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Does Norepinephrine Modify the Effects of Inhaled Nitric Oxide in Septic Patients with Acute Respiratory Distress Syndrome?

Laurent Papazian, M.D., Ph.D.,* Fabienne Bregeon, M.D.,* Françoise Gaillat, M.D.,* Elsa Kaphan, M.D.,† Xavier Thirion, M.D.,† Pierre Saux, M.D.,* Monique Badier, M.D.,‡ Régine Gregoire, M.D.,† François Guin, M.D.,§ Yves Jammes, M.D.,|| Jean-Pierre Auffray, M.D.§

Background: Hypoxia-related pulmonary vasoconstriction enhanced by norepinephrine could be deleterious in patients with the acute respiratory distress syndrome (ARDS) and sepsis. A prospective study compared the effects of nitric oxide on cardiorespiratory parameters, including the evaluation of right ventricular function in patients with ARDS and sepsis who were receiving or not receiving norepinephrine.

Methods: During a 15-month period, 27 patients with ARDS and sepsis were prospectively investigated (group 1: 15 patients not receiving norepinephrine; group 2: 12 patients receiving norepinephrine). Right ventricular ejection fraction was measured by thermodilution. After baseline measurements, nitric oxide was administered at increasing inspiratory concentrations.

Results: The ratio of oxygen tension in arterial blood to the fractional concentration of oxygen in inspired gas increased in the two groups. After logarithmic transformation of the data, an analysis of variance was performed that did not show any difference between the two groups. A dose-dependent decrease in mean pulmonary arterial pressure was observed in the two groups. This decrease and the increase in right ventricular ejection fraction induced by inhaled nitric oxide were more marked when patients received norepinephrine ($P < 0.0001$).

Conclusion: Norepinephrine did not influence the beneficial effects of inhaled nitric oxide administered to patients with

ARDS and sepsis on oxygenation. (Key words: Mechanical ventilation; sepsis; vasoconstriction.)

PREVIOUS experimental and clinical studies have established that inhaled nitric oxide (NO) is a selective pulmonary vasodilator in pulmonary hypertension.¹ It has been shown to be beneficial in hypoxemic patients with acute respiratory distress syndrome (ARDS) by reducing pulmonary arterial pressure and improving arterial oxygenation.² Inhaled NO, like endogenous NO, relaxes the smooth muscles in arteries and veins by activating soluble guanylate cyclase and increasing cyclic guanosine 3'-5'-monophosphate. Increased pulmonary artery pressure in ARDS, which results from the combined effects of hypoxic vasoconstriction, the release of mediators, and microthrombosis of pulmonary circulation,^{3,4} represents an increase in the outflow pressure load on the right ventricle (RV). This can decrease right ventricle ejection fraction (RVEF) and increase RV volume,⁵ causing RV dysfunction.⁶

Administration of catecholamines increases systemic blood pressure and is used in the critical care setting to obtain adequate tissue perfusion pressure.⁷ Recently, the use of norepinephrine has been reconsidered in patients with septic shock and a persistent low systemic vascular resistance index.^{7,8} Acute dysfunction of the RV occurs frequently with septic shock and may be a major limiting factor of survival.^{9,10} The lack of deleterious effect of norepinephrine on RV function has been shown in patients in septic shock.¹¹ However, an elevated pulmonary vascular resistance index induced by norepinephrine could be deleterious in patients with ARDS who have hypoxia-related pulmonary vasoconstriction. Recent research has suggested that only 40% of ARDS patients with associated septic shock responded to inhaled NO.¹² This would appear to conflict with the results of a study by Mourgeon *et al.*,¹³ who showed that the increase in arterial oxygenation observed in ARDS

* Staff Intensivist, Service de Réanimation.

† Staff Epidemiologist, Service d'Information Médicale.

‡ Staff Physiologist, Laboratoire de Physiopathologie.

§ Professor, Service de Réanimation.

|| Professor, Laboratoire de Physiopathologie.

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Address reprint requests to Dr. Papazian: Réanimation Polyvalente, Hôpital Sainte-Marguerite, 13274 Marseille Cedex 9, France. Address electronic mail to: lpapazia@ap-hm.fr

patients was more marked when ARDS was associated with septic shock treated by norepinephrine. Therefore, our objectives in this prospective study were (1) to compare the dose-response profile of inhaled NO in ARDS patients with sepsis who were receiving norepinephrine with those of patients who were not receiving norepinephrine, and (2) to examine the effects of norepinephrine and inhaled NO on RV function.

Materials and Methods

Patients

During a 15-month period, 27 patients with sepsis (group 1: 15 patients not receiving norepinephrine; group 2: 12 patients receiving norepinephrine) with ARDS diagnosed on or after admission to the medicosurgical intensive care unit of Sainte-Marguerite University Hospital in Marseille, France, were prospectively investigated early in the course of their ARDS (<4 days) after written informed consent was obtained from each patient's next of kin. The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Marseille and supported by l'Assistance Publique Hôpitaux de Marseille and the French Ministry of Health (Projet Hospitalier de Recherche Clinique, 1994). We used the definition of ARDS recommended by the American-European Consensus Conference.¹⁴ Septic shock, sepsis, and the systemic inflammatory response syndrome were defined according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference.¹⁵ In the current study, patients with septic shock received norepinephrine when systolic arterial pressure was < 90–100 mmHg despite fluid expansion. The goal of fluid expansion when patients received norepinephrine was to obtain a pulmonary artery occlusion pressure between 12 and 18 mmHg at baseline (before administration of inhaled NO). Mechanical ventilation preceding the study had lasted 6 ± 4 days. All patients were sedated and paralyzed with a continuous infusion of sufentanil, midazolam, and vecuronium bromide, and the lungs were ventilated using conventional volume-controlled mechanical ventilation (Puritan Bennett 7200 series, Carlsbad, CA). For each patient, tidal volume, respiratory rate, and fractional concentration of oxygen in inspired gas ($F_{I_{O_2}}$) were adjusted to maintain the minute ventilation constant throughout the study. To detect changes in $F_{I_{O_2}}$ induced by inhalation of NO, $F_{I_{O_2}}$ was monitored continuously using an oxygen analyzer

(NOX 4000; Sérès, Aix-en-Provence, France). All patients had a radial artery catheter (Seldicath, Plastimed, Saint Leu la Forêt, France) and a pulmonary artery catheter equipped with a fast-response thermistor (model 93 A-434H-7.5F; Baxter Healthcare Corp., Irvine, CA) that was inserted percutaneously through the right jugular or the left axillary vein and positioned so that the distal port was in the pulmonary artery and the proximal port was in the right atrium, just above the tricuspid valve.

Measurements

Systolic arterial pressure, diastolic arterial pressure, systolic pulmonary arterial pressure, diastolic pulmonary arterial pressure, pulmonary artery occlusion pressure, and right atrial pressure were measured at end-expiration. The supine zero reference level was the mid-axilla. Right ventricular end-diastolic and end-systolic volume indices were calculated from the RVEF and the stroke volume. Right ventricular ejection fraction and cardiac output were measured by thermodilution using three to five boluses of 10-ml glucose solution between 6°C and 10°C, injected *via* a closed system (Co-set; Baxter Healthcare Corp.) at end-inspiration to improve the reproducibility of the measurement and also to minimize the influence of changes in intrathoracic pressure on RVEF. Injection temperature was measured by a thermistor located at the proximal port of the right atrial lumen. The mean of three measurements is reported. Right ventricular ejection fraction was evaluated with an algorithm based on an exponential curve analysis using a computer (Edwards Cardiac Output computer REF-1; Baxter Healthcare Corp.), as previously described and validated.¹⁶ The use of this algorithm reduces the variability of RVEF measurement to <8% in the absence of atrial fibrillation.¹⁷ Patients with cardiac dysrhythmias were not included. In all but two patients, two-dimensional echocardiography was performed at the bedside. Tricuspid regurgitation was ruled out using Doppler echocardiography. Cardiac index, oxygen delivery index, oxygen consumption index, oxygen extraction ratio, right and left ventricular stroke work indices, venous admixture (Q_{VA}/Q_T), systemic vascular resistances and pulmonary vascular resistances (PVRI) were calculated using standard formulas. Systemic and pulmonary arterial blood samples were withdrawn simultaneously within 3 min of the measurement of cardiac output. Arterial pH, oxygen tension in arterial blood ($P_{a_{O_2}}$), partial oxygen pressure in mixed venous blood, and carbon dioxide tension in arterial blood were measured using a blood gas analyzer (278-blood gas system; Ciba Corning,

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Medfield, MA). Hemoglobin concentration, arterial and mixed venous oxygen saturations, and methemoglobin levels were measured using a calibrated hemoximeter (270-CO-oxymeter; Ciba Corning). The following respiratory parameters were collected: exhaled tidal volume, peak inspiratory pressure, mean inspiratory pressure, and respiratory rate. Respiratory dynamic compliance was calculated as [peak inspiratory pressure – positive end-expiratory pressure]/tidal volume. Volume-controlled mechanical ventilation settings (except adjustments to maintain constant minute ventilation) and vasoactive agents and fluid administration rates remained constant throughout the study.

Nitric Oxide Administration

Nitric oxide was released from a tank containing NO in nitrogen at a concentration of 450 parts per million (ppm; Air Liquide, Meudon, France) and was delivered continuously within the inspiratory limb of the ventilator just after the Cascade II humidifier *via* a flowmeter delivering flows within a range of 1–999 ml/min (Air Liquide). Intratracheal gas was sampled using continuous aspiration through the endotracheal tube, permitting inspiratory, expiratory, and mean concentrations of NO and NO₂ continuous determination using a chemoluminescence apparatus (NOX 4000, Sères). The flowmeter was set to reach the desired inspiratory tracheal concentration.

Protocol

The study lasted approximately 6 h for each patient. Ventilator settings were not modified throughout the study period. The protocol consisted of seven consecutive phases for the first group (ARDS patients not receiving norepinephrine) and eight consecutive phases for the second group (ARDS patients receiving norepinephrine). For the second group, measurements were performed just before norepinephrine was introduced. Subsequent measurements were performed for the two groups. Baseline measurements were made after 1 h of steady-state conventional mechanical ventilation. After these baseline measurements were taken, NO was administered at increasing inspiratory concentrations of 0.5, 2, 5, 10, and 20 ppm. Each concentration was given for 30 min. In the two groups, a second baseline was obtained 30 min after NO was discontinued.

Statistical Methods

Data are expressed as mean \pm SD. Statistical calculations were performed using the SPSS 6.1 package (Chi-

cago, IL). Significant differences were analyzed by parametric (general factorial analysis of variance) or nonparametric (Friedman multiple comparison test) tests when required. The Mann-Whitney U test was used to assess differences between groups for a given concentration of inhaled NO. For intragroup changes, the Friedman test or Dunnett's *t* test for multiple comparisons were applied to compare the various time points with control values. When a correlation was calculated, Pearson's coefficient of correlations was used. When distribution was not normal, Spearman's rank correlation was used. A probability value < 0.05 indicated significance.

Results

Patients

Among the 27 patients enrolled in the study (15 men, 12 women; mean age, 51.1 ± 17.1 yr), 7 were admitted to the intensive care unit after multiple trauma, 6 were admitted with postoperative complications after major surgery, and 14 were admitted for an acute medical illness (table 1). On admission, the mean SAPS II score was 45.5 ± 18.8 and the mean APACHE III score was 81.2 ± 32.0 . Eight of the 15 patients included in group 1 had sepsis,¹⁵ whereas the remaining seven patients were considered as having a systemic inflammatory response syndrome¹⁵ at the time of enrollment in the study. A source of infection was found in all seven of these patients during the 48-h period after the study. All the patients included in group 2 had septic shock when they were enrolled in the study. The severity of ARDS was assessed by a lung injury score > 2.5 in all patients (mean, 3.1 ± 0.3). The mortality rate for the 27 patients was 52% (group 1, 40%; group 2, 67%; difference not significant). On inclusion, peak inspiratory airway pressure was 33.1 ± 6.0 cmH₂O and the mean airway pressure was 19.9 ± 4.0 cmH₂O for all 27 patients. Mean dynamic compliance was 25.0 ± 7.9 ml/cmH₂O. When blood gases at baseline were considered, the mean PaO₂/F_iO₂ was 103 ± 34 mmHg, and mean carbon dioxide tension in arterial blood was 42.4 ± 8.5 mmHg. The mean positive end-expiratory pressure was 11.3 ± 1.8 cmH₂O with a F_iO₂ > 0.70 in 16 of these 27 patients. Mean tidal volume was 511 ± 92 ml, and the inspiration:expiration ratio was $> 1:2$ in all but three patients. Only six patients included in this study received dobutamine ($7\text{--}17 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) throughout the study. The mean dose of norepinephrine required to maintain a systolic arterial pressure > 100 mmHg was 1.0 ± 0.7

Table 1. Characteristics of the Population

Patient Number	Principal Diagnosis	Cause of ARDS	Norepinephrine	Age (yr)/Sex	LIS	APACHE III	Outcome
1	Polytrauma	Lung contusion	No	50/M	3.0	62	S
2	Polytrauma	Lung contusion	No	49/F	3.5	83	S
3	Polytrauma	Lung contusion	No	44/F	3.2	51	S
4	Coma	Peritonitis	No	31/F	3.5	93	D
5	Lung transplantation	Cytomegalovirus pneumonia	No	25/M	3.2	81	D
6	Postoperative respiratory insufficiency	Cytomegalovirus pneumonia	No	74/F	3.2	106	D
7	Myocardial infarction	Herpesvirus pneumonia	No	67/F	3.5	56	D
8	Small bowel occlusion	Peritonitis	No	75/M	3.0	94	D
9	Coma	Aspiration pneumonia	No	23/F	3.0	71	S
10	Mediastinitis	Cytomegalovirus pneumonia	No	74/M	2.5	94	D
11	Postoperative respiratory insufficiency	Cytomegalovirus pneumonia	No	67/M	3.0	54	S
12	Polytrauma	Lung contusion	No	42/F	2.7	47	S
13	Polytrauma	Lung contusion	No	30/M	3.0	60	S
14	Polytrauma	Bacterial pneumonia	No	32/F	3.7	41	S
15	Community-acquired pneumonia	Community-acquired pneumonia	No	58/F	3.5	32	S
16	Small bowel occlusion	Peritonitis	Yes	72/M	2.7	67	S
17	Small bowel infarction	Peritonitis	Yes	66/M	3.0	88	D
18	Postoperative respiratory insufficiency	Bacterial pneumonia	Yes	58/M	3.5	69	D
19	Pancreatitis	Pancreatitis	Yes	70/F	2.7	120	D
20	Myocardial infarction	Bacterial pneumonia	Yes	61/M	3.2	187	D
21	Polytrauma	Bacterial pneumonia	Yes	56/M	3.7	83	D
22	Coma	Aspiration pneumonia	Yes	30/M	3.5	136	D
23	Pancreatitis	Pancreatitis	Yes	40/M	3.0	66	S
24	Community-acquired pneumonia	Community-acquired pneumonia	Yes	51/F	2.7	83	S
25	Coma	Bacterial pneumonia	Yes	58/M	3.0	92	D
26	Kidney transplantation	Tuberculosis	Yes	54/M	3.2	105	D
27	Coma	Aspiration pneumonia	Yes	23/F	3.2	71	S

S = survivor; D = died.

$\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($0.2\text{--}2.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). No modification of the infusion rate of dobutamine and norepinephrine and no fluid expansion were undertaken during the study period. Inspiratory airway pressures (peak inspiratory pressure, mean inspiratory pressure), tidal volume, and respiratory dynamic compliance were unchanged throughout the study (data not shown). The methemoglobin concentration when inhaling 20 ppm NO ($0.4\% \pm 0.3\%$) was not different from the initial baseline concentration ($0.2\% \pm 0.1\%$).

Effects of Norepinephrine on Hemodynamic and Gas Exchange

The administration of norepinephrine to the 12 patients included in group 2 (before the introduction of NO) did not induce any modification of gas exchange (table 2). From a hemodynamic perspective, norepinephrine induced a significant increase in mean arterial pressure, systemic vascular resistances, and mean pulmonary arterial pressure (MPAP). Nevertheless, RVEF

and RV volumes did not vary after norepinephrine was introduced.

Dose-Response Effects of Nitric Oxide on Gas Exchange According to the Presence or Absence of Norepinephrine (table 3)

Using a nonparametric test (Friedman test) made it possible to observe an increase in $\text{PaO}_2:\text{FiO}_2$ ratio for the two groups. No significant difference (using the Mann-Whitney U test) was observed between the two groups for each concentration of inhaled NO studied separately (fig. 1). Logarithmic transformation of the data led to normally distributed values of $\text{PaO}_2:\text{FiO}_2$. Therefore we performed a two-way analysis of variance that did not show any difference between the two groups.

No significant relation could be identified between NO-induced changes of the $\text{PaO}_2:\text{FiO}_2$ ratio and the baseline $\text{PaO}_2:\text{FiO}_2$ ratio.

A reduction in carbon dioxide tension in arterial blood

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Table 2. Hemodynamic and Respiratory Changes Induced by Norepinephrine

	Before NE	During NE infusion	ANOVA (P)
PaO ₂ /FiO ₂ (mmHg)	93 ± 35	99 ± 48	NS
MAP (mmHg)	52 ± 8	83 ± 10	<0.0001
MPAP (mmHg)	28 ± 7	33 ± 3	<0.01
PVRI (dyne · s · cm ⁻⁵ · m ²)	473 ± 196	492 ± 150	NS
PAOP (mmHg)	12 ± 5	16 ± 5	<0.05
RAP (mmHg)	9 ± 2	12 ± 3	NS
CI (L · min ⁻¹ · m ⁻²)	3.5 ± 1.1	3.7 ± 0.9	NS
RVEF (%)	32 ± 8	32 ± 5	NS
RVEDVI (ml · m ⁻²)	110 ± 31	111 ± 22	NS
RVESVI (ml · m ⁻²)	76 ± 26	77 ± 17	NS
SVRI (dyne · s · cm ⁻⁵ · m ²)	970 ± 228	1523 ± 474	<0.005
Q _{VA} /Q _T (%)	38 ± 12	43 ± 15	NS

MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistances indexed; PAOP = pulmonary artery occlusion pressure; RAP = right atrial pressure; CI = cardiac index; RVEF = right ventricular ejection fraction; RVEDVI = right ventricular end-diastolic volume index; RVESVI = right ventricular end-systolic volume index; SVRI = systemic vascular resistances indexed; Q_{VA}/Q_T = venous admixture; NS = not significant.

was observed for the two groups, whereas minute ventilation remained constant throughout the study.

Dose-Response Effects of Nitric Oxide on Circulatory Parameters According to the Presence or Absence of Norepinephrine (table 4)

A dose-dependent decrease of MPAP was observed in the two groups (fig. 2). This effect was more pronounced in patients receiving norepinephrine ($P < 0.0001$ by analysis of variance). At baseline (and for each dose of inhaled NO administered), MPAP was higher in the latter patients ($P < 0.0001$ by analysis of variance). Although RVEF was lower at baseline ($P < 0.0001$ by analysis of variance) in patients receiving norepinephrine, a greater increase in this parameter was observed when these patients received NO compared with the patients who did not receive norepinephrine ($P < 0.0001$ by analysis of variance). However, these changes in RVEF are probably of limited clinical value.

No significant relation could be identified between NO-induced changes of the PaO₂/FiO₂ ratio and the NO-induced variation in MPAP or PVRI. No significant relation was found between the maximal change of MPAP during NO inhalation and the baseline value of MPAP. A correlation was noted between the maximal decrease of MPAP and the maximal increase in RVEF ($r = 0.43$, $P < 0.05$).

Dose-Response Effects of Nitric Oxide on Derived Factors According to the Presence or Absence of Norepinephrine (table 5)

Although PVRI significantly decreased in the two groups, the decrease in PVRI induced by inhaled NO was more marked in patients who received norepinephrine than in patients who did not receive norepinephrine ($P < 0.0001$ by analysis of variance). The maximal change of PVRI during NO inhalation correlated with baseline PVRI value in both groups ($r = -0.80$, $P < 0.0001$ in group 1; $r = -0.79$, $P < 0.002$ in group 2). The reduction in RV stroke work index was more pronounced in group 2 than in group 1 ($P < 0.0001$ by analysis of variance).

Stroke volume, left ventricular stroke work index, oxygen consumption index, oxygen delivery index, and oxygen extraction ratio remained unchanged throughout the study period (data not shown).

Discussion

Acute respiratory distress syndrome is accompanied by acute pulmonary hypertension and, sometimes, acute RV dysfunction. Attempts to reduce pulmonary hypertension by administering an intravenous vasodilator are hazardous in this situation because systemic vasodilation can reduce systemic blood pressure and perfusion of the RV, leading to acute heart failure. Frostell *et al.*¹⁸ have shown that during hypoxia in healthy volunteers, the dilatory effect of 40 ppm inhaled NO on the pulmonary artery pressure was a rapid onset with complete reversal of pulmonary hypertension within the first minute of breathing NO. In their study, calculation of the stroke work index for the right and left ventricles showed the ability of inhaled NO to reduce RV work selectively during hypoxia. Improvement in the PaO₂ could be made from therapies aimed at reducing pulmonary blood flow in shunting areas while increasing the flow in normally ventilated areas. The maintenance of a gradient of vascular resistance between ventilated regions receiving NO and regions where perfusion is reduced by hypoxic vasoconstriction would be particularly advantageous during the early stages of ARDS. This would be particularly true in the presence of situations characterized by a reduced or abolished hypoxic vasoconstriction response, such as pulmonary infection, septicemia, direct lung trauma, and septic shock.¹⁹ In addition, endogenous release of NO can also modulate hypoxic vasoconstriction.²⁰ Marshall *et al.*²¹ have suggested that a posi-

Table 3. Dose-Response Effects of Nitric Oxide on Gas Exchange

	Baseline	NO 0.5 ppm	NO 2 ppm	NO 5 ppm	NO 10 ppm	NO 20 ppm	Baseline 2	P Value
Pa_{O_2}/Fi_{O_2} (mmHg)								
Not receiving NE (n = 15)	108 ± 34	118 ± 37	135 ± 57*	142 ± 72*	146 ± 80*	144 ± 87†	101 ± 33	0.02
Receiving NE (n = 12)	99 ± 48	122 ± 67	142 ± 86*	157 ± 107†	164 ± 119†	164 ± 125†	103 ± 48	0.00001
Sv_{O_2}								
Not receiving NE (n = 15)	74 ± 6	75 ± 7	77 ± 6	76 ± 8	76 ± 8	76 ± 7	74 ± 8	NS
Receiving NE (n = 12)	70 ± 10	68 ± 10	70 ± 11	73 ± 10	75 ± 8	72 ± 8	68 ± 8	0.02
Pa_{CO_2} (mmHg)								
Not receiving NE (n = 15)	43 ± 8	42 ± 9	41 ± 10	40 ± 7‡	40 ± 8‡	41 ± 9‡	42 ± 10	0.0001
Receiving NE (n = 12)	43 ± 9	43 ± 10	43 ± 11	42 ± 11‡	41 ± 10‡	41 ± 11‡	42 ± 9	0.0001
pH								
Not receiving NE (n = 15)	7.36 ± 0.07	7.37 ± 0.07	7.38 ± 0.08	7.39 ± 0.08‡	7.39 ± 0.07‡	7.38 ± 0.08‡	7.37 ± 0.08	0.0001
Receiving NE (n = 12)	7.32 ± 0.08	7.33 ± 0.08	7.33 ± 0.08	7.34 ± 0.08‡	7.34 ± 0.07‡	7.35 ± 0.08‡	7.34 ± 0.08	0.0001

Pa_{O_2}/Fi_{O_2} analyzed by Friedman test; other parameters analyzed by analysis of variance.

Comparisons versus baseline: * $P < 0.05$ by contrast analysis. † $P < 0.01$ by contrast analysis. ‡ $P < 0.01$ by Dunnett post hoc test.

tive oxygen content change is only seen with NO when some constriction in addition to hypoxic pulmonary vasoconstriction is present in small arteries or veins or both. Therefore, the gain in Pa_{O_2} observed with NO should be enhanced when combined with an infused vasoconstrictor. The vasoconstrictor used in combination with NO should mimic or enhance hypoxic vasoconstriction. This has been suggested by clinical studies in which inhaled NO was associated with a selective pulmonary vasoconstrictor, such as almitrine.^{22,23} Almitrine increased the respiratory response to inhaled NO,^{22,23} suggesting that enhancement of hypoxic pulmonary vasoconstriction in nonventilated lung areas could favor the diversion of blood flow toward better ventilated lung areas (where NO preferentially induced vasodilation). In nonventilated lung areas, mixed venous oxygen tension is primarily responsible for eliciting hypoxic pulmonary vasoconstriction.²⁴ When hypoxic pulmonary vasoconstriction is enhanced using almitrine, a decrease in intrapulmonary shunt occurs with an increase in oxygenation. In contrast, the decrease in hypoxic pulmonary vasoconstriction induced by extracorporeal blood flow in ARDS patients treated by venovenous extracorporeal lung assist results in an increase in intrapulmonary shunt.²⁵ The importance of the reinforcement of hypoxic pulmonary vasoconstriction in

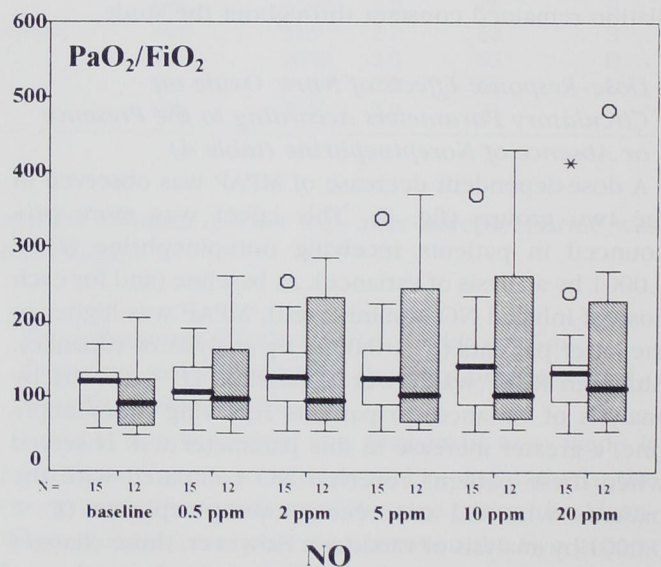


Fig. 1. Dose-response analysis of inhaled nitric oxide in patients with (group 2: 12 patients; open bars) and without (group 1: 15 patients; hatched bars) norepinephrine (NE). For the median ratio of oxygen pressure in arterial blood to the fractional concentration of oxygen in inspired gas (25, 50, and 75 percentiles), the largest and smallest values that are not outliers are reported. Outliers (cases with values between 1.5 and 3 box-lengths from the upper or lower edge of the box) are presented as open circles. Extremes (cases with values more than 3 box-lengths from the upper or lower edge of the box) are represented by a cross.

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Table 4. Dose-Response Effects of Nitric Oxide on Circulatory Parameters

	Baseline	NO 0.5 ppm	NO 2 ppm	NO 5 ppm	NO 10 ppm	NO 20 ppm	Baseline 2	ANOVA (P)
HR (beats · min ⁻¹)								
Not receiving NE (n = 15)	96 ± 16	97 ± 16	96 ± 18	94 ± 16	95 ± 16	94 ± 18	99 ± 18	NS
Receiving NE (n = 12)	105 ± 21	102 ± 20	99 ± 20	100 ± 19	99 ± 20	99 ± 20	106 ± 20	NS
MAP (mmHg)								
Not receiving NE (n = 15)	74 ± 14	72 ± 13	72 ± 13	70 ± 12	71 ± 11	73 ± 10	73 ± 14	NS
Receiving NE (n = 12)	83 ± 10	82 ± 12	79 ± 14	82 ± 13	82 ± 12	86 ± 10	80 ± 11	NS
MPAP (mmHg)								
Not receiving NE (n = 15)	27 ± 7	25 ± 7*	25 ± 8*	24 ± 7*	24 ± 7*	25 ± 7*	28 ± 8	0.0001
Receiving NE (n = 12)	33 ± 3	30 ± 4*	29 ± 3*	29 ± 4*	28 ± 4*	29 ± 4*	32 ± 4	0.0001
PAOP (mmHg)								
Not receiving NE (n = 15)	12 ± 5	11 ± 6	11 ± 5	11 ± 5	11 ± 5	11 ± 5	11 ± 5	NS
Receiving NE (n = 12)	16 ± 5	15 ± 5	15 ± 5	14 ± 4	14 ± 4	15 ± 5	15 ± 5	NS
RAP (mmHg)								
Not receiving NE (n = 15)	8 ± 5	7 ± 5	8 ± 5	7 ± 4	7 ± 4	7 ± 5	8 ± 5	NS
Receiving NE (n = 12)	12 ± 3	10 ± 3	10 ± 3	9 ± 2	9 ± 3	9 ± 3	9 ± 3	NS
CI (L · min ⁻¹ · m ⁻²)								
Not receiving NE (n = 15)	4.0 ± 1.7	4.1 ± 1.7	4.1 ± 1.7	4.0 ± 1.7	4.1 ± 1.7	4.2 ± 1.7	4.2 ± 1.8	NS
Receiving NE (n = 12)	3.7 ± 0.9	3.7 ± 0.9	3.8 ± 0.9	3.7 ± 0.9	3.7 ± 1.0	3.7 ± 1.0	3.7 ± 0.9	NS
RVEF (%)								
Not receiving NE (n = 15)	38 ± 8	40 ± 9	39 ± 9	41 ± 8*	40 ± 8*	41 ± 8*	38 ± 9	0.001
Receiving NE (n = 12)	32 ± 5	35 ± 7	36 ± 7*	36 ± 7*	35 ± 6*	36 ± 7*	33 ± 6	0.001

HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; RAP = right atrial pressure; CI = cardiac index; RVEF = right ventricular ejection fraction; NS = not significant.

* $P < 0.01$ by Dunnett post hoc test (versus baseline).

the improvement in oxygenation was supported by a recently published clinical study²⁶ that showed that using a nonselective vasoconstrictor (phenylephrine) in

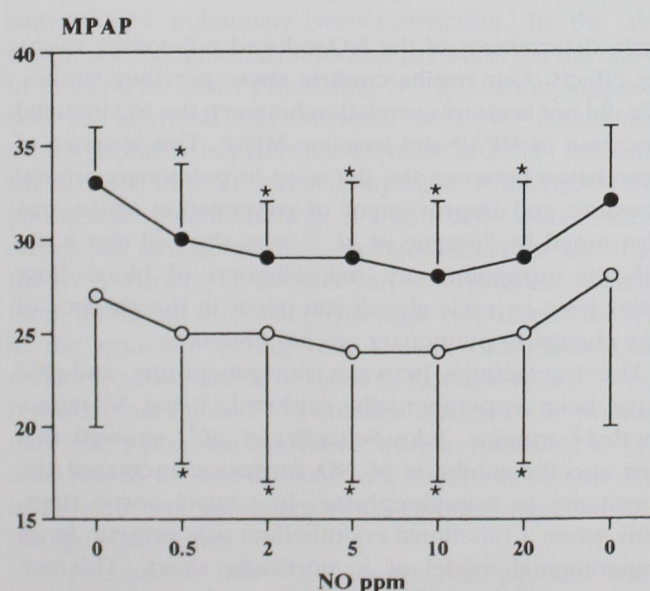


Fig. 2. The effect of nitric oxide on mean pulmonary arterial pressure (mean ± SD) in patients receiving norepinephrine (n = 12; closed symbols) and in those who did not receive norepinephrine (n = 15; open symbols).

combination with inhaled NO resulted in a significant increase in $\text{PaO}_2:\text{FiO}_2$ ratio when compared with NO alone, but only in patients considered as phenylephrine responders (increase of the $\text{PaO}_2:\text{FiO}_2$ of at least 10 mmHg). The results of this latter study²⁶ suggested that inhaled NO can reverse phenylephrine-induced vasoconstriction in well-ventilated areas. Our results showed that in septic patients who received norepinephrine, inhaled NO provided a significant increase in the $\text{PaO}_2:\text{FiO}_2$ ratio. However, this increase was comparable to those observed in patients who did not receive norepinephrine. Using a logistic regression model, Mantelkow *et al.*²⁷ showed in a retrospective analysis of 88 ARDS patients that vasopressor requirement did not affect the response to inhaled NO. After controlling for other variables, these authors also found that the absence of septic shock was a positive predictor of the response to inhaled NO. This was not the case in the current study, in which patients with septic shock were compared with such patients without circulatory shock. Studying responders to inhaled NO, Mourgeon *et al.*¹³ showed that although the dose response of MPAP and PVRI was not influenced by the presence of septic shock and the use of norepinephrine, the dose response of the $\text{PaO}_2:\text{FiO}_2$ ratio was modified by septic shock and norepinephrine. They ob-

Table 5. Dose-Response Effects of Nitric Oxide on Derived Factors

	Baseline	NO 0.5 ppm	NO 2 ppm	NO 5 ppm	NO 10 ppm	NO 20 ppm	Baseline 2	ANOVA (P)
PVRI (dyne · s · cm ⁻⁵ · m ²)								
Not receiving NE (n = 15)	437 ± 211	397 ± 191*	394 ± 200*	388 ± 191*	387 ± 173*	394 ± 199*	458 ± 257	0.01
Receiving NE (n = 12)	492 ± 150	452 ± 165*	425 ± 115*	449 ± 119*	421 ± 76*	454 ± 147*	512 ± 138	0.01
RVEDVI (ml · m ⁻²)								
Not receiving NE (n = 15)	106 ± 28	106 ± 27	106 ± 29	102 ± 24	105 ± 26	107 ± 25	109 ± 26	NS
Receiving NE (n = 12)	111 ± 22	109 ± 24	109 ± 23	105 ± 22	110 ± 28	107 ± 26	112 ± 23	NS
RVESVI (ml · m ⁻²)								
Not receiving NE (n = 15)	66 ± 21	66 ± 21	66 ± 21	60 ± 16*	64 ± 19	64 ± 19	66 ± 22	0.05
Receiving NE (n = 12)	77 ± 17	72 ± 18	70 ± 17	68 ± 17*	72 ± 21	69 ± 20	76 ± 17	0.05
RVSWI (g · m · m ⁻²)								
Not receiving NE (n = 15)	15 ± 9	14 ± 8	13 ± 7	13 ± 7*	14 ± 7*	14 ± 8*	16 ± 11	0.0001
Receiving NE (n = 12)	19 ± 4	17 ± 6*	16 ± 5*	17 ± 7*	16 ± 5*	17 ± 6*	21 ± 5	0.0001
SVRI (dyne · s · cm ⁻⁵ · m ²)								
Not receiving NE (n = 15)	1,347 ± 366	1,271 ± 330	1,274 ± 350	1,269 ± 378	1,260 ± 346	1,274 ± 337	1,311 ± 412	NS
Receiving NE (n = 12)	1,523 ± 474	1,501 ± 434	1,403 ± 354	1,557 ± 475	1,570 ± 477	1,623 ± 442	1,477 ± 473	NS
Q _{VA} /Q _T (%)								
Not receiving NE (n = 15)	38 ± 10	37 ± 15	36 ± 16	35 ± 15	35 ± 16	35 ± 11	42 ± 13	0.05
Receiving NE (n = 12)	43 ± 15	35 ± 11	35 ± 12	35 ± 12	36 ± 16	34 ± 15	38 ± 12	0.05

PVRI = pulmonary vascular resistances indexed; RVEDVI = right ventricular end-diastolic volume index; RVESVI = right ventricular end-systolic volume index; RVSWI = right ventricular stroke work index; SVRI = systemic vascular resistances indexed; Q_{VA}/Q_T = venous admixture; NS = not significant.

* P < 0.01 by Dunnett post hoc test (versus baseline).

served a greater increase of the PaO₂:FiO₂ ratio and the absence of a plateau effect when patients received norepinephrine, whereas in patients without septic shock, they observed a plateau effect. When our results were expressed in terms of PaO₂:FiO₂ value, a difference between the two dose-response profiles was not apparent. In most patients, the inspiratory concentration of 5 ppm or less seems to be sufficient to improve oxygenation.^{23,28} Even if the NO delivery and measurement system used in the current study does not allow for a precise evaluation of inspired NO concentration, the trends observed in the dose-responses are valid.

Bigatello *et al.*²⁸ showed that breathing 2–4 ppm NO appeared as effective as 20 ppm NO at improving arterial oxygenation and decreasing MPAP. Puybasset *et al.*²⁹ showed that therapeutic concentrations of NO were in the range 0.1 to 2 ppm for patients who did not receive norepinephrine. Such low inspired NO doses should minimize any possible toxicity caused by NO inhalation. Bigatello *et al.*²⁸ and Puybasset *et al.*³⁰ found that the baseline level of pulmonary vascular resistance is the

main determinant of the NO-induced pulmonary vascular effects. Our results confirm these previous studies. We did not find any correlation between the NO-induced decrease in MPAP and baseline MPAP. This absence of correlation between the decrease in pulmonary arterial pressure and improvement of oxygenation status was also noted by Sprague *et al.*,²⁰ who showed that a significant intrapulmonary redistribution of blood flow away from hypoxic alveoli can occur in the absence of any change in pulmonary arterial pressure.

The interactions between norepinephrine and NO have been experimentally explored. Using N^G-monomethyl-L-arginine, Julou-Schaeffer *et al.*³¹ showed that this specific inhibitor of NO formation increased the sensitivity to norepinephrine, in control aortic rings, only when a functional endothelium was present. In an experimental model of hemorrhagic shock, Thiernemann *et al.*³² showed that the vascular hyporeactivity to vasoconstrictor agents (including norepinephrine) is mediated by NO, showing the potential negative effect of NO on norepinephrine-induced vasoconstriction. Fi-

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nally, in an experimental model, Pilati *et al.*³³ showed that the release of NO helps to maintain RV output during the release of norepinephrine induced by the massive sympathetic nervous system activity.

The RV dysfunction occurs even in the presence of a normal or high cardiac output, suggesting that the RV may be more susceptible than the left ventricle to the hemodynamic changes of sepsis. The inability of the RV to adequately increase its work output if its afterload is increased (such as by using a vasoconstrictor agent), as reflected by pulmonary arterial hypertension, is relevant in severe postseptic ARDS. Norepinephrine-induced pulmonary hypertension represents an additional increase in RV afterload that could precipitate RV failure. Martin *et al.*¹¹ showed that the administration of norepinephrine in patients with septic shock induced a significant increase in PVRI without a further deterioration of RV performance with no change in the RV end-diastolic ejection fraction. In the current study, the infusion of norepinephrine did not induce significant changes in RV end-diastolic ejection fraction in ARDS patients who received norepinephrine. This lack of deterioration of RV function could be explained by a positive inotropic effect of norepinephrine, the correction of systemic hypotension, which improved the right coronary perfusion pressure, or both.

The current study shows that the addition of inhaled NO to norepinephrine completely reverses norepinephrine-induced pulmonary vasoconstriction. In the absence of a change of intrathoracic pressure, the decrease in both MPAP and PVRI during NO inhalation suggests that RV afterload may decrease with NO inhalation, which probably explains the increase in RVEF. Because the increase in RVEF was accompanied by decreased RV end-systolic volume indices at a constant cardiac index during NO inhalation, these changes reflect the fact that the RV is working on another part of its pressure-volume loop, indicating a normal physiologic response of the RV in the presence of different loading conditions. Our results are comparable to those of Rossaint *et al.*,³⁴ who reported that inhaled NO induced a decrease in pulmonary artery pressure associated with an increased RVEF, a decreased RV end-diastolic index and a decreased RV end-systolic volume index while cardiac index did not change significantly.

In conclusion, this study shows that patients with ARDS and sepsis who require a vasoactive drug such as norepinephrine seem to respond to inhaled NO in a manner similar to those who do not require norepinephrine.

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