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The Response to Repeated Nitric Oxide Inhalation Is Inconsistent in Patients with Acute Respiratory Distress Syndrome

Miriam Treggiari-Venzi, M.D., Bara Ricou, M.D.,† Jacques-André Romand, M.D.,† Peter M. Suter, M.D.‡*

Background: **Nitric oxide (NO) is administered frequently in patients with acute respiratory distress syndrome (ARDS) and pulmonary hypertension. The efficacy of this therapy over several days is not well known. The authors first determined the consistency of the response to repeated administration of NO and then the baseline variables that were associated with improvement in patients with severe ARDS.**

Methods: **In a prospective trial, 32 mechanically ventilated patients with severe ARDS received 10 parts per million NO by inhalation. In 22 of these patients, its effect was tested repeatedly (up to four times) in several days. Improvement was defined as an increase >10% in the ratio of pressure of oxygen in arterial blood (P_{aO_2}) to the inspiratory pressure of oxygen (FiO_2) from baseline. Patients showing such an improvement were maintained on NO inhalation.**

Results: **Twelve of the 22 patients (54%) showed a clinically significant and reproducible increase in the P_{aO_2}/FiO_2 ratio with NO, from 74 ± 30 mmHg (mean ± SD) to 95 ± 41 mmHg ($P < 0.001$). In three patients (14%), P_{aO_2} did not improve, even with multiple exposures. In seven patients (32%), an inconsistent response was seen on different days. Mean pulmonary artery pressure decreased for the entire group from 34 ± 10 mmHg to 29 ± 9 mmHg ($P < 0.01$), but this decrease did not correlate with the increase in P_{aO_2} in individual patients. The baseline P_{aO_2}/FiO_2 ratio and mixed venous oxygenation (P_{vO_2}) were significantly lower, and the venous admixture was greater in patients showing beneficial effects of NO inhalation on P_{aO_2}.**

Conclusions: **Repeated NO inhalation caused a consistent improvement in P_{aO_2} in about one half of these patients with severe ARDS; no significant benefit or inconsistent effects on pulmonary gas exchange were noted in the others. These findings could be related to the complexity of the mechanisms regulating the vasomotor changes in this syndrome. Severe baseline hypoxemia may be associated with a more favorable effect of NO on P_{aO_2}. (Key words: Acute lung injury; human endothelium-derived relaxing factor; hypoxia; lung; pulmonary hypertension.)**

NITRIC oxide (NO) is produced by endothelial cells and participates in the regulation of local vasomotor tone by relaxing vascular smooth muscle cells.[1,2] In acute respiratory failure and in pulmonary artery hypertension, an absolute or relative (or both) deficit of NO or an unbalanced state between vasoconstriction and vasodilation of pulmonary vessels may occur. Thus therapy with NO given by inhalation has been used to treat severe pulmonary hypertension[3] as well as arterial hypoxemia in acute respiratory distress syndrome (ARDS).[4] The rationale for NO therapy is based on its selective vasodilatory effect in ventilated lung regions, thereby improving the overall match of ventilation and perfusion.[4] Studies of limited numbers of patients reported that inhalation of NO at doses of 5-40 parts per million (ppm) improves arterial oxygenation and selectively decreases pulmonary artery pressure in patients with ARDS, and it remains efficient over several days of administration.[4,5]

However, inconsistent effects of NO inhalation on both gas exchange and pulmonary artery pressure have been suggested in severe ARDS[6,7] and septic ARDS.[8] Worsening of gas exchange has been shown in chronic obstructive pulmonary disease.[9] The purpose of the present study therefore was to determine, first, the consistency of response to repeated exposure to inhaled NO in patients with severe ARDS, defined by an improvement in systemic oxygenation of more than 10%. In addition, we examined the association between baselines arterial or mixed (or both) venous oxygen tension and the response to NO.

* Chief Resident in Anesthesiology.

† Médecin-adjoint, Division of Surgical Intensive Care.

‡ Professor and Chief, Division of Surgical Intensive Care.

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Address reprint requests to Dr. Suter: Division of Surgical Intensive Care, University Hospital of Geneva, CH-1211 Geneva 14—Switzerland. Address electronic mail to: elag@diogenes.hcuge.ch

Materials and Methods

The study was approved by the Committee for Ethics in Human Research of our institution. Thirty-two patients with severe ARDS and associated pulmonary arterial hypertension were given NO by inhalation. ARDS was defined according to the recent American-European consensus conference on ARDS,[10] including acute respiratory insufficiency requiring mechanical ventilation, an arterial oxygen partial pressure (P_{aO_2}) to inspired oxygen fraction (FiO_2) ratio (P_{aO_2}/FiO_2) <200 mmHg, requirement of a positive end-expiratory pressure of ≥ 5 cm H_2O, bilateral pulmonary infiltrates evident on a chest radiograph, a pulmonary artery occlusion pressure ≤ 18 mmHg, and a lung injury severity score according to Murray *et al.*[11] of ≥ 2.5. Pulmonary hypertension was defined as a mean pulmonary artery pressure (MPAP) >25 mmHg.

Patients were monitored for clinical reasons with a central venous catheter, a radial arterial catheter, and, at least at the first exposure to NO, a pulmonary artery catheter to assess pulmonary hemodynamics, cardiac output measurement by thermodilution, and for mixed venous blood gas (P_{vO_2}) analysis. All patient lungs were mechanically ventilated using Hamilton Veolar (Rhäzuns, Switzerland), Dräger Evita (Lübeck, Germany), or Siemens 900 C (Siemens Elema, Solna, Sweden) ventilators. Tidal volume was set to limit peak inspiratory airway pressure <50 cm H_2O, and minute ventilation was adapted for an arterial *p*H ≥ 7.30. The minimal FiO_2 was chosen to obtain a P_{aO_2} between 55 and 65 mmHg and the positive end-expiratory pressure level to achieve optimal compliance.[12] Nitric oxide was delivered from a tank containing a mixture of 400 ppm NO in nitrogen (AGA, Pratteln, Switzerland). Nitric oxide was administered continuously through a T-piece inserted proximal to the endotracheal tube, and its gas flow was adjusted to minute ventilation to obtain an average concentration of 10 ppm. Nitric oxide and NO_2 concentrations at the level of the endotracheal tube and expiratory limb of the breathing circuit, respectively, were assessed by a chemiluminescence analyzer (Eco-Physics System, Zürich, Switzerland). Arterial methemoglobin concentrations were measured daily.

Study Design

When a patient was deemed eligible for NO inhalation, baseline data were collected. Nitric oxide was then given to achieve a mean concentration of 10 ppm and all measurements were repeated 30 min later. A test result was considered positive when the P_{aO_2}/FiO_2 ratio, corrected for NO gas flow, increased by $>10\%$. In patients who responded, NO was continued. In those who did not respond, NO was discontinued.

To test the consistency of NO response, 22 patients, who still met the definition of ARDS, were studied again 48–72 h later. In patients who had continued to receive NO during the interim, NO inhalation was halted for a minimum of 2 h before data were collected and a second exposure to NO was studied. This sequence was repeated up to day 10. The maximum number of tests were four in any individual. Twenty-two patients had more than one test: nine had two, eight had three, and five had four tests at the defined time intervals. Ten patients had one NO test only, and they are only included for the analysis of association between baseline gas exchange values and the response to NO.

Data Analysis

The responses to the first and subsequent inhalations of NO were compared for blood gases, Q_s/Q_t, arterial oxygen content and transport, cardiac output, and pulmonary artery and systemic pressure changes. Values are expressed as means ± SD. To account for interdependence of observations made in the same patient, standard errors were estimated using methods for cluster sampling[13] as implemented on Epi Info 6.[14] Patients were assigned to different groups according to their response to NO inhalation, for P_{aO_2}/FiO_2: R = responder (patient with consistently positive tests); NR = nonresponder (patient with consistently negative tests), and IR = inconsistent response (patient with both types of response during repeated trials). Baseline variables analyzed for association with the response to NO included P_{aO_2}, P_{aO_2}/FiO_2, measured oxygen saturation (SaO_2) (ABL 520 system, Copenhagen, Denmark), P_{vO_2}, Q_s/Q_t, P_{aCO_2}, MPAP, and pulmonary vascular resistance.

These values were compared with values obtained during NO inhalation in individual patients and baseline observations of the responders were compared with baseline data of nonresponders using simple regression. A P value <0.05 was considered significant.

Results

Between October 1992 and June 1996, 32 consecutive patients with severe ARDS were prospectively included in this study. Fifteen of these were referred from other hospitals for ARDS management. The delay between onset of ARDS and first exposure to NO averaged 4.4 ± 5.6 days (range, 0–17 days).

Table 1. Demographic Data

Patient No.	Age (yr)/ Sex	Underlying Disease	APACHE II	Murray's Lung Injury Score	PEEP (cmH_2O) First NO Test	Pa_{O_2}/FI_{O_2} (mmHg)	Outcome
1	23/M	Multiple trauma (T)	28	3.25	10	76	S
2	27/F	Multiple trauma	30	3.75	12	64	D
3	47/F	Multiple trauma	36	3	8	122	S
4	23/F	Multiple trauma (T)	25	3.5	11	53	S
5	30/F	Multiple trauma	22	3.25	10	74	S
6	25/M	Multiple trauma	22	3.3	13	58	S
7	24/F	Multiple trauma (T)	33	3.75	12	61	S
8	51/M	Multiple trauma	37	3.5	10	50	D
9	25/F	Multiple trauma (T)	35	3.75	15	97	S
10	69/F	Multiple trauma (T)	40	3.75	13	92	D
11	50/M	Multiple trauma (T)	25	3.5	10	76	S
12	30/M	Multiple trauma	36	2.75	5	138	D
13	25/F	Multiple trauma	31	3.5	10	109	S
14	24/M	Multiple trauma (T)	36	3.75	16	85	D
15	63/M	Septic shock (T)	39	3.25	10	53	D
16	58/M	Septic shock	47	3.25	11	51	D
17	61/M	Septic shock (T)	33	3.5	10	59	D
18	66/M	Septic shock (T)	30	3.5	12	49	D
19	54/M	Septic shock	33	3.25	6	95	D
20	29/F	Septic shock	28	3.75	15	85	S
21	51/F	Pneumonia	32	3.75	14	60	S
22	46/F	Pneumonia	29	3	5	83	D
23	13/M	Pneumonia (T)	34	3.5	12	46	S
24	33/M	Pneumonia (T)	31	3.5	9	65	S
25	23/F	Pneumonia	24	3.25	7	55	S
26	78/M	Pneumonia	34	3.5	12	61	D
27	29/F	Aspiration pneumonia	30	3	5	45	D
28	41/M	Aspiration pneumonia (T)	31	3	5	54	S
29	60/M	Peritonitis (T)	27	3.25	10	55	S
30	47/F	Peritonitis	32	3.5	10	77	D
31	46/F	Hemorrhagic shock	42	3.5	13	34	D
32	65/F	Hemorrhagic shock (T)	33	2.75	5	110	S
Mean ± SD	42 ± 17		32 ± 6	3.4 ± 0.3	10 ± 3	71 ± 25	Mortality 15/32 (47%)

T = transfer from other hospital; S = survivor; D = died.

Seventy-two NO inhalation tests were performed, and pulmonary hemodynamics and cardiac output were obtained for 66 of these. Ten patients were tested only once, because they died of multiple-organ failure (n = 8) or were transferred to another intensive care unit (n = 2) within 48 h after the first NO trial. The overall mean FIO_2 for all tests was 0.78, and the average FIO_2 at initial tests was 0.87 (median, 0.97; range, 0.55–1.0).

Table 1 shows patient age, diagnosis, APACHE II and lung injury scores, baseline P_{aO_2}/FIO_2, and outcome.

Consistency of Nitric Oxide Effects on Arterial Oxygen Pressure

Table 2 shows data concerning the repeated effects of NO on oxygenation. Of the 22 patients with more than one test, 3 (14%) did not have an increase in P_{aO_2} during NO inhalation; *i.e.*, they had consistently "negative" test results. Seven other patients (32%) had inconsistent responses during 21 observation; *i.e.*, during their clinical course, arterial oxygenation increased on some days but not on others: 52% of their test results were "positive" and 48% were negative. In the last 12 patients (54%), P_{aO_2} increased consistently by more than 10% in the 33 tests performed (fig. 1). The P_{vO_2}, oxygen saturation, arterial oxygen content, and oxygen transport increased significantly and Qs/Qt decreased during NO inhalation in positive test results for P_{aO_2} (table 3).

Considering each subsequent NO trial separately for all patients, we observed a constant percentage of positive and negative responses for P_{aO_2} to NO, at 69% *ver-*

Table 2. Individual Pa_{O_2}/FI_{O_2} (mmHg) Response to NO on Different Days

Patient No.	Test 1			Test 2			Test 3			Test 4			Duration of Investigation (days)
	NO off	NO on	% Change	NO off	NO on	% Change	NO off	NO on	% Change	NO off	NO on	% Change	
5	55	78	42 POS	66	77	16 POS	152	152	0 NEG	129	155	20 POS	7
6	50	47	−7 NEG	44	53	21 POS	80	93	16 POS	206	213	3 NEG	7
13	54	54	0 NEG	60	54	−11 NEG	46	49	6 NEG	67	63	−6 NEG	10
14	65	75	16 POS	52	60	16 POS	35	65	89 POS	85	123	44 POS	7
28	59	71	20 POS	75	85	13 POS	108	129	19 POS	104	143	38 POS	7
4	61	68	12 POS	71	70	−1 NEG	96	198	105 POS				7
11	98	150	54 POS	99	100	1 NEG	128	135	5 NEG				5
12	53	68	27 POS	69	86	25 POS	89	117	32 POS				7
15	110	138	25 POS	162	122	−25 NEG	149	99	−33 NEG				6
17	123	138	12 POS	130	162	24 POS	145	208	44 POS				6
23	59	65	12 POS	62	78	27 POS	93	119	27 POS				6
26	49	66	35 POS	43	51	19 POS	44	50	14 POS				7
29	46	61	32 POS	100	151	51 POS	54	94	74 POS				6
3	76	93	23 POS	111	159	43 POS							4
9	76	80	6 NEG	91	97	6 NEG							3
10	60	70	17 POS	50	125	151 POS							4
16	56	66	19 POS	41	61	50 POS							4
22	83	128	54 POS	72	89	23 POS							4
25	93	73	−22 NEG	60	75	25 POS							3
30	95	83	−13 NEG	61	61	0 NEG							4
31	85	91	7 NEG	91	103	13 POS							4
32	37	44	20 POS	43	48	14 POS							4
1	35	41	20 POS										1
2	53	61	14 POS										1
7	45	60	33 POS										1
8	64	78	22 POS										1
18	78	78	1 NEG										1
19	138	141	2 NEG										1
20	74	87	18 POS										1
21	109	104	−5 NEG										1
24	61	63	4 NEG										1
27	51	66	29 POS										1
Mean	70	81	17	75	89	23	94	116	31	118	139	20	
SD	25	29	17	31	35	34	41	50	39	54	54	21	

POS: >10% increase; NEG <10% increase.

sus 31%, 73% *versus* 27%, and 69% *versus* 31% at the first, second, and third exposures, respectively. The analysis over time of individual responses for P_{aO_2} to NO inhalation showed that 81% (13 of 16) of the positive responders at the first trial were consistently positive at the second trial and 88% (seven of eight) continued to have positive responses at the third trial. Among negative responders at first exposure to NO, only 50% (three of six) were consistently negative again at the second trial, and only one patient remained a nonresponder at the third trial. Fifty-seven percent (four of seven) of inconsistent responders showed a positive response at first exposure, and 75% (three of four) of these positive responders turned to negative responses at the second trial, whereas the nonresponders at the initial trial subsequently all became responders.

Relation between Baseline Conditions and Response

Considering all trials of NO administration (n = 72), the baseline P_{aO_2}/FIO_2 ratio and P_{vO_2} were lower with positive than in negative test results: P_{aO_2}/FIO_2 was 74 ± 30 mmHg compared with 97 ± 42 mmHg ($P < 0.01$; fig. 2), P_{vO_2} was 34 ± 5 mmHg compared with 39 ± 7 mmHg ($P < 0.05$), and oxygen saturation was 79 ± 12% compared with 86 ± 8% ($P < 0.01$). In addition,

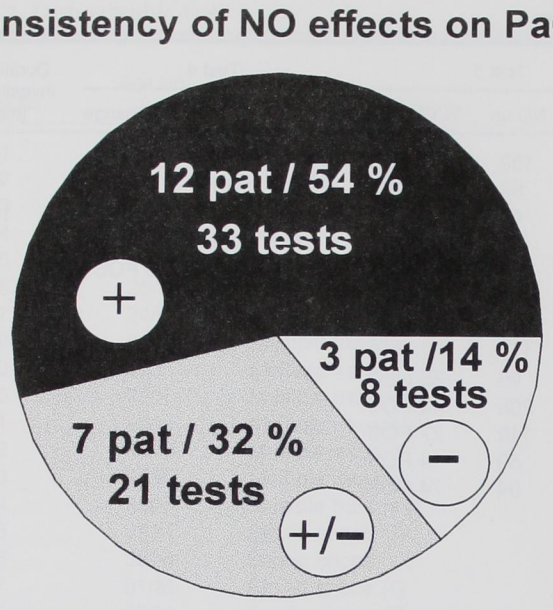

Fig. 1. Distribution of the effects of nitric oxide inhalation on arterial oxygen tension (P_{aO_2}). Consistently positive tests (+) are defined as an increase >10% in P_{aO_2} from baseline in repeated tests (*blackened square*); consistently negative tests (−) indicate lesser or no improvement (*square*). Patients with inconsistent responses (*shaded square*, ±) had variably positive or negative test results. The number of patients (%) and the number of tests performed for each group of patients are shown inside the pieces of the pie.

baseline Q_s/Q_t was higher in patients with positive test results, at 54 ± 14 compared with 42 ± 11% ($P < 0.05$).

Hemodynamics

Mean pulmonary artery pressure and pulmonary vascular resistance decreased significantly during NO inhalation for the ARDS group as a whole (from 34 ± 10 mmHg to 29 ± 9 mmHg; $P < 0.001$, table 3), but only 6 of 18 (33%) consistently had such decreases by more than 10% when tested on different days. Concordance of a decrease in MPAP with an increase in P_{aO_2} was observed in 21 of 32 patients and in 43 of the 66 tests, but no significant correlation (by linear regression analysis) between changes in P_{aO_2} and in MPAP nor pulmonary vascular resistance was noted (r = −0.15 and −0.05, respectively).

The hospital mortality rate for our patients with ARDS was 47% (15 of 32), and there was no significant difference in outcome between responders and nonresponders to NO inhalation for P_{aO_2}.

Methemoglobin concentration never exceeded 3 μM; that is, it remained <1% of the respective hemoglobin values. The concentration of NO_2 measured in the endotracheal tube and in the expiratory limb of the respiratory circuit never exceeded 1 ppm.

Discussion

This investigation shows that only 54% of patients with severe ARDS have a clinically significant and consistent improvement in arterial oxygenation during NO inhalation. Thirty-two percent of patients showed an inconsistent effect, and in 14% no change or a deterioration of P_{aO_2} on different days of their clinical course was seen. Similarly, NO caused a consistent decrease in pulmonary arterial pressure in only one third of the patients studied. Baseline P_{aO_2}/FiO_2 and P_{vO_2} were significantly lower, whereas Q_s/Q_t was higher in patients who increased arterial oxygenation with NO. Some patients maintained positive responses even in the later phases, when FiO_2 could be decreased to 0.5, whereas in others no effect of NO inhalation was observed even in the acute phase of the disease (*i.e.*, during the first 3 days). Finally, the mortality rate seems not to be related to the response to NO inhalation.

These results are consistent with data from patients with ARDS described in a preliminary report of a multicenter study[15] and observations in other pulmonary diseases.[8,16] Our findings contradict those of a previous investigation that observed a consistently positive response in ARDS.[4] More recently, Rossaint *et al.*[6] and Kraff *et al.*[8] reported a significant increase in P_{aO_2} during NO inhalation in 40–80% of patients with severe or septic ARDS, with the percentage of positive effects depending on the criteria chosen to define significant changes. Looking at each trial separately in the present study, a positive response in P_{aO_2} occurred in 70%, and this percentage remains constant for repeated trials. The inconsistent effect of NO on pulmonary hemodynamics observed in our patients with severe ARDS also contrasts with the consistently successful NO application described in non-ARDS types of pulmonary hypertension, such as persistent pulmonary hypertension in neonates, in children with congenital heart disease, and in patients after mitral valve replacement.[17–20]

The inconsistent or absent responses to NO inhalation observed in many of our patients likely reflect the complexity of pulmonary vascular involvement in this disease. We could speculate that in responder patients a reduction of the endogenous endothelial release of NO could have induced a predominance of hypoxic vaso-

Table 3. Effects of NO Inhalation on Gas Exchange and on Pulmonary Hemodynamics

	All Tests		"Positive Tests" for Pa_{O_2} (n = 50)		"Negative Tests" (n = 22)	
	Without NO	NO Inhalation	Without NO	NO Inhalation	Without NO	NO Inhalation
Pa_{O_2} (mmHg)	57 ± 14	68 ± 19*	54 ± 13	70 ± 21*	64 ± 13‡	61 ± 12
Pa_{O_2}/FI_{O_2} (mmHg)	79 ± 35	94 ± 40*	74 ± 30	95 ± 41*	97 ± 42‡	92 ± 40
Sa_{O_2}	81 ± 11	87 ± 9*	79 ± 12	87 ± 9*	86 ± 8‡	85 ± 7
Q_s/Q_t (%)	52 ± 17	45 ± 15*	54 ± 14	44 ± 12*	42 ± 11§	44 ± 16
Pa_{CO_2} (mmHg)	66 ± 29	64 ± 27	64 ± 25	63 ± 23	69 ± 40	68 ± 36
*p*H	7.30 ± 0.08	7.30 ± 0.08	7.30 ± 0.08	7.30 ± 0.08	7.28 ± 0.09	7.29 ± 0.09
MPAP (mmHg)	34 ± 10	29 ± 9*				
PVR (dyne·s·cm^{-5})	260 ± 178	199 ± 134*				
MAP (mmHg)	72 ± 14	72 ± 14				
CO (L·min^{-1})	7.7 ± 2.7	7.7 ± 2.8				
Ca_{O_2} (ml/100 ml)	10.9 ± 2.5	11.6 ± 2.5†				
D_{O_2} (ml/mn)	901 ± 309	948 ± 336*				

Data are expressed as mean ± SD.

Ca_{O_2} = arterial oxygen content; CO = cardiac output; D_{O_2} = oxygen transport; FI_{O_2} = inspired oxygen fraction; MAP = mean systemic arterial pressure; MPAP = mean pulmonary artery pressure; Pa_{CO_2} = arterial CO_2 tension; Pa_{O_2} = arterial oxygen tension; PVR = pulmonary vascular resistances; Q_s/Q_t = intrapulmonary shunt; Sa_{O_2} = arterial oxygen saturation.

* $P < 0.01$ *versus* Without NO.

† $P < 0.05$ *versus* Without NO.

‡ $P < 0.01$ *versus* baseline values of "positive tests."

§ $P < 0.01$ *versus* baseline values of "positive tests."

constriction, thus increasing pulmonary vascular resistance. Previous studies showed that NO is continuously released to regulate pulmonary vascular tone[21,22] and that endothelium-dependent relaxation is impaired in animals exposed to chronic alveolar hypoxia.[23]

Indeed, NO only partially reverses hypoxic vasoconstriction in anesthetized dogs.[24,25] This does not necessarily imply that hypoxic vasoconstriction is counterregulated by NO. Other factors than NO are involved in the development of pulmonary hypertension and increased Q_s/Q_t in ARDS. Mediators such as endothelin, prostaglandin $F_2\alpha$, cytokines, and free radicals enhance hypoxic pulmonary vasoconstriction in ARDS, and NO inhalation seems able to reduce the release of oxygen-reactive species by activated leukocytes and cytokines,[26] accounting for the discrepancy between the effect of NO on P_{aO_2} and MPAP. Our results are consistent with a multifactorial origin of pulmonary hypertension in ARDS involving factors not reversible by NO-induced dilation.[16] Previous reports have noted that a lower P_{vO_2} is associated with a higher degree of hypoxic vasoconstriction.[27] In the present study, lower baseline P_{aO_2} and P_{vO_2} values were observed in patients showing positive effects of NO on P_{aO_2}.

Basal rates of NO production and the degree of its reduction may be different in individual patients with ARDS. In addition, intrapulmonary diffusion of NO to lesser ventilated regions could reverse hypoxic vasoconstriction in these areas, thereby increasing intrapulmonary shunt.[28] We could speculate that, in this case, the effect of NO would be comparable to an intravenous infusion of a pulmonary vasodilator, inducing a decrease in MPAP and arterial oxygenation.[29]

Barberà *et al.*[9] reported no improvement in arterial oxygenation with NO in patients with chronic obstructive pulmonary disease in whom hypoxemia is mainly due to pulmonary ventilation-perfusion mismatching and much less to Q_s/Q_t. In our study, patients with positive responses had significantly higher baseline Q_s/Q_t values, supporting the findings by Barberà *et al.*[9]; that is, patients most likely to benefit from NO inhalation seem to be those in whom increased shunt is the principal determinant of hypoxemia. The possibility that NO could increase venous admixture *via* systemic recirculation cannot be excluded. In the lungs, S-nitrosylation of hemoglobin occurs and NO can enter the systemic circulation by binding to hemoglobin, forming S-nitrohemoglobin, or by binding to proteins containing thiol groups such as albumin. These compounds constitute a NO reservoir, allowing delayed release and possi-

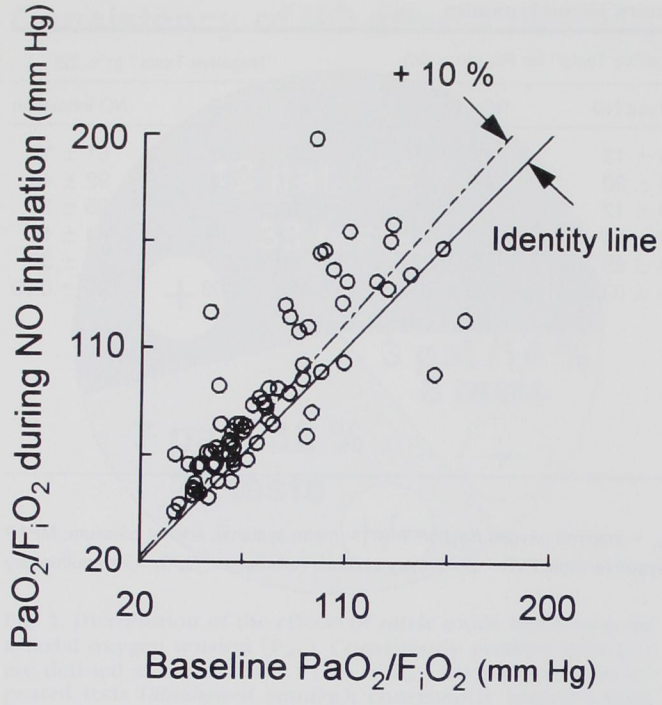

Fig. 2. Relation between individual baseline ratio of arterial oxygen tension to inspired fraction of oxgyen (n = 72 tests) recorded without nitric oxide (NO) and the corresponding values obtained during NO inhalation in 32 patients with severe acute respiratory distress syndrome. The continuous line crossing the panel represents identity between measurements obtained with and without NO, and the dotted line corresponds to +10% difference from the identity line.

ble recirculation in the pulmonary vascular tree.[30-32] No systemic hemodynamic effects are observed despite this perhaps because of a more marked dependence of the pulmonary circulation on NO to regulate its vascular tone compared with other vascular beds.[33]

The presence (or absence) of a positive effect of NO on gas exchange does not seem to be related to outcome in our patient series. In addition, the clinical effect of the changes in arterial oxygenation observed during NO inhalation remains to be shown. It is recognized that ARDS patients rarely die from hypoxia,[34] and the relevance of a decrease of 5-7 mmHg of MPAP in absence of right ventricular failure is not clear. As suggested by others,[15] the limit for clinical significance could be set at 20% for P_{aO_2}. In this case, the proportion of consistently positive responders would decrease to 23% in our series. The interpretation of the effect of NO can also be influenced by spontaneous variability of P_{aO_2} in this type of patient. In the present study, this problem was minimized by choosing a 10% cutoff to define an increase.

Our data suggest that even patients who are nonresponders one day may become responders the next day. If the initial NO test does not show an effect, it does not imply that it is not worth testing again, particularly when hypoxemia persists.

It should be emphasized that the slow-response chemiluminescence analyzer used allowed us to estimate mean NO concentration only, but not to determine peak and minimal levels or the importance of changes during the respiratory cycle.[35] Newer systems of delivery result in improved stability of NO concentration during inspiration. Nitric oxide inhalation withdrawal should be done progressively to avoid an important decrease in P_{aO_2}, an increase in MPAP, or both.

In conclusion, NO inhalation produces a consistently beneficial effect on P_{aO_2} in only 50-60% of patients with severe ARDS. Our data suggest that the decision to start this therapy should be made on a clinical basis and the response assessed repeatedly. Clinicians should be aware that NO inhalation is of uncertain benefit in ARDS; there is no evidence at present for lower mortality and morbidity rates. Because its effects may vary during the clinical course, blood gas changes should be checked frequently. A low baseline P_{aO_2}/FiO_2 value and high venous admixture are associated with a more favorable reaction to NO inhalation.

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