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Prolonged Inhalation of Low Concentrations of Nitric Oxide in Patients with Severe Adult Respiratory Distress Syndrome

Effects on Pulmonary Hemodynamics and Oxygenation

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Background: **Nitric oxide (NO) inhalation selectively decreases pulmonary artery hypertension and improves arterial oxygenation in patients with the adult respiratory distress syndrome (ARDS). In this study of patients with severe ARDS, we sought to determine the effect of inhaled NO dose and time on pulmonary artery pressure and oxygen exchange and to determine which patients with ARDS are most likely to show this response.**

Methods: **Thirteen patients with severe ARDS (hospital mortality 67%) inhaled 0–40 parts per million (ppm) NO. Seven of these patients continued to breathe 2–20 ppm NO for 2–27 days.**

Results: **Inhaling 5–40 ppm NO decreased mean pulmonary artery pressure in a dose-related fashion (from 34 ± 7 to 30 ± 7 mmHg at 20 ppm NO). Systemic arterial pressure did not change. The ratio of arterial oxygen tension to inspired oxygen fraction increased (from 126 ± 36 to 149 ± 38 mmHg) and the venous admixture decreased (from 31.2 ± 5.5 to 28.2 ± 5.2%) without a clear dose–response effect. During prolonged NO inhalation, 2–20 ppm NO effectively reduced mean pulmonary artery pressure (38 ± 7 *vs.* 31 ± 6 mmHg) and increased arterial oxygen tension (79 ± 10 *vs.* 114 ± 27 mmHg) without evidence of tachyphylaxis. The decrease of pulmonary vascular resistance during NO inhalation correlated with the level of pulmonary vascular resistance without NO (r = −0.72). The reduction of venous admixture correlated with the level of venous admixture without NO (r = −0.78).**

Conclusions: **Long-term NO inhalation at low concentrations selectively decreases mean pulmonary artery pressure and improves arterial oxygen tension in patients with ARDS. The selective pulmonary vasodilation effect is most pronounced in ARDS patients with the greatest degree of pulmonary vasoconstriction. (Key words: Endothelium-derived relaxing factor. Lung(s): acute pulmonary hypertension; adult respiratory distress syndrome. Pharmacology: nitric oxide.)**

ACUTE pulmonary artery hypertension is characteristic of severe adult respiratory distress syndrome (ARDS).[1] Mechanical obstruction and compression of the pulmonary vasculature as well as vasoconstriction may variably contribute to the increased pulmonary artery pressure.[2] Pulmonary hypertension fosters the development of pulmonary edema,[3,4] increases the workload of the right ventricle,[5,6] and may be associated with an increased mortality.[1] Attempts to use intravenous vasodilators in patients with ARDS have been hindered by the occurrence of systemic hypotension and worsening hypoxemia.[7,8]

Previous experimental and clinical work has established that inhaled nitric oxide (NO) is a selective pulmonary vasodilator in a variety of pathologic conditions associated with pulmonary artery hypertension. Inhalation of 40–80 parts per million (ppm) NO reversed acute pulmonary hypertension due to hypoxia, the infusion of the thromboxane analog U46619, and the heparin–protamine reaction in awake lambs,[9,10] as well as hypoxic pulmonary vasoconstriction in human volunteers.[11] NO inhalation reduced pulmonary vascular hypertension associated with congenital heart disease in children,[12] primary pulmonary hypertension,[13] and after mitral valve replacement.[14] NO inhalation improved arterial oxygenation in newborns with persis-

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tent pulmonary hypertension.[15,16] In all these studies, systemic arterial pressure was not affected by NO inhalation.

The current study was planned to extend the work of investigators at the University of Berlin, Germany, who recently reported[17] that inhaled NO selectively reduces pulmonary artery pressure and improves arterial oxygenation in patients with ARDS. The hypothesis of both studies was that inhaled NO would increase arterial oxygen tension (Pa_{O_2}) by selectively dilating lung vessels in ventilated alveoli, thereby improving the overall match of ventilation and perfusion.

In the current study, we extended the prior study[17] by delivering increasing doses of NO for a brief period of time to critically ill patients with ARDS. This was done to more thoroughly determine the dose–response effect of inhaled NO on pulmonary hypertension and oxygen (O_2) exchange. Prolonged NO inhalation subsequently was continued in 7 of 13 patients. During long-term exposure (2–27 days), we investigated the persistence over time of the hemodynamic and respiratory effects of NO inhalation. In contrast to the prior study,[17] we sought the minimal inspired NO concentration that would effectively decrease mean pulmonary artery pressure (MPAP) and increase Pa_{O_2} in patients with ARDS. Furthermore, we attempted to identify those patients who are most likely to respond to NO inhalation on the basis of their baseline physiologic characteristics.

Materials and Methods

Approval for the experimental use of NO in patients with ARDS was obtained from the FDA. The investigational protocol was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital. Written informed consent was obtained from each patient's family.

NO gas (Airco, Riverton, NJ) was stored in nitrogen (N_2) at 800–880 ppm. Nitrogen dioxide (NO_2) comprised up to 1% of the NO (*e.g.*, 800-ppm NO cylinders contained up to 8 ppm NO_2). NO in N_2 was then diluted with N_2 from a cylinder (or with air during prolonged inhalation) by a standard low-flow blender (Bird Blender, Palm Springs, CA) and thus delivered to the air intake of the ventilator (Siemens Servo 900c or Puritan-Bennett 7200). In the ventilator, the NO/N_2 (or NO/air) mixture was blended with O_2 and administered to the patient in the concentration desired (2–40 ppm) during inspiration. One-way valves within the ventilator prevented back-flow of O_2-containing gas into the NO cylinder. During the initial dose–response trial the inspired NO concentration in the inspiratory limb of the breathing circuit was monitored continuously with a chemiluminescence[18] analyzer (model 14A, Thermo Environmental Instruments, Franklin, MA). During prolonged NO inhalation, the inspired NO concentration was measured at least once daily with the same instrument. The inspired concentration of NO_2 also was measured by chemiluminescence and remained less than 5% of the NO concentration. Gas exiting from the expiratory limb of the ventilator circuit and from the analyzer was scavenged.

Patients

A total of 14 studies were performed over a period of 15 months in 13 sequential patients with ARDS and pulmonary hypertension. ARDS was defined by the following criteria: (1) acute respiratory insufficiency requiring mechanical ventilation; (2) a Pa_{O_2} to inspired oxygen fraction (FI_{O_2}) ratio (Pa_{O_2}/FI_{O_2}) $\leq$ 250 mmHg with positive end-expiratory pressure $\geq$ 5 cmH_2O; (3) bilateral pulmonary infiltrates on chest radiograph; (4) a pulmonary artery occlusion pressure $\leq$ 18 mmHg. Pulmonary hypertension was defined as a MPAP $\geq$ 25 mmHg. One patient (patient 4, table 1) had a pulmonary artery occlusion pressure of 21 mmHg at the time of study while the lungs were ventilated at 25 cmH_2O positive end-expiratory pressure. She was included in the study because she had clinical criteria of ARDS without other evidence of left ventricular dysfunction. One patient (patient 11) was studied on two occasions in the initial dose–response trial; in the first instance she did not have pulmonary hypertension. The severity of ARDS was graded according to Murray *et al.*[19] The presence of associated organ failure at the time of study was recorded. Renal failure was defined as a serum creatinine concentration $\geq$ 3 mg/dl; liver failure as a serum bilirubin concentration $\geq$ 4 mg/dl; and coagulopathy as a platelet count $\leq$ 90,000/mm^3 and prothrombin time $\geq$ 1.5 times control, partial thromboplastin time $\geq$ 1.5 times control, or hematocrit $\leq$ 20%. All patients were monitored *via* radial and pulmonary artery catheters and were sedated with intravenous morphine sulfate and diazepam. *d*-Tubocurarine was administered by intravenous infusion for muscle relaxation in ten patients. The mode of mechanical ventilation as well as all other aspects of each patient's care were guided by the attending physician. No intravenous vasodilators were used.

Table 1. Clinical Data

Patient No.	Principal Diagnosis	Other OSF	Age (yr)	Outcome	Days of Mechanical Ventilation before Study	ARDS Score	MPAP (mmHg)				Pa_{O_2}/FI_{O_2} (mmHg)				Days of NO
							Short-term		Prolonged		Short-term		Prolonged		
							Pre-NO	20 ppm NO	Off NO	2–20 ppm NO	Pre-NO	20 ppm NO	Off NO	2–20 ppm NO	
1	Streptococcal pneumonia		22	S	7	3.5	33	31			120	146			
2	Neoplastic PE	K	44	D	4	3	32	31			184	163			
3	Pneumonectomy Ca	K, L	55	D	11	3.5	25	23			188	223			
4	Bowel obstruction	K, L	35	D	12	3.75	35	35			118	171			
5	Multiple lung resections Ca		71	D	7	3.75	31	28	33	26	89	82	66	93	4
6	Fecal peritonitis	C	69	D	3	3.25	33	25	28	26	119	129	83	94	2
7	Necrotizing pancreatitis		39	D	3	3.5	32	29	32	28	81	117	77	93	7
8	Diabetic coma		27	S	13	3.5	38	35			181	188			
9	Gunshot wound chest		33	S	5	3.75	43	38	44	36	107	181	73	106	17
10	Fecal peritonitis	K	34	D	13	3.75	32	31	37	30	123	139	77	110	27
11	Mandibular resections Ca		45	D	5	3.75	20	16			143	110			
					11	4	30	21	37	30	127	160	78	136	23
12	Esophagogastrectomy Ca		51	D	10	3.25	43	42	48	41	91	102	99	166	18
13	Postpartum PE		33	S	5	3.5	48	42			96	178			
	Mean ± SD		44 ± 14		7.8 ± 4	3.5 ± 0.3	34 ± 7	30 ± 7	38 ± 7	31 ± 6	126 ± 36	149 ± 38	79 ± 10	114 ± 27	14 ± 10

Ca = cancer; C = coagulopathy; D = dead; K = kidney; L = liver; MPAP = mean pulmonary artery pressure; OSF = organ system failure; PE = pulmonary embolism; S = survivor.

Dose–Response Trial

After a 20-min baseline equilibration at 0.9 FI_{O_2}, NO was delivered at increasing inhaled concentrations of 5, 10, 20 and 40 ppm. Each concentration was breathed for 20 min. Because of the brief duration of action of inhaled NO,[10–17,20–22] increasing NO concentrations were delivered without returning to baseline between each dose level. A second baseline was obtained 20 min after discontinuing NO. The FI_{O_2} was maintained at 0.9 throughout the trial. The following measurements were obtained at both baselines and at each inspired NO concentration: exhaled tidal volume, peak inspiratory pressure, mean inspiratory pressure, respiratory rate, heart rate, systolic and diastolic systemic and pulmonary artery pressure, central venous pressure, pulmonary artery occlusion pressure, and cardiac output. Hemodynamic measurements were obtained at end-exhalation with the patient supine and the pressure transducers zeroed to ambient pressure at the mid-axillary line. Cardiac output was measured in triplicate by thermodilution. Mean systemic arterial pressure and MPAP were calculated as ([systolic − diastolic pressure]/3) + diastolic pressure. Systemic vascular resistance and pulmonary vascular resistance (PVR) were calculated by standard formulas. Respiratory dynamic compliance was calculated as (peak inspiratory pressure − positive end-expiratory pressure)/tidal volume. Arterial and mixed venous blood gas tensions were measured with a Corning 178 *p*H/blood gas analyzer (Corning Medical and Scientific, Halstead, Essex, UK). Venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) and O_2 delivery were calculated with standard formulas. Methemoglobin concentration was measured by spectrophotometry (IL 282 co-oximeter, Instrumentation Laboratories, Lexington, MA) before NO inhalation and immediately after the 40 ppm NO inhalation period.

Prolonged Nitric Oxide Inhalation

Long-term administration of NO was approved by the Subcommittee on Human Studies after the first four patients were studied in the dose–response trial. Of the subsequent nine patients (see table 1), patients 8 and 11 did not receive prolonged inhalation because their initial response to NO was considered minimal. Patient 11 received prolonged inhalation after her second trial. Patient 13 no longer met our definition of ARDS during the 1st day of prolonged inhalation (Pa_{O_2}/FI_{O_2} was > 250 mmHg) and was excluded from further study. After completion of the dose–response trial, NO inhalation, beginning at 10–20 ppm NO, was continued in seven

patients. NO inhalation was temporarily discontinued daily and hemodynamic and gas exchange measurements were obtained at constant FI_{O_2} before, during, and after discontinuation of NO inhalation. Subsequently, NO inhalation was resumed only if MPAP increased or Pa_{O_2} decreased when the NO was discontinued. In the last four patients, on each day we attempted to decrease the inspired NO concentration, provided the beneficial effect on MPAP and Pa_{O_2} persisted at the reduced concentration. Methemoglobin concentrations were measured daily.

Statistical Analysis

Values are expressed as mean ± standard deviation (mean ± SD). A paired *t* test was used to compare values on and off NO inhalation. Analysis of variance for repeated measures and a Bonferroni *t* test for multiple comparisons were used to analyze the dose–response curves. Linear regression analysis was used to examine the association between two variables. Because of differences in the duration of prolonged NO inhalation, some patients contributed more observations then others. Accordingly, statistical tests were conducted using patients as the unit analysis. For correlation coefficients, this was implemented with a "jackknife" procedure,‖ whereby repeated correlations are performed with n − 1 patients, excluding a different patient each time. For paired comparisons, values obtained in each patient were averaged. A *P* value less than 0.05 was accepted for statistical significance.

Results

The clinical characteristics and individual responses to NO inhalation of the 13 patients are reported in table 1. All had severe acute respiratory failure.[19] Three patients (patients 3, 5, and 6) had chronic obstructive pulmonary disease. Five patients had cancer. Ten patients were recovering from major abdominal or thoracic surgery. All 13 patients were receiving continuous intravenous infusions of vasoactive drugs in addition to a low dose of dopamine at the time of study. Nine of 13 patients died during their intensive care unit course (67% mortality). Six of the seven patients who received prolonged NO inhalation died.

‖ Efron B: The jackknife, the bootstrap and other resampling plans. SIAM, Society of Industrial and Applied Mathematics. Philadelphia, 1982.

Dose–Response Trial

MPAP decreased in a dose-related fashion during the inhalation of increasing inspired NO concentrations (5–40 ppm) in 11 patients (fig. 1). Patients 1 and 4 received only one and two doses of NO, respectively and were not included in the analysis. The percent maximum reduction of MPAP at each NO concentration was different from baseline and the percent reduction at 40 ppm NO was higher than at 5 ppm NO (analysis of variance for repeated measures: $P < 0.0001$, *t* test between values at 5 and 40 ppm NO: $P < 0.05$). Fifty percent of the maximum reduction of MPAP was obtained during inhalation of 5 ppm NO and 90% between 20 and 40 ppm NO. The Pa_{O_2}/FI_{O_2} ratio increased during inhalation of 5–40 ppm NO, but a dose–response effect was not detectable because of large variations among patients.

The effects of short-term NO inhalation are summarized in table 2, where the physiologic measurements obtained during breathing of 20 ppm NO are compared to the preexposure baseline levels. These did not differ from the postexposure values (*P* values ranged between 0.73 and 0.99). MPAP decreased during inhalation of 20 ppm NO from 34 ± 7 to 30 ± 7 mmHg ($P < 0.001$). Pulmonary vascular resistance decreased from 228 ± 152 to 190 ± 108 dyn·s·cm^{-5} ($P < 0.05$). The Pa_{O_2}/FI_{O_2} ratio increased from 126 ± 36 to 149 ± 38 mmHg

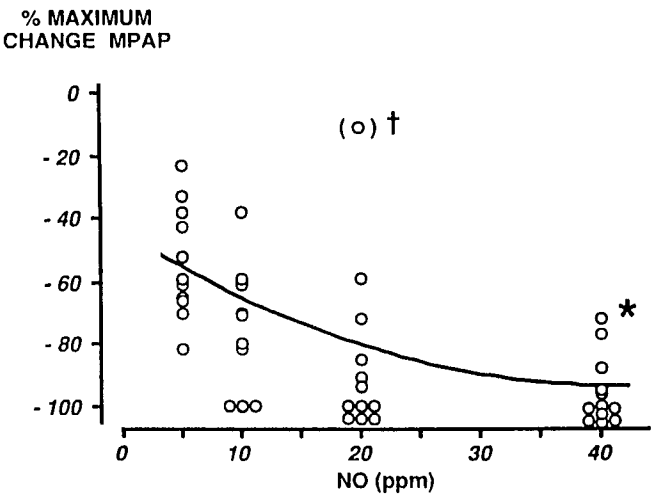

Fig. 1. Dose–response effect of nitric oxide (NO) inhalation on mean pulmonary artery pressure (MPAP) in 11 patients with adult respiratory distress syndrome (12 observations). Values are expressed as the percent of maximal response. Analysis of variance for repeated measures: $P < 0.0001$. *Mean value at 40 ppm NO was significantly different from mean value at 5 ppm NO. + = positive value (+100%).

Table 2. Physiologic Response to NO Inhalation

	Short-term Protocol (n = 14)			Prolonged Inhalation (n = 7)		
	Pre-NO	20 ppm NO	*P* Value	Off NO	2–20 ppm NO	*P* Value
Mean pulmonary artery pressure (mmHg)	34 ± 7	30 ± 7	<0.001	38 ± 7	31 ± 6	<0.001
Pulmonary vascular resistance (dyne · s^{-1} · cm^{-5})	228 ± 152	190 ± 108	<0.05	241 ± 68	181 ± 50	<0.01
Mean systemic pressure (mmHg)	77 ± 14	73 ± 16	NS	74 ± 8	73 ± 5	NS
Central venous pressure (mmHg)	14 ± 4	14 ± 5	NS	15 ± 4	14 ± 3	NS
Pulm arterial occlusal pressure (mmHg)	15 ± 4	14 ± 4	NS	15 ± 3	15 ± 2	NS
Cardiac output (l/min)	7.5 ± 2.2	7.4 ± 2	NS	7.7 ± 2	7.7 ± 2	NS
Heart rate (beats/min)	101 ± 14	99 ± 13	NS	106 ± 14	105 ± 16	NS
Pa_{O_2}/FI_{O_2} (mmHg)	126 ± 36	149 ± 38	<0.01	79 ± 10	114 ± 27	<0.01
$\dot{Q}_{VA}/\dot{Q}_T$ (%)	31.2 ± 5.4	28.2 ± 5.4	<0.05	43.6 ± 6.6	34.4 ± 4.2	<0.001
$\dot{D}_{O_2}$ (ml/m)	1039 ± 302	1026 ± 285	NS	927 ± 207	1011 ± 224	NS
Methemoglobin (%)	0.8 ± 0.6	1 ± 0.8	NS		1.3 ± 0.7	

Values are mean ± SD. NS = not significant ($P \geq 0.05$); $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture; $\dot{D}_{O_2}$ = oxygen delivery.

($P < 0.01$) and $\dot{Q}_{VA}/\dot{Q}_T$ decreased from 31.2 ± 5.4 to 28.2 ± 5.4% ($P < 0.05$). Heart rate, mean systemic arterial pressure, cardiac output, central venous pressure, pulmonary artery occlusion pressure, and O_2 delivery did not change significantly. Inspiratory airway pressures (peak inspiratory pressure, mean inspiratory pressure), tidal volume, and respiratory dynamic compliance were unchanged. The methemoglobin concentration at the end of 40 ppm NO inhalation (1 ± 0.8%) was not different from the initial baseline concentration (0.8 ± 0.6%).

Prolonged Nitric Oxide Inhalation

Seven patients breathed 2–20 ppm NO for an average of 14 days (range 2–27 days). The physiologic effects of a brief daily discontinuation of NO are summarized in tables 1 and 2. The baseline measurements (off NO) were compared to the average of the two determinations on NO (before and after discontinuation). The two determinations on NO did not differ from each other (*P* values ranged between 0.58 and 0.95). MPAP, PVR, and $\dot{Q}_{VA}/\dot{Q}_T$ decreased significantly during inhalation of 2–20 ppm NO, while the Pa_{O_2}/FI_{O_2} ratio increased. All the other hemodynamic variables that we measured did not change. Inspiratory airway pressures (peak inspiratory pressure, mean inspiratory pressure), tidal volume, and respiratory dynamic compliance were unchanged. The methemoglobin concentration was less than 3% in all but one patient (patient 10), who had a baseline methemoglobin concentration of 2.5% and a peak value of 4.3% after 27 days of NO inhalation.

In no instance was long-term NO inhalation interrupted because of a lack of effect. MPAP, PVR, and $\dot{Q}_{VA}/\dot{Q}_T$ always decreased and Pa_{O_2} always increased while NO was breathed, as compared to the measurements obtained during the daily temporary discontinuation (fig. 2).

Tachyphylaxis and Minimal Effective Concentration

The effect of NO inhalation on Pa_{O_2} persisted throughout the entire exposure period. The average increase of the Pa_{O_2}/FI_{O_2} ratio associated with NO inhalation was similar on the 1st day (30 ± 25 mmHg) and on the last day (45 ± 45 mmHg, $P = 0.35$) of prolonged NO breathing. The daily increases of the Pa_{O_2}/FI_{O_2} ratio due to NO inhalation in the seven patients who received prolonged NO inhalation are illustrated in figure 3. The decrease of MPAP associated with NO inhalation also persisted over time (−5 ± 2 mmHg on the 1st day as compared to −6 ± 4 mmHg on the last day, $P = 0.5$), though with a marked variation among patients. The NO concentration never needed to be increased in the course of long-term inhalation to decrease MPAP or increase Pa_{O_2}. Thus, tachyphylaxis did not occur.

To define the minimal NO concentration capable of decreasing pulmonary hypertension and increasing arterial oxygenation, we attempted to progressively reduce the inspired NO concentration each day during prolonged exposures in the last four patients. An in-

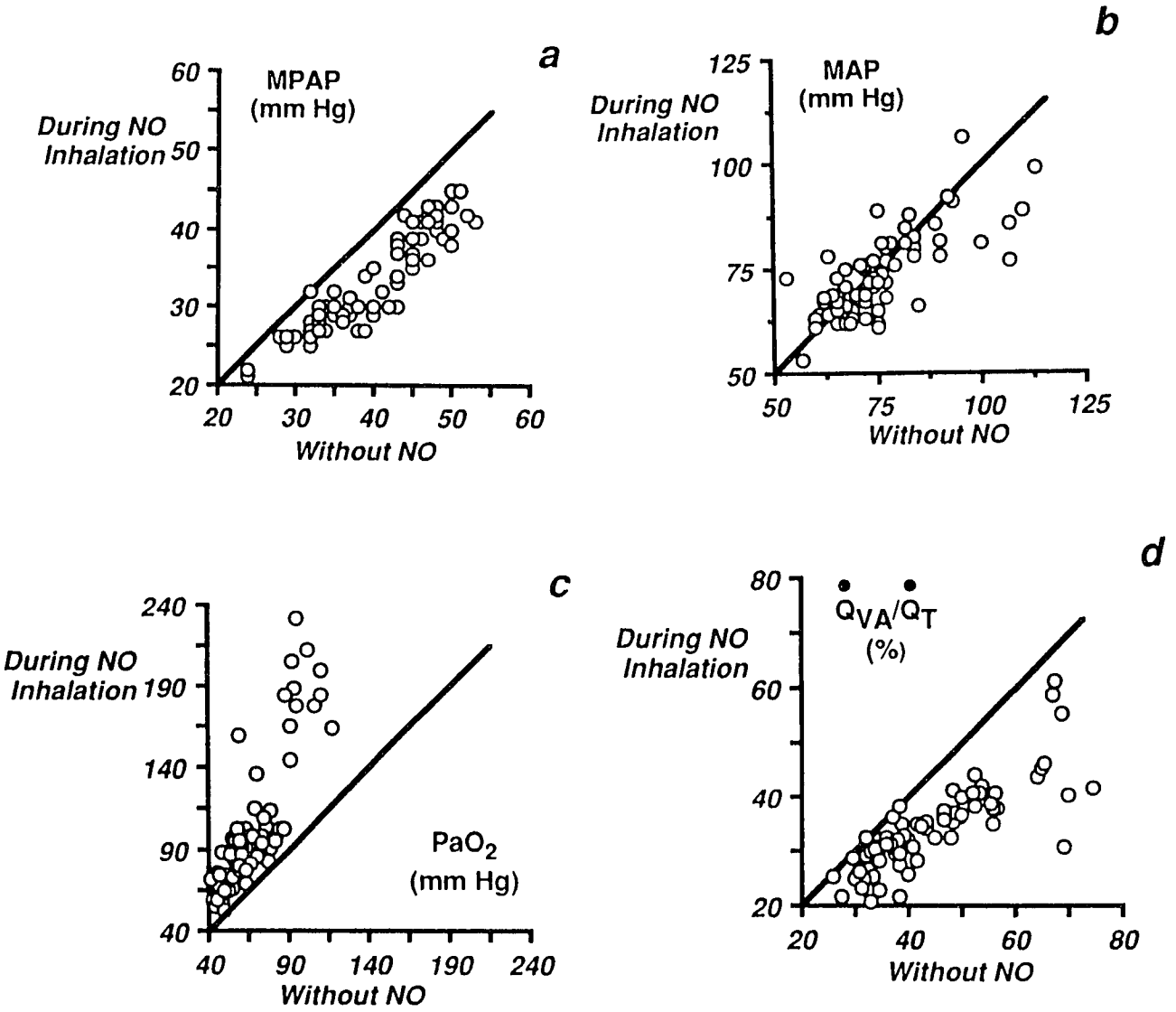

Fig. 2. Individual responses of seven patients with adult respiratory distress syndrome to nitric oxide (NO) inhalation during prolonged exposure (75 observations, 2–24 per patient). Values recorded daily without NO are plotted against the values recorded during NO inhalation. The line crossing each panel represents identity between measurements obtained with and without NO inhalation. (*A*) MPAP = mean pulmonary artery pressure. (*B*) MAP = mean systemic arterial pressure. (*C*) Pa_{O_2} = arterial oxygen tension. (*D*) $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture.

haled concentration of 2–4 ppm NO effectively decreased MPAP and increased Pa_{O_2} in all four patients. The average inspired NO concentrations inhaled during long-term NO breathing are reported in figure 3.

Physiologic Determinants of the Response to Nitric Oxide Inhalation

During prolonged NO inhalation, the reduction of PVR correlated with the baseline level of PVR without NO ($r = -0.72$, $P < 0.001$, fig. 4A). Likewise, the reduction of MPAP during inhalation of NO correlated with the level of MPAP without NO ($r = -0.53$, $P < 0.001$, fig. 4B). The reduction of $\dot{Q}_{VA}/\dot{Q}_T$ during NO inhalation correlated with the level of $\dot{Q}_{VA}/\dot{Q}_T$ at baseline ($r = -0.78$, $P < 0.001$, fig. 4C). The decrease of PVR or MPAP, as well as the reduction of $\dot{Q}_{VA}/\dot{Q}_T$, during prolonged NO breathing were not related to the mixed venous O_2 tension at baseline, the patients' age, or the

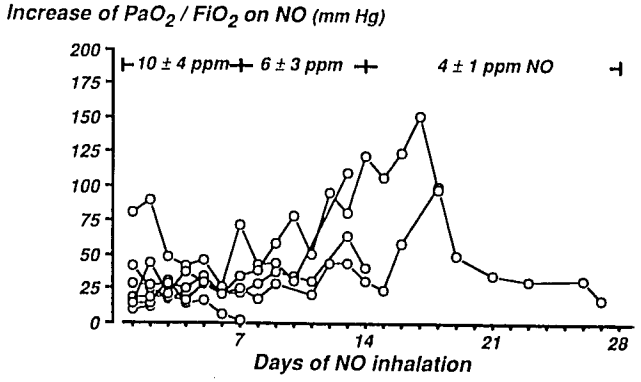

Fig. 3. Daily changes of the ratio of arterial oxygen tension to inspired oxygen fraction (Pa_{O_2}/FI_{O_2}) associated with nitric oxide (NO) inhalation in seven patients with adult respiratory distress syndrome: absence of tachyphylaxis to prolonged NO inhalation. Values represent the difference between measurements recorded during NO inhalation and measurements recorded during temporary discontinuation of NO inhalation. Average inspired NO concentrations are reported.

duration of tracheal intubation before study. Respiratory compliance did not show a significant correlation with the hemodynamic and gas exchange effects of NO inhalation.

Discussion

Inhaling 2–40 ppm NO selectively decreased pulmonary artery pressure and improved arterial oxygenation in 13 critically ill patients with severe ARDS and acute pulmonary hypertension. These effects were rapidly reversed when NO was discontinued. Our findings confirm the results recently published by Rossaint *et al.*[17] Our studies differ in several important respects.

The decrease of MPAP observed in our initial trial of inhalation of several increasing concentrations of NO (5–40 ppm) was dose-related (fig. 1). Such a response has not previously been reported in a clinical trial of NO inhalation and confirms prior experimental findings

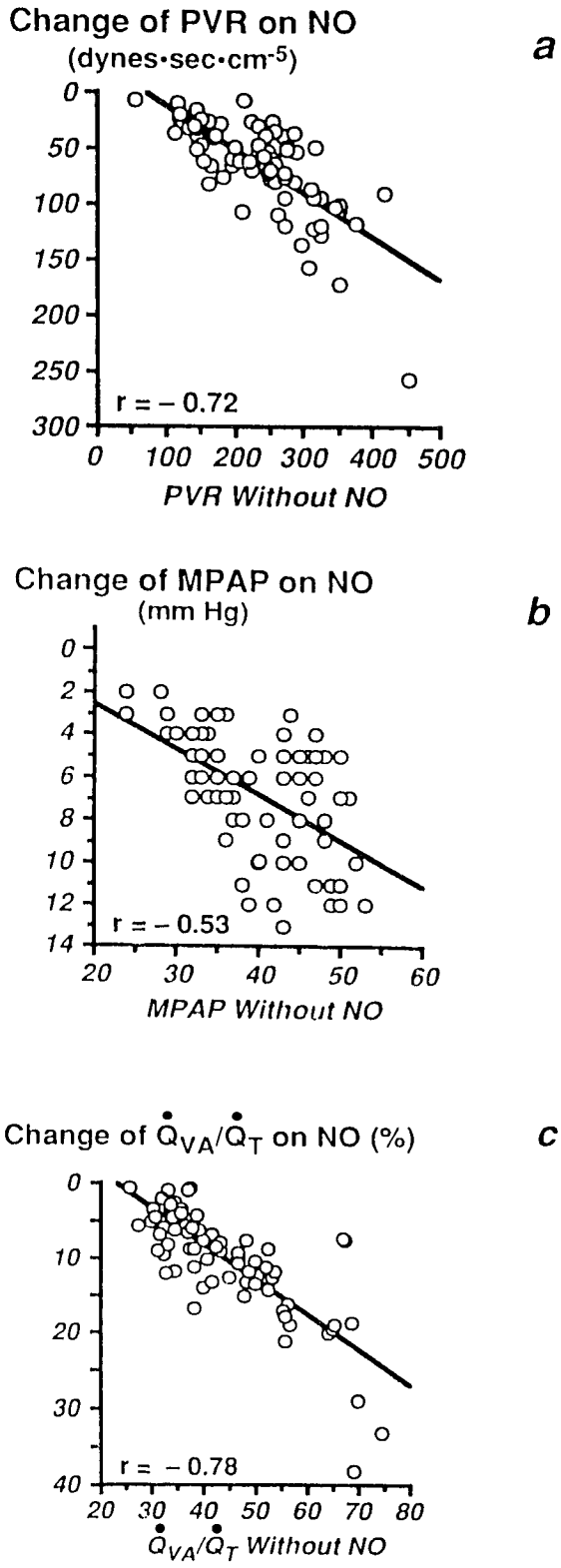

Fig. 4. Physiologic response of seven patients with adult respiratory distress syndrome to prolonged nitric oxide (NO) inhalation. Values recorded during temporary daily discontinuation of NO inhalation are plotted against the change of those values produced by NO breathing at constant NO and oxygen concentrations. (*a*) PVR = pulmonary vascular resistance (r = −0.72, $P < 0.001$). (*b*) MPAP = mean pulmonary artery pressure (r = −0.53, $P < 0.001$). (*c*) $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture (r = −0.78, $P < 0.001$).

in lambs.[9,10,20] A cumulative effect secondary to the consecutive administration of increasing doses is unlikely to have occurred because of the brief duration of action of inhaled NO documented in previous clinical and experimental studies[9,17,20–22] as well as in the current study. The dose–response was not studied during prolonged inhalation of 2–20 ppm NO. It is possible that the reactivity of the pulmonary vasculature to exogenous NO may change over the course of a patient's illness.

The increase of Pa_{O_2} during the initial dose–response trial was not clearly dose-related. Inspired NO concentrations lower than 5 ppm should be studied to detect if a dose–response is present. During long-term NO inhalation, 2–4 ppm NO often increased the Pa_{O_2} more than did 20 ppm NO (fig. 3). NO inhalation may improve O_2 exchange at a lower dose than the concentration required to produce a measurable vasodilator effect.

Low inspired NO concentrations were examined in the current study. Fifty percent of the maximum decrease of MPAP during the initial dose–response trial occurred during breathing of 5 ppm NO, and the maximum reduction of MPAP was reached at a concentration of 20 ppm or less in seven of the 11 patients studied (fig. 1). Based upon this observation, we were able to successfully decrease the inspired NO concentration during prolonged exposures in the last four patients. In these patients, breathing 2–4 ppm NO appeared to be as effective as 20 ppm NO at improving arterial oxygenation and decreasing MPAP (fig. 3). Such low inspired NO doses should minimize any possible toxicity caused by NO inhalation. Although to our knowledge this is currently the lowest dose of NO reported to be effective,[12–17] we did not test the effect of NO concentrations less than 2 ppm. During prolonged NO inhalation, the average Pa_{O_2} was approximately 30 mmHg higher with NO than without NO (93 ± 30 *vs.* 64 ± 12 mmHg, $P < 0.01$).

Such an improvement of Pa_{O_2} can assist respiratory management by allowing a reduction of FI_{O_2} or positive end-expiratory pressure or both. This however, may not translate into improved outcome. Whereas Rossaint *et al.*[17] reported a survival rate of 85%, the mortality in the current study remained very high. Conclusions on the effect of NO inhalation on survival of patients with ARDS should not be drawn from these two studies, which were not designed for this purpose.

We attempted to determine those patients who would best respond to NO inhalation. A marked variation was observed during our study in the hemodynamic and respiratory effects of NO inhalation, both among patients and within the same patient at different times. It is possible that preexisting pulmonary disease as well as the ongoing infusion of vasoactive drugs contributed to the observed variability. We found that the PVR at baseline correlated with the decrease of PVR achieved during NO inhalation ($r = -0.72$, fig. 4A). A similar finding was recently reported in cardiac surgery patients with pulmonary hypertension while they breathed NO.[21] The MPAP at baseline also correlated with the decrease of MPAP during breathing of NO ($r = -0.53$, fig. 4B). The patient with the lowest MPAP at the time of initial study (patient 11, table 1) had only a minor decrease of MPAP and PVR and no change of Pa_{O_2} during 20 ppm NO inhalation. Six days later, the same patient was studied again when her PVR and MPAP were higher. The effect of NO breathing on MPAP and Pa_{O_2} was much more pronounced. In our patients, the PVR at baseline best indicated the degree of pulmonary vasoconstriction reversible by NO inhalation. The greatest degree of acute pulmonary hypertension appeared to correlate with a favorable response to NO inhalation.

The magnitude of $\dot{Q}_{VA}/\dot{Q}_T$ at baseline correlated with the reduction of $\dot{Q}_{VA}/\dot{Q}_T$ during NO inhalation ($r = -0.78$, fig. 4C). The results obtained by Rossaint *et al.*[17] with the multiple inert gas elimination technique suggest that NO inhalation increases the Pa_{O_2} by improving the match of ventilation and perfusion ($\dot{V}/\dot{Q}$). Our observation indicates that those patients with the most severe $\dot{V}/\dot{Q}$ mismatch are most likely to benefit from NO inhalation. It is possible that inhalation of NO can alter gas exchange in more than one way. Dupuy *et al.*[22] studied guinea pigs with increased airway tone due to a methacholine infusion and noted a potent bronchodilator effect during NO inhalation. Airway resistance was not measured in our study. However, mean and peak inspiratory airway pressures, as well as compliance, did not change at any time during NO breathing.

Tachyphylaxis did not occur during prolonged NO inhalation. The increase of Pa_{O_2} and the decrease of MPAP was sustained over time. It is worthwhile noting that acute discontinuation of inhaled NO was difficult in two patients (patients 11 and 12). These patients rapidly developed hypoxemia and hemodynamic instability after NO was discontinued acutely. Reinstitution of NO inhalation rapidly ameliorated these effects. Both patients had been treated with NO for more than 2 weeks and were breathing very low inspired NO

concentrations at that time (2–5 ppm). Their clinical course was deteriorating because of progressive multiple organ failure. It is possible that the increase of PVR and acute hypoxemia at the time of NO discontinuation was associated with acute dilatation and dysfunction of the right ventricle. Right ventricular dilatation may impair diastolic filling of the left ventricle through ventricular interference. Ventricular arrhythmias and systemic hypotension also may arise from these phenomena, as we observed in these two patients.

The likelihood of toxicity from prolonged inhalation of low concentrations of NO appears minimal. Although large doses of NO can be lethal because of acute pulmonary edema and severe methemoglobinemia,[23] there is no evidence in experimental animals of acute toxicity at the doses used in our study.[24,#] Pulmonary damage from NO may be related to the production and inhalation of NO_2, which is highly toxic to the respiratory epithelium,[25] and the formation of peroxynitrite within aqueous solutions. The rate of conversion of NO to NO_2 is directly proportional to the square of the NO concentration, the residence time of NO in O_2, and the $F_{I_{O_2}}$.[26] The high gas flow rates that we delivered during mechanical ventilation make any significant accumulation of NO_2 unlikely. In none of our patients were we able to measure more than 0.5 ppm NO_2 in the inspired and exhaled gas. Methemoglobin concentrations did not change during the inhalation of 5–40 ppm NO for the short period of time of the dose–response trial and did not increase significantly during prolonged exposures.

In the current study, NO was delivered during inspiration directly *via* the ventilator. This avoided adding a nebulizer to the breathing circuit and resulted in a simpler system then the one utilized by Rossaint *et al.*[17] It was highly reliable even at the lowest inspired NO concentration.

The results of the current study suggest a strategy for future studies of NO inhalation in patients with ARDS:

1. Patients with a greater magnitude of acute pulmonary hypertension (MPAP ≥ 30 mmHg) are more likely to respond to NO inhalation.
2. Patients may be variably responsive to NO inhalation at different times in their clinical course. The lack of a significant effect at one time does not preclude a beneficial response several days later.
3. The hemodynamic and the respiratory effects of NO may occur at a different dose range. NO should first be inhaled at a relatively high inspired concentration (20–40 ppm), but the inspired dose may be decreased rapidly over time to 2–4 ppm or an even lower concentration.
4. Rapid withdrawal of inhaled NO resulting in hypoxemia and acute pulmonary vasoconstriction may be problematic during prolonged exposures. Addition of exogenous NO could reduce native NO production[27] or alter cyclic guanosine monophosphate metabolism. A better understanding of these interactions may provide improved strategies for safely discontinuing NO after prolonged inhalation. Currently, gradual discontinuation is advised.
5. The toxicity of chronic breathing of low-concentration NO remains to be determined. Efforts should be made to minimize the amount of NO (and NO_2) that is administered. Appropriate safety measures include scavenging NO_2 with soda lime, closely monitoring the inspired concentrations of NO and other oxides of N_2, and daily measurements of methemoglobin concentrations.
6. A controlled, randomized outcome trial is needed before NO inhalation becomes standard therapy for ARDS. Other areas that need further investigation include the potential effects of inhaled NO on platelet function, bacterial defenses and cytokine release.

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