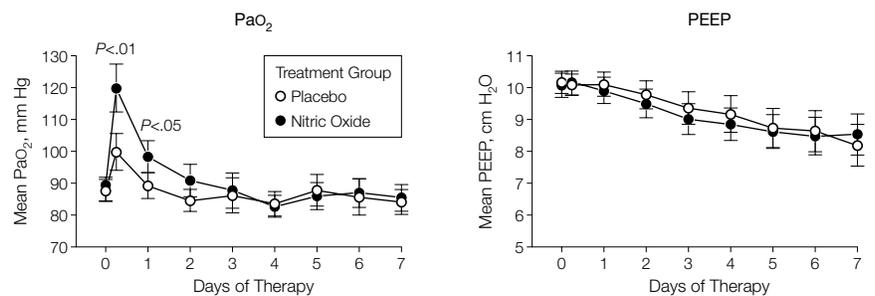


Data are mean (1.96 SEs). There was a statistically significant increase in the group means of PaO₂ during the initial 24 hours that resolved by 48 hours.

cessful 2-hour unassisted ventilation trial, days alive after reaching oxygenation criteria, or mortality. The difference in mean pulmonary artery pressure at baseline, although statistically significant, is not clinically relevant and unlikely to have influenced response. Although PEEP-induced lung recruitment will influence the effect of inhaled nitric oxide on oxygenation,[24] this protocol did not address PEEP interaction with inhaled nitric oxide to optimize oxygenation benefit.

The lack of correlation between oxygenation changes and long-term outcome in our study was also seen in the ARDS Network study of low and traditional tidal volumes. In that trial of 861 patients with ARDS, those receiving the 6 mL/kg of predicted body weight tidal volume during mechanical ventilation had lower mean $PaO_2$ than those randomized to receive the higher tidal volume but had a statistically lower mortality rate.[25]

The lack of clinical outcome benefit from the use of inhaled nitric oxide in this general population of patients with non–sepsis-induced ARDS is consistent with the results reported in smaller studies and large, randomized trials.[19-21] We previously[19] described 176 patients with non–sepsis-induced ARDS who received inhaled nitric oxide at doses ranging from 1.25 to 40 ppm. We found short-term improvements in oxygenation, but there was no benefit of pooled inhaled nitric oxide vs placebo on duration of mechanical ventilation, hospital stay, or mortality.

Lundin et al[20] assessed the effects of inhaled nitric oxide in an open-label study of 180 patients with acute lung injury who responded to a test dose of inhaled nitric oxide of 2, 10, or 40 ppm with a 20% increase in $PaO_2$. Inhaled nitric oxide was administered at the lowest effective dose observed for each patient during the testing phase of the study. Although the development of severe respiratory failure was lower in the inhaled nitric oxide group, there was no difference between groups with respect to the course of reversal of acute lung injury, the number of patients alive and not receiving mechanical ventilation, or mortality. Finally, the Groupe d'Etude sur le NO inhalé au cours de l'ARDS (GENOA) trial, published in abstract form, reported physiologic improvements with inhaled nitric oxide but no clinical outcome benefits as measured by mortality or the duration of mechanical ventilation.[21] A meta-analysis[26] also concluded that a composite of clinical trials showed no benefit of inhaled nitric oxide in ARDS. Inhaled nitric oxide as a potential adjunct therapy following lung transplantation has produced mixed results.[27,28]

There are many potential reasons for this lack of long-term benefit despite initial improvements in oxygenation. In the trials described herein and in smaller studies,[17,18] inhaled nitric oxide induced improvements in oxygenation that were maintained only during the first 24 to 48 hours. The reason for this is unclear, because withdrawal or reinstitution of inhaled nitric oxide in earlier studies of individual patients suggested a continued effect for more than 7 days.[16] These initial observations may have reflected rebound deterioration with the withdrawal of inhaled nitric oxide rather than continued effectiveness. It is also possible that the 5-ppm inhaled nitric oxide dose will, over time, diffuse into poorly ventilated areas and negate the selective pulmonary vasodilation achieved with initial inhaled nitric oxide administration. Other explanations include the possibility that the trial was not optimally designed to allow the acute physiologic effects of inhaled nitric oxide to translate into long-term benefit. Different trial conditions that may have yielded better results could include combination with other interventions, such as lung recruitment, a different selection of patients, or a different dosing regimen. Recently it has been demonstrated that when the initial dose of inhaled nitric oxide in ARDS is chosen by dose response curve, oxygenation benefit is subsequently lost in many patients, but maintained at a lower dose.[29] Daily dose response curves may optimize inhaled nitric oxide effect. Finally, it is possible that the oxygenation benefit of inhaled nitric oxide was offset by toxicity. Considerable controversy exists about the cytotoxic vs cytoprotective effects of nitric oxide.[30] The higher incidence of infection in the inhaled nitric oxide group is interesting in light of a recent report[31] of antibacterial properties of inhaled nitric oxide in an animal model of pneumonia.

It is clear that using the current dosing regimen, inhaled nitric oxide does not improve clinical outcomes in patients with moderately severe acute lung injury. There were no subgroups that benefited from inhaled nitric oxide, either primary vs secondary, degree of hypoxemia, or degree of pulmonary pressures. The results of this study do not support the routine use of inhaled nitric oxide in hospitalized patients with acute lung injury.

## CONCLUSIONS

In patients with documented moderately severe acute lung injury but without sepsis or other organ system failure, inhaled nitric oxide at 5 ppm did not improve any of the measured patient benefit outcomes. This lack of effect on patient benefit outcomes was seen despite a statistically significant improvement in the acute physiology that resolved between 24 and 48 hours. These data do not support the routine use of inhaled nitric oxide in the treatment of acute lung injury or ARDS. Inhaled nitric oxide may be considered as a salvage therapy in acute lung injury or ARDS patients who continue to have life-threatening hypoxemia despite optimization of conventional mechanical ventilator support.

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