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Physiologic Determinants of the Response to Inhaled Nitric Oxide in Patients with Acute Respiratory Distress Syndrome

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Background: **The response to inhaled nitric oxide (NO) in patients with acute respiratory distress syndrome (ARDS) varies. It is unclear which patients will respond favorably and whether the initial response persists over time. The authors defined a clinically useful response to inhaled NO as an increase of more than 20% of the ratio of the partial pressure of oxygen (Pa_{O_2}) to the inspiratory fraction of oxygen (FIO_2), a decrease of more than 20% of pulmonary vascular resistance, or both. The authors hypothesized that patients who initially respond favorably are likely to show persistent improvements of gas exchange and hemodynamics after 48 h of NO inhalation.**

Methods: **The medical records and collected research data of 88 patients with ARDS who received 92 trials of NO inhalation between March 1991 and February 1996 were reviewed.**

Results: **Fifty-three of the 92 trials (58%) produced a clinically significant response to NO. In the responding patients who continued to receive NO therapy (n = 43), the Pa_{O_2}/FIO_2 ratio remained higher (120 ± 46 *vs.* 89 ± 32 mmHg before NO; $P < 0.01$) and the mean pulmonary artery pressure remained lower (35 ± 8 *vs.* 40 ± 12 mmHg before NO; $P < 0.01$) at 48 h. Only 33% of the patients with septic shock responded to inhaled NO compared with 64% of those without septic shock ($P < 0.02$).**

Conclusions: **Most patients with ARDS had clinically useful responses to NO inhalation. Patients with an initial favorable response maintained the improvement at 48 h. Patients with septic shock were less likely to respond favorably. (Key words: Gases: nitric oxide. Lung: acute respiratory distress syndrome; pulmonary hypertension. Ventilation: mechanical.)**

Acute pulmonary hypertension and increased venous admixture are characteristic of the acute respiratory distress syndrome (ARDS).[1] Current therapies for ARDS include treatment of underlying infections and support with supplemental inspired oxygen, endotracheal intubation, and mechanical ventilation with positive end-expiratory pressure. Although these measures can effectively improve arterial oxygenation, they do not reduce pulmonary hypertension, which fosters pulmonary edema, increases right ventricular afterload, and has been associated with increased mortality rates.[2] Furthermore, high inspired oxygen concentrations and alveolar pressures associated with mechanical ventilation can cause additional damage to the lung parenchyma.[3]

Nitric oxide (NO) is a potent endogenous vasodilator with a very short half-life.[4] Nitric oxide produces vascular relaxation by activating guanylate cyclase and increasing intracellular concentrations of guanosine 3′,5′-cyclic monophosphate (cGMP). Inhalation of low concentrations of NO produces local vasodilation of the pulmonary circulation and reduces acute pulmonary hypertension of diverse causes.[5,6] By selectively vasodilating ventilated areas of the pulmonary vasculature, inhaled NO can also improve the matching of perfusion to ventilation and reduce venous admixture in acutely injured lungs.[7] Because of its high affinity for hemoglobin, inhaled NO is rapidly inactivated in blood and does not vasodilate the systemic circulation.

Multiple small case series and a randomized, prospective, multiple-center trial have documented that inhalation of low doses of NO can effectively reduce pulmonary hypertension and increase the arterial oxygen tension of a select population of patients with ARDS.[8-12] Few definitive data, however, are available on the determinants of response, on the safety of NO inhalation,

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and on its effect on outcome in patients with ARDS. Furthermore, because of the experimental nature of this therapy, investigators have used widely different delivery systems, inhaled concentrations, measurement techniques, and patient populations. At the Massachusetts General Hospital, we have used NO inhalation on an experimental basis to treat acute respiratory failure of various causes since March 1991. Unlike the patients in a recent multiple-center study,[12] the patients we studied frequently had septic shock and significant extrapulmonary organ system dysfunction. All had severe respiratory failure. We designed the current study to review our initial, 5-yr practice of NO inhalation for patients with ARDS and to address the following questions:

1. What is the incidence of a significant beneficial response to NO inhalation?
2. What factors are predictive of the patient's initial responsiveness to NO?
3. Is an initial beneficial response sustained for 48 h?

Methods

We reviewed the medical records and computer-archived research data of all adult patients with acute respiratory failure, acute pulmonary hypertension, or both who received inhaled NO as part of experimental protocols approved by the Subcommittee on Human Studies of the Massachusetts General Hospital. All patients or their families gave written informed consent before treatment with inhaled NO. Retrospective data collection for the current review was performed for all patients who received inhaled NO between March 1, 1991 and September 1, 1995; prospective data collection was subsequently continued until February 29, 1996.

Definitions

ARDS was defined according to the criteria of the American-European Consensus Conference: (1) acute respiratory insufficiency requiring mechanical ventilation; (2) a partial pressure of oxygen (Pa_{O_2} to inspiratory fraction of oxygen (FI_{O_2}) ratio less than 200 mmHg; (3) bilateral pulmonary consolidations on chest radiograph; (4) a pulmonary artery occlusion pressure $\geq$ 18 mmHg or absence of clinical signs of left atrial hypertension.[1] Patients treated with inhaled NO who did not meet these criteria were not included in the current review.

We defined "responders" as those patients in whom NO inhalation resulted in a clinically meaningful physiologic improvement; that is, an increase of the Pa_{O_2}/FI_{O_2} ratio of $\geq$ 20% from baseline, a decrease of pulmonary vascular resistance (PVR) $\geq$ 20% from baseline after 30 min of NO treatment, or both. This definition is similar to one used in a recent multiple-center trial of NO.[12] All other patients were considered to be "nonresponders." We defined as "NO trial only" those trials of NO inhalation that lasted $\geq$ 4 h and "NO treatment" as those that lasted more than 4 h.

Criteria for the definition of organ system failure were modified from Knaus *et al.*[13] Hemodynamic failure was defined as a mean systemic arterial pressure (MAP) $\geq$ 55 mmHg or arterial *p*H $\geq$ 7.24 with a partial pressure of carbon dioxide (Pa_{CO_2}) $\geq$ 48 mmHg or the need for inotropic or vasopressor agents to maintain an adequate systemic blood pressure in the absence of hypovolemia. This definition of vasopressor infusion excluded individual practice preferences such as the use of low doses of dopamine or dobutamine (< 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for potential renal effects or to increase cardiac output in normotensive patients. Coagulopathy was defined as a platelet count $\geq$ 90,000/mm^3 and a prothrombin time or a partial thromboplastin time $\geq$ 1.5 times control or a hematocrit concentration $\geq$ 20%. Liver failure was total serum bilirubin concentration $\geq$ 4 mg/dl. Renal failure was considered to be serum creatinine concentration $\geq$ 2.5 mg/dl. All determinations were made less than 12 h before NO administration.

Systemic inflammatory response syndrome (SIRS) was defined according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference[14] as the presence of two or more of the following conditions: temperature more than 38°C or less than 36°C; heart rate more than 90 beats/min; respiratory rate more than 20 breaths/min or Pa_{CO_2} less than 32 mmHg; white blood count more than 12,000 cells/mm^3, less than 4,000 cells/mm^3, or more than 10% immature (band) forms. The SIRS category includes those patients who, in addition to meeting SIRS criteria, had a documented source of infection, without evidence of organ failure other than the lung (*i.e.*, sepsis in the ACCP/SCCM Consensus Conference[14]). Septic shock was defined as the presence of SIRS (including sepsis) associated with hypotension (mean arterial pressure less than 90 mmHg or a reduction of more than 40 mmHg from baseline in the ab-

sence of other causes of hypotension) persisting despite adequate fluid resuscitation, along with the presence of organ system dysfunction. Patients receiving inotropic or vasopressor agents may no longer have been hypotensive by the time they manifested hypoperfusion abnormalities or organ dysfunction, yet they were still considered to have septic shock.

Clinical and Laboratory Data Collection

The following data were recorded for all patients who fulfilled the criteria for ARDS:

1. Clinical characteristics. Age, sex, diagnosis, medications, cause of ARDS, days of mechanical ventilation and hospitalization, presence of SIRS, septic shock, and organ system failure were recorded. The Lung Injury Score described by Murray *et al.*[15] was computed just before NO administration. The APACHE II score described by Knaus *et al.*[16] was computed using data collected within 12 h before NO administration.
2. Gas exchange and ventilatory variables. Arterial and mixed venous blood gas tensions and *p*H, $F_{I_{O_2}}$, the mode of mechanical ventilation, positive end-expiratory pressure, peak inspiratory pressure, tidal volume, and dynamic respiratory system compliance [(peak inspiratory pressure − positive end-expiratory pressure)/tidal volume] were recorded. These variables were recorded just before NO administration, 30 min after the beginning of NO inhalation, and approximately 48 h later (48 ± 12 h).
3. Hemodynamic variables. Heart rate, systolic and diastolic systemic arterial pressure, central venous pressure, systolic and diastolic pulmonary artery pressure (PAP), pulmonary artery occlusion pressure, and cardiac output were recorded immediately before NO, at 30 min, and 48 h after the beginning of NO inhalation. Mean systemic arterial pressure and mean pulmonary arterial pressure were calculated as (systolic − diastolic pressure)/3 + diastolic pressure. Hemodynamic measurements were always obtained at end exhalation with the supine zero reference level taken at the mid-axillary line. Thermodilution cardiac output was measured three times. Systemic vascular resistance, PVR, and venous admixture were calculated using standard formulas. Requirements for vasopressor and/or inotropic therapy immediately before NO inhalation and 48 h after its initiation were also recorded.
4. Laboratory data. All hematologic and chemical values necessary to calculate the APACHE II score, as well as to assess coexisting organ system failure, were measured within 12 h before the administration of NO. Methemoglobin concentration was measured immediately before and 30 min after initiation of inhaled NO and daily or every other day thereafter. Initial and subsequent daily doses of inhaled NO were recorded. Inspired nitrogen dioxide (NO_2) concentration was measured when patients were maintained on an inspired NO concentration of ≥ 20 ppm and an $F_{I_{O_2}} \geq 75\%$.
5. Clinical outcome. The total duration of mechanical ventilation and the duration of intensive care unit and hospital stays were recorded. Survival was measured from the date of first NO administration to the date of death or hospital discharge.

Method of Nitric Oxide Administration

Nitric oxide was administered to all patients using the methods described previously.[9] Nitric oxide source gas (780–880 ppm; Airco, Riverton, NJ) was stored in nitrogen (N_2). Nitric oxide in nitrogen was then mixed with nitrogen or air (Bird Blender, Palm Springs, CA) and delivered to the air intake of a Puritan-Bennett 7200 ventilator (Carlsbad, CA). In the ventilator, the NO/N_2 mixture was blended with oxygen and administered to the patient during inspiration. Inspired NO and NO_2 concentrations were measured with a chemoluminescence analyzer (model 14A, Thermo Environmental Instruments, Franklin, MA; or model $CLD700AL_{med}$, Eco Physics, Postfach, Switzerland) or with an NO electrochemical analyzer (Bedfont Scientific, Kent, UK). The inspired concentration of NO_2 was intermittently monitored with an electrochemical NO_2 analyzer (Bedfont Scientific).

Statistical Analysis

Normally distributed data are expressed as means ± SD. Nonparametrically distributed data are expressed as medians and ranges. Group means were compared by paired or unpaired *t* test or Wilcoxon by signed-rank test, as appropriate. Rates were compared by the chi-squared test. We used a multivariate logistic regression model (SPSS 6.0 statistical package; SPSS Software, Chicago, IL) to analyze the effect of multiple variables on the responsiveness to NO inhalation. Linear regressions were used to examine the association between two variables. Estimates of survival were based on the

Table 1. Characteristics of NO Inhalation in the 88 ARDS Study Patients

	Median	Range
Days on NO treatment	8	<1–71
NO dose at start (ppm)	20	5–80
NO dose at 48 hr (ppm)	10	4–30
NO dose on discontinuation (ppm)	10	0.1–24
Methemoglobin (%)	0.8	0–3.9
NO_2 inhaled (ppm)	0.4	0–4.3

Kaplan- Meier method; comparison of survival between groups was based on the log-rank test (NCSS 6.0 statistical package; NCSS, Kaysville, Utah). All tests of significance were two tailed, and probability values less than 0.05 were considered significant.

Results

Patient Characteristics

One hundred twenty-one adult intensive care unit patients received NO inhalation for acute respiratory failure, acute pulmonary hypertension, or both at our hospital during the 5-yr period between March 1991 and March 1996. Thirty-three of these patients received NO for indications other than ARDS (cardiac surgery, lung transplantation, or lung-volume reduction surgery). Eighty-eight patients fulfilled the criteria for ARDS and were included in the analysis. Inhaled NO was administered during 92 trials in these patients: four patients received two trials 48 h to 14 months apart. The median inspired NO concentration at the start of treatment was 20 ppm (range, 5–80 ppm); one patient received 80 ppm NO, two patients received 40 ppm, and all others received a maximum of 20 ppm. The inspired dose was decreased to 10 ppm (range, 4–30 ppm) by 48 h (table 1). Thirteen of these patients were included in a previously published study of NO inhalation.[9]

During the 5-yr period of the current review, the customary NO dose for prolonged treatment was reduced from 20 ppm to ≤ 5 ppm. Over the range of inhaled NO concentrations, we could not document a significant dose-response effect for any variable. Accordingly, data from all levels were combined for further analysis.

The mean age of the patients with ARDS was 52 ± 16 yr. Fifty-three were men, and 35 were women. The patients had received mechanical ventilation for 8 ± 6 days before enrollment. Their APACHE II score was 27 ± 6 and their Lung Injury Score score was 3.3 ± 0.6. Table 2 shows the underlying causes of ARDS. The incidence of sepsis and organ system failure at the time of NO treatment is shown in table 3. Seventy-three patients (83%) met the definition of SIRS, and 21 patients (24%) had septic shock. Sixty patients (68%) had at least a second organ system failure in addition to acute respiratory failure. The rate of survival to hospital discharge was 28%.

Table 2. Etiology of ARDS in the 88 Study Patients

	No. (%)
Pneumonia	
Medical	23 (26)
Post-surgical	16 (18)
Aspiration of gastric contents	
Medical	10 (11)
Post-surgical	7 (8)
Burns	6 (7)
Multiple trauma	6 (7)
Pancreatitis	3 (3)
Peritonitis	2 (2)
Fat embolism	1 (1)
Toxic shock syndrome	1 (1)
Near drowning	1 (1)
Other (etiology unknown)	
Medical	4 (5)
Post-surgical	8 (9)

Initial Response to Inhaled Nitric Oxide

Table 4 summarizes the physiologic changes occurring after the first 30 min of NO inhalation in the 92 trials. The Pa_{O_2}/FI_{O_2} ratio increased from 92 ± 38 to 117 ± 58 mmHg. Mean PAP (37 ± 10 to 34 ± 8 mmHg),

Table 3. Physiologic Abnormalities Associated with ARDS in the 88 Study Patients at the Time of Initiation of NO Treatment

	No. (%)
Systemic inflammatory response syndrome	73 (83)
Septic shock	21 (24)
Organ system failure in addition to acute respiratory failure	60 (68)
Hemodynamic	46 (52)
Coagulopathy	20 (23)
Hepatic	18 (20)
Renal	17 (19)
Vasopressor requirement	46 (52)

Table 4. Initial Physiologic Response to Inhaled NO in the 88 ARDS Patients (92 Trials)

	Pre-NO	30 min NO Inhalation
Pa_{O_2}/FI_{O_2} ratio (mmHg)	92 ± 38	117 ± 58*
Pulmonary vascular resistance (dyne·s·cm^{-5})	312 ± 217	255 ± 171*
Mean PA pressure (mmHg)	37 ± 10	34 ± 8*
Mean systemic arterial pressure (mmHg)	75 ± 13	76 ± 14
Heart rate (beats/min)	111 ± 21	108 ± 20*
Cardiac output (L/min)	7 ± 2.8	7 ± 3.1
Central venous pressure (mmHg)	14 ± 5	13 ± 5
PA occlusion pressure (mmHg)	15 ± 5	15 ± 5
Venous admixture (%)	39 ± 13	34 ± 14*

Data are mean ± SD. A pulmonary artery (PA) catheter was present in 74 of the 92 trials.

* $P < 0.05$ *versus* pre-NO values.

PVR (312 ± 217 to 255 ± 171 dyne·s^{-1}·cm^{-5}) and venous admixture (38 ±13% to 34 ±14%) decreased ($P < 0.05$ for all comparisons). Ventilatory parameters and systemic hemodynamics did not change. Of the 92 trials conducted in 88 patients, 53 trials (58%) in 51 patients produced a clinically significant response to NO, and 39 trials (42%) in 37 patients did not.

Table 5 compares the baseline physiologic variables in the 92 trials in responding and nonresponding patients. Septic shock was present in 38% of nonresponders and in 14% of responders ($P < 0.01$). By univariate analysis, patients without septic shock had a significantly higher response rate (65%) to NO inhalation than did those with septic shock (33%; $P < 0.02$). Patients with a serum creatinine concentration greater than 2.5 mg/dl were less likely to respond to NO ($P < 0.02$). In addition, patients ventilated for less than 1 week before NO tended to have an increased response rate to inhaled NO ($P = 0.06$). Age, APACHE II score, lung injury score, and systemic hemodynamic variables at baseline did not differ between responders and nonresponders.

The effects of several baseline variables of interest (age, PAP, serum creatinine concentration, septic shock, days of mechanical ventilation, arterial *p*H, and vasopressor requirements) on the response to inhaled NO were selected *a priori* to any analysis and then were examined using a multivariate logistic regression model. Only septic shock remained a significant discriminant for responsiveness to NO inhalation; after controlling for all the other variables listed, the absence of septic shock remained a positive predictor of responsiveness (odds ratio: 3.4; $P < 0.05$).

We correlated baseline pulmonary hemodynamic and gas exchange variables with the magnitude of the response to NO inhalation in those patients with pulmonary artery catheters in place and complete hemodynamic data available (n = 63). The percentage changes of PVR and mean PAP after 30 min of NO inhalation were linearly correlated with their respective baseline values ($r^2 = 0.43$, $P < 0.05$ for PVR and $r^2 = 0.38$, $P < 0.05$ for mean PAP; fig. 1). In addition, patients with an increased PVR tended to have a greater improvement of Pa_{O_2}/FI_{O_2} after 30 min of NO inhalation ($r^2 = 0.34$, $P < 0.05$; fig. 2).

Prolonged Nitric Oxide Therapy

Of the 88 study patients, 21 received NO inhalation for ≥ 4 h. Reasons for early discontinuation were (1) accordance with early experimental protocols (n = 7), (2) insignificant initial clinical response to NO (n = 12), and (3) withdrawal of therapy in terminally ill patients (n = 2).

Table 5. Baseline Characteristics of ARDS Patients Who Had a Clinically Significant Response to NO Inhalation *versus* Those Who Did Not

	Responders	Nonresponders
No. of patients	51	37
Age	51 ± 16	53 ± 16
APACHE II score	27 ± 6	27 ± 5
Lung Injury Score	3.2 ± 0.5	3.3 ± 0.5
Days ventilated prior to NO	7 ± 7	10 ± 11
Pa_{O_2}/FI_{O_2} ratio (mmHg)	91 ± 34	92 ± 43
Pulmonary vascular resistance (dyne·s·cm^{-5})	333 ± 232	285 ± 191
Mean pulmonary artery pressure (mmHg)	38 ± 12	34 ± 7
Positive end-expiratory pressure (mmHg)	13 ± 4	12 ± 3
Cardiac output (L/min)	6.7 ± 2.4	7.5 ± 3.4
Serum creatinine (mg/dl)	1.4 ± 0.7	2.0 ± 1.4*
Serum bilirubin (mg/dl)	3 ± 4	3 ± 7
Platelet count (10^9/mm^3)	170 ± 118	192 ± 135
White cell count (10^3/mm^3)	19 ± 9	18 ± 9
Systemic inflammatory response syndrome	38 (75%)	34 (92%)
Vasopressor requirement	24 (47%)	22 (59%)
Septic shock	7 (14%)	14 (38%)*

Data are mean ± SD.

* $P < 0.05$.

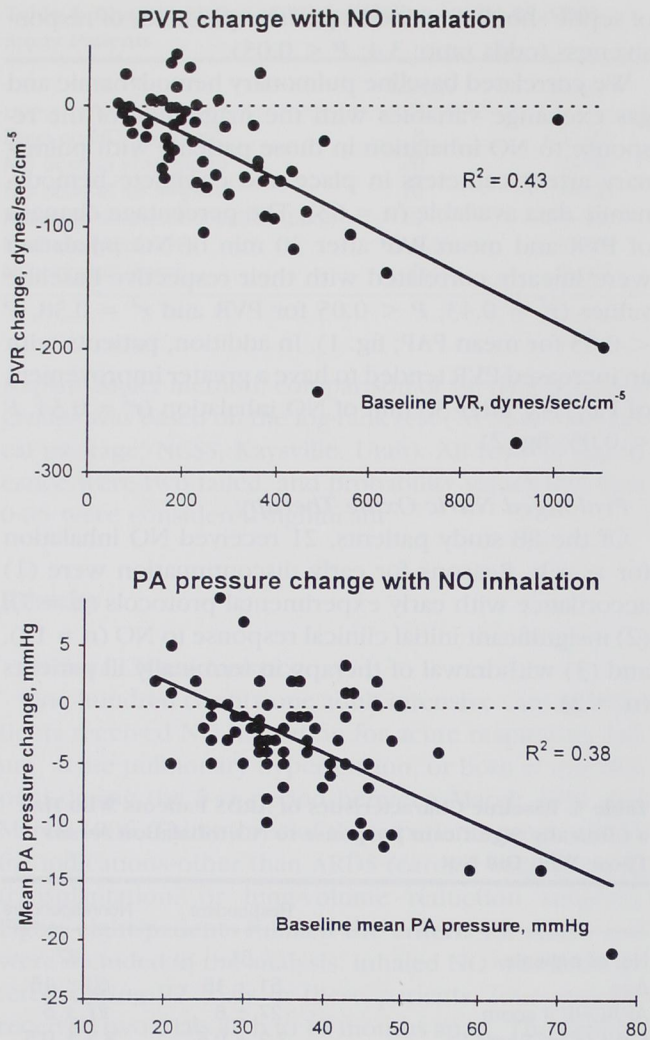

Fig. 1. ***Top panel,*** **Linear correlation between pulmonary vascular resistance (PVR) before NO inhalation and the change of PVR associated with NO inhalation in 63 trials of NO in ARDS patients; $P < 0.05$.** ***Bottom panel,*** **Linear correlation between mean pulmonary arter (PA) pressure before NO inhalation and the change of mean PA pressure associated with NO inhalation in 71 trials of NO in ARDS patients; $P < 0.05$.**

Sixty-seven patients received long-term NO inhalation (16 h to 71 days; median, 8 days). After 48 h, the Pa_{O_2}/FI_{O_2} ratio remained significantly higher compared with the baseline value (108 ± 43 mmHg *vs.* 87± 32 mmHg; $P < 0.05$). Mean PAP was decreased slightly, although this difference was not significant (35 ± 8 mmHg at 48 h compared with 38 ± 10 mmHg, n = 58; $P = 0.06$).

The response to NO inhalation at 48 h was compared for patients who initially had a significant response and were continued on NO (n = 45 trials) and patients who either were nonresponders or only received a trial of NO (n = 47 trials). As summarized in table 6, the Pa_{O_2}/FI_{O_2} ratio remained higher at 48 h than pre-NO values in the responders who were continued on NO (120 ± 46 mmHg *vs.* 89 ± 32 mmHg; $P < 0.01$) but not in the nonresponders/nontreatment group (110 ± 51 mmHg *vs.* 103 ± 45 mmHg). The mean PAP remained lower at 48 h in the responders/treated group than in the pre-NO values (35 ± 8 *vs.* 40 ± 12 mmHg; $P < 0.01$) but not in the nonresponders/nontreatment group (33 ± 8 *vs.* 34 ± 7 mmHg). No other parameters were significantly different from baseline in either group. The median number of days spent in the hospital, days in the intensive care unit, and the number of days receiving mechanical ventilation were comparable between the two groups. The median survival was 24 days in the responders/treated group (30-day survival rate, 43%) compared with 18 days in the nonresponse/nontreatment group (30-day survival rate, 36%). This difference was not significant.

No major adverse events or deaths could be attributed to NO inhalation. The institution of NO inhalation was never associated with significant deterioration of hemodynamics or gas exchange. The median inhaled NO_2 concentration was 0.4 ppm (range, 0–4.3 ppm). Four patients had a NO_2 concentration greater than 2 ppm: all were receiving

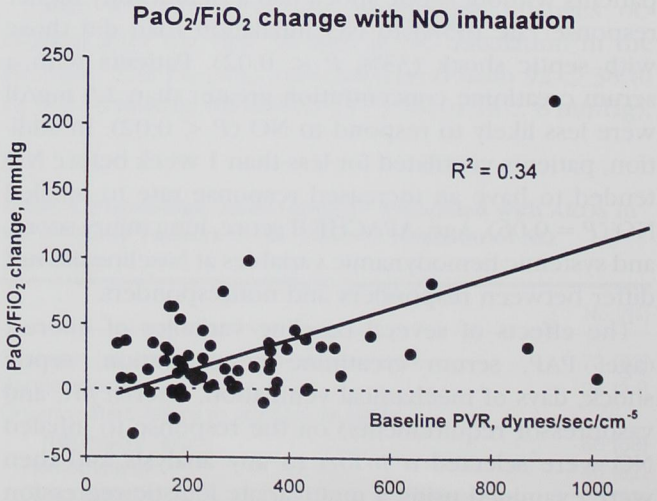

Fig. 2. Linear correlation between pulmonary vascular resistance (PVR) before NO inhalation and the change of Pa_{O_2}/FiO_2 ratio associated with NO inhalation in 63 trials of NO in ARDS patients; $P < 0.05$.

Table 6. Outcome of 88 ARDS Patients Who Received Inhaled NO

	Responders Treated (n = 43)	Nonresponders Trial Only (n = 45)
Pa_{O_2}/FI_{O_2} ratio pre-NO (mmHg)	89 ± 32	103 ± 45
Pa_{O_2}/FI_{O_2} ratio at 48 h (mmHg)	120 ± 46*	110 ± 51
Mean pulmonary artery pressure pre-NO (mmHg)	40 ± 12	33 ± 8
Mean pulmonary artery pressure at 48 h (mmHg)	35 ± 8*	34 ± 7
Pulmonary vascular resistance pre-NO (dyne·s·cm^{-5})	341 ± 214	267 ± 207
Pulmonary vascular resistance at 48 h (dyne·s·cm^{-5})	301 ± 154	282 ± 279
Dynamic respiratory compliance pre-NO (ml/cm H_2O)	26 ± 11	22 ± 9
Dynamic respiratory compliance at 48 h (ml/cm H_2O)	25 ± 10	22 ± 7
Days hospitalized after NO	31 (9–105)	28 (2–141)
Days in ICU after NO	27 (9–80)	25 (2–90)
Days of mechanical ventilation after NO	25 (4–81)	23 (3–103)
30-day survival after NO (%)	43	36

Values are mean ± SD or median (range) for nonparametric data. Treatment was defined as >4 h of NO inhalation. Responders had a ≥20% increase in Pa_{O_2}/FI_{O_2} ratio and/or a ≥20% decrease in pulmonary vascular resistance with inhaled NO.

* $P < 0.05$ *versus* pre-NO values.

20 ppm NO while also receiving 95% FI_{O_2}. In three of them, NO was discontinued within 1 h; the fourth patient was receiving 10 ppm NO and an FI_{O_2} of 70% by 24 h, and the NO_2 level decreased to less than 1 ppm. The median methemoglobin concentration during NO treatment was 0.8% (range, 0–3.9%). The patient with the highest methemoglobin concentration also had severe hyperlipidemia, which interferes with co-oximetry and may have produced a falsely high value.[17]

With discontinuation of NO inhalation, five patients (6%) developed "rebound," which is acutely increased pulmonary hypertension, hypoxemia, and hemodynamic instability. All these patients were receiving high levels of ventilatory support and required vasopressor therapy for septic shock. Reinstitution of NO inhalation promptly corrected these manifestations and NO withdrawal was postponed until the patient was less severely ill.

Discussion

We describe a large series of patients with ARDS of diverse causes who received inhaled NO. Preexisting organ system dysfunction and septic shock were commonly present. In our series, most patients had a favorable immediate clinical response (defined as an improvement of more than 20% of oxygenation and/or decrease of pulmonary hypertension) to inhaled NO. This favorable response appeared to persist for the first 48 h of therapy. The presence of septic shock was associated with a decreased likelihood of response. Adverse consequences of rebound with discontinuation of inhaled NO occurred in 6% of the trials.

Incidence of a Clinically Significant Beneficial Effect of Nitric Oxide Inhalation

Fifty-eight percent of patients with ARDS had a clinically significant response to inhaled NO. This finding is consistent with other reports. Rossaint *et al.*[18] reported that the Pa_{O_2}/FI_{O_2} ratio failed to increase in 17% of patients with severe ARDS by at least 10 mmHg, and the mean PAP failed to decrease in 37% by > 3 mmHg after inhalation of 10–20 ppm NO. McIntyre *et al.*[19] observed minimal improvement (Pa_{O_2}/FI_{O_2} ratio increase <20%; mean PAP decrease <10%) in 5 of 16 trials (31%) after 20 and 40 ppm NO, respectively. Wysocki *et al.*[20] found that 10 of 17 (59%) patients did not respond to inhaled NO. These variable response rates may be attributed to the different definitions of a clinically important response and the different patient populations studied. We chose a relatively conservative definition that was comparable to that used in a recent phase 2 randomized multiple-center clinical trial.[12] In that trial, which was limited to patients with ARDS without septic shock or significant extrapulmonary organ system dysfunction, a response rate of 65% was reported. Our patients were relatively older and quite ill. The average age of our patients was 52 yr, and their APACHE II scores averaged 27. For comparison, the average age of the patients studied by Rossaint *et al.*[18] was 28 yr, and their average APACHE II score was 18.5.

Factors Correlating with the Patient's Initial Responsiveness to Nitric Oxide

We investigated the possible determinants of the physiologic response to NO, with the aim of identifying patients that may receive the most beneficial effect from NO inhalation. In our study population, 67% of patients with coexisting septic shock did not respond or responded only minimally to inhaled NO. Our findings are consistent with those of Krafft *et al.*,[21] who reported

that 60% of 25 patients with septic ARDS requiring vasopressor and inotropic support did not respond to inhaled NO. In contrast to their study, we compared trials in patients with ARDS with septic and nonseptic shock and found that 64% of patients without septic shock responded. It has been suggested that the variability in response could be explained in part by the use of exogenous catecholamines in the patients with septic shock.[22] Increased catecholamine concentrations conceivably could interfere with the action of NO by exacerbating pulmonary arterial constriction. In our series, however, the use of vasopressors was not significantly different between the responders and the nonresponders. It is also possible that patients with septic shock have an impaired vasodilator response to exogenously administered NO, related to the massive release of endogenous NO, which contributes to the severe hypotension in septic shock.[23] In a sepsis-induced acute lung injury animal model of hyporesponsiveness to inhaled NO, Holzmann *et al.*[24] found that the pulmonary vasodilator response to inhaled NO was impaired after endotoxin administration. The impairment of NO-induced vasodilation was associated with decreased cGMP release into the lung perfusate. This decrease was partly attributable to increased activity of pulmonary cGMP-phosphodiesterases, the enzyme group responsible for breaking down cGMP in the lung. Whether a similar increase of phosphodiesterases activity occurs in the lung of humans with sepsis is unknown. If phosphodiesterases activity in the human lung is increased during sepsis, administration of inhaled NO might fail to increase tissue levels of cGMP sufficiently to produce clinically significant vasodilation.

Renal dysfunction was significantly more common among nonresponders, and the mean serum creatinine concentration was higher in this group (table 5). However, on multivariate analysis, renal failure was associated with the presence of septic shock. In the presence of septic shock, the association of renal failure with an impaired response to inhaled NO was less significant ($P = 0.07$), suggesting that it is a marker for patients with more severe perfusion abnormalities.

Although it did not reach statistical significance ($P = 0.06$), a short course of respiratory failure (< 7 days) tended to be associated with a clinically significant response to inhaled NO. Patients with a more protracted clinical course may have a decreased vasodilator response to inhaled NO because of more severe lung injury with vascular remodeling or complicating factors such as superimposed sepsis or pneumonia.

We and others previously reported a correlation between the baseline PVR and the degree of pulmonary vasoconstriction reversible by NO inhalation.[9,25,26] In our study, the baseline PVR correlated with the degree of reduction of PVR during NO inhalation ($r^2 = 0.43$; $P < 0.05$) and, to a lesser extent, baseline PAP correlated with the degree of reduction of PAP ($r^2 = 0.38$; $P < 0.05$). Patients with marked pulmonary hypertension appeared to exhibit the greatest response to NO inhalation. Baseline values for PVR and mean PAP were not independently associated with the presence or absence of a significant clinical response (a "responder" as defined in Methods) when examined by multivariate analysis. Several patients with a high PVR failed to respond to inhaled NO. Inhaled NO will not reduce PAP if PVR is not elevated, such as when pulmonary artery hypertension is due primarily to an increase in pulmonary blood flow. The degree of arterial hypoxemia did not predict the extent of pulmonary vasodilation observed with inhaled NO.[9]

Effects of Inhaled Nitric Oxide Treatment

A sustained effect of NO inhalation on arterial oxygenation and pulmonary hypertension, without evidence of tachyphylaxis, has been previously suggested.[9] Our data confirmed these findings in those patients who had initially responded well to NO and subsequently continued to receive therapy. We did not collect data later than 48 h; as the clinical course progresses, the possible effects of NO would be obscured by other events that make data analysis impossible in the absence of a control group.

Overall, there were no significant differences between the response/treatment group and the nonresponse/nontreatment group in hospital or intensive care unit stay, the number of days receiving mechanical ventilation, or survival rate. The significance of NO responsiveness and therapy on long-term outcome in patients with ARDS remains to be conclusively demonstrated with prospectively designed, controlled studies.

Methemoglobin and Nitrogen Dioxide Formation

The acute toxicity associated with NO includes NO_2 formation, methemoglobinemia, and peroxynitrite formation. High inhaled NO concentrations ($\geq 2\%$) rapidly produce methemoglobinemia and death in experiments with animals.[27] Inhalation of low concentrations of NO

for prolonged periods, however, appears free of acute toxicity.[9,18] Nitrogen dioxide is produced spontaneously from NO and oxygen and is an atmospheric pollutant that has been shown in animal studies to produce toxic effects including severe parenchymal lung injury and death.[28] Lung injury secondary to NO_2 inhalation has been reported after exposure to concentrations as low as 2 ppm.[29-33] Changes included alveolar cell hyperplasia, loss of cilia, and increased bronchial reactivity. Based on these observations, we aim to maintain inspired NO_2 concentrations < 2 ppm at all times. Previous work has shown that NO_2 production in breathing systems during NO inhalation increases with increasing $F_{I_{O_2}}$ and NO concentration, low minute ventilation, and increased lung volumes.[34] We routinely measure the inspired NO_2 concentration when there is an increased risk for NO_2 production; that is when $F_{I_{O_2}} \geq 80\%$ with an NO inspired concentration ≥ 20 ppm. In these circumstances, we also premix the NO with nitrogen instead of air. With the use of lower inhaled NO concentrations (< 10 ppm), we have uniformly been able to maintain the inspired NO_2 concentration well below 2 ppm.

Methemoglobin is produced when the heme iron of hemoglobin is oxidized from Fe^{+2} to Fe^{+3}.[35] In the oxidized form, the oxygen affinity of the hemoglobin increases and oxygen unloading to the tissues is impaired.[36] Normal methemoglobin levels are $< 2\%$; levels $< 5\%$ do not require treatment. Methemoglobinemia during NO inhalation has been previously reported, especially in newborns, but its incidence appears low and is related to the inhaled NO dose.[37,38] In a clinical study, Wessel *et al.*[39] reported methemoglobin concentrations greater than 5% in 4 of 123 patients who received inhaled NO. Our current report is consistent with previous studies in adults[8,9,11,18,19,40] that concluded that clinically significant methemoglobinemia is very rare after exposure to NO concentrations of < 40 ppm. It is important to realize that hyperlipidemia may interfere with the determination of methemoglobin concentrations by co-oximetry and result in falsely elevated values.[17]

A potentially serious adverse effect related to NO treatment that we observed was the onset of acutely increased pulmonary hypertension and hypoxemia with sudden discontinuation of treatment. This adverse effect of NO inhalation has been reported previously.[9,41,42] The cause of this rebound effect is unknown. Suggested mechanisms include a decrease of NO synthase activity or an increase of tissue cGMP-phosphodiesterase activity as a result of exogenous NO.[22,42] We have noticed that this phenomenon may occur even after slowly decreasing the inspired NO concentration over several days and discontinuing very low levels of NO (< 1 ppm). Currently, we continue inhaled NO until the requirements for ventilatory support are minimal (*i.e.*, 40% $F_{I_{O_2}}$ and < 10 cm H_2O positive end-expiratory pressure) and vasopressor or inotropic therapy is no longer required. We also temporarily increase the $F_{I_{O_2}}$ to 60–80% when discontinuing NO. Discontinuation of inhaled NO has been well tolerated under these conditions and reinstitution of inhaled NO, inotropic support, or vasodilator therapy has not been required.

Although prolonged inhalation of low doses of NO appears safe, the potential long-term toxic effects remain unclear.[43] The effects of inhaled NO on surfactant, free radical, and peroxynitrite production are unknown. Therefore we continue to be cautious during NO inhalation by administering low concentrations of inhaled NO, monitoring the inspired NO concentration closely, and using delivery systems that are simple and safe.

Limitations and Conclusions

The main limitation of our study is its retrospective nature. Until definitive, controlled studies are published, our large series of patients may provide guidance to the critical care practitioners and clinical investigators with regard to the physiologic determinants of the response to inhaled NO in patients with ARDS.

Inhaled NO caused a clinically important improvement of oxygen exchange, pulmonary hypertension, or both in 58% of patients with ARDS. The absence of septic shock was the best predictor of a favorable response to NO inhalation. Additional characteristics that may be helpful in identifying those patient populations most likely to have the greatest beneficial response to NO inhalation include marked pulmonary hypertension, the absence of renal failure, and a short course of respiratory failure before therapy.

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