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Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome

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Abstract. *Objective:* To assess the additive effect of inhaled nitric oxide (NO) and intravenous almitrine bismesylate (ALM) on gas exchange.
Design: Prospective self-controlled study.
Setting: 3 medico-surgical intensive care units.
Patients: 17 patients with severe hypoxemia (PaO_2/FIO_2 ratio: 88±30 mmHg, venous admixture: 47±7%) and elevated mean pulmonary artery pressure (MPAP: 30±5 mmHg) due to adult respiratory distress syndrome (ARDS).
Interventions: 5 conditions were studied: 1) baseline, 2) 5 to 10 ppm of NO during 30 min, 3) discontinuation of NO during 30 min, 4) ALM infusion (0.5 mg/kg) during 30 min, 5) ALM infusion (0.5 mg/kg) during 30 min in combination with 5 to 10 ppm of NO.
Measurement and results: The PaO_2/FIO_2 ratio rose from 88±30 to 98±37 mmHg (NS) with NO alone, and from 92±25 to 130±56 mmHg ($p<0.01$) with NO+ALM ($p<0.05$ vs NO alone). Seven patients were considered as "NO-responders" (rise in PaO_2/FIO_2 ratio of 10 mmHg or more with NO); in this subgroup the PaO_2/FIO_2 ratio rose from 87±30 to 128±39 mmHg ($p<0.05$) with NO alone, and from 93±20 to 169±51 mmHg ($p<0.01$) with NO+ALM ($p<0.05$ versus NO alone). MPAP decreased from 30±5 to 26±5 mmHg ($p<0.01$) with NO alone, increased slightly from 28±5 to 31±5 mmHg (NS) with ALM alone and decreased to 27±5 mmHg ($p<0.05$) with NO+ALM.
Conclusions: NO+ALM had additive effects on gas exchange while decreasing MPAP in patients with ARDS. The effects of NO alone were small and non significant, except in a subgroup of 7 patients in whom the combination of both therapies had the more pronounced results.

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Key words: Inhaled nitric oxide – Almitrine bismesylate – Adult respiratory distress syndrome

Adult respiratory distress syndrome (ARDS) is a life-threatening pulmonary disease characterized by severe impairment in arterial oxygenation due to right-to-left intrapulmonary shunt. High levels of inspired oxygen fraction are used routinely to improve arterial oxygenation in ARDS patients but may damage the diseased lung [1]. Recently, inhaled nitric oxide (NO) has been shown to act as a selective pulmonary vasodilator and to improve arterial oxygenation in patients with ARDS [2]. Pulmonary vasodilation in well aerated regions of the lung is thought to be the main mechanism to explain the observed decrease in shunt. Also, intravenous almitrine bismesylate (ALM) may improve arterial oxygenation in patients with ARDS by enhancement of hypoxic pulmonary vasoconstriction, potentially acting preferentially in the non-ventilated regions of the lungs [3]. Both treatments may improve, by two different mechanisms, the matching between ventilation and perfusion of the lungs. Because ARDS combines well ventilated regions and non-ventilated regions [4], we hypothesized that the association of inhaled NO with intravenous ALM may improve arterial oxygenation to a greater extent than each drug alone. We therefore examined the effects on arterial oxygenation of NO alone, ALM alone and NO associated with ALM in 17 severely hypoxemic patients with ARDS.

Patients and methods

Patients

Fifteen men and two women, mean age 44±17 years, free of previous lung disease, severely hypoxemic and mechanically ventilated because of ARDS, were investigated (Table 1). ARDS was defined by the following criteria: presence of bilateral pulmonary infiltrates, absence of left heart

Table 1. Characteristics of the patients, diagnosis related to ARDS, severity of the underlying disease, of the ARDS and outcome

No.	Age/sex (years)	Diagnosis related to ARDS	SAPS	LIS	PaO_2 (mmHg)	FIO_2 (%)	PEEP (cmH_2O)	Outcome
1	49/F	Aspiration	12	3.00	45	100	8	Survived
2	71/M	Sepsis post CPB	14	2.75	71	100	5	Died
3	64/M	Bacterial pneumonia	6	3.25	53	100	10	Died
4	72/M	Abdominal sepsis	17	3.25	82	100	10	Died
5	28/M	Tuberculosis	17	3.25	91	100	8	Died
6	25/M	Viral pneumonia[a]	20	2.75	94	100	10	Died
7	44/M	Sepsis post neurosurgery	15	3.25	77	100	12	Died
8	19/M	Sepsis post neurosurgery	14	3.00	60	100	13	Died
9	52/M	Lung contusion	14	3.00	56	100	12	Died
10	43/M	Sepsis post neurosurgery	11	2.75	86	80	10	Survived
11	22/F	Aspiration	15	3.00	58	100	10	Survived
12	66/M	Sepsis post CPB	17	3.25	98	80	5	Died
13	29/M	Viral pneumonia[a]	12	3.00	98	100	9	Survived
14	53/M	Bacterial pneumonia	14	3.50	143	100	8	Died
15	35/M	Abdominal sepsis	15	3.66	93	100	13	Survived
16	52/M	Aspiration	14	3.00	135	100	10	Died
17	37/M	Aspiration	14	3.00	97	70	10	Survived
Mean	44		14	3.09	84	95	9	
SD	17		3	0.25	27	10	2	

Abbreviations: ARDS, adult respiratory distress syndrome; SAPS, simplified acute physiologic score [6]; LIS, lung injury score [5]; PEEP, positive end expiratory pressure; CPB, cardiopulmonary bypass; SD, standard deviation
[a] Immunosuppression

failure (cardiac index above 3 l/min/m^2) and a pulmonary wedge pressure lower than 18 mmHg, PaO_2/FIO_2 ratio lower than 150 mmHg, lung injury score above 2.5, as defined by Murray and coworkers [5]. ARDS was caused by aspiration ($n = 4$), viral or bacterial pneumonia ($n = 5$), lung contusion and multiple trauma ($n = 1$) or was associated with sepsis ($n = 7$). Severity of ARDS was assessed by a mean lung injury score of 3.0 ± 0.2, a mean PaO_2/FIO_2 ratio of 88 ± 30 mmHg, a mean venous admixture of $47 \pm 7\%$ and a mean pulmonary artery pressure of 30 ± 5 mmHg. In 10 of these 17 patients lung injury was associated with at least one other organ failure [6]. Severity of the underlying disease was assessed by a mean SAPS [7] of 14 ± 3 and 11 patients died while 6 were discharged alive from the ICU (Table 1).

NO inhalation

NO was released from a tank containing nitric oxide in nitrogen at a concentration (C_b) of 225 ppm (CFPO, Meudon la Fôret, France) and was delivered continuously at the Y piece (tip of the endotracheal tube) of the breathing circuit to ensure an homogeneous mixture of NO within the lung. Although NO was delivered continuously at the Y piece, it can be assumed that only NO delivered during the inspiratory time was part of the inspiratory gas mixture. For a given inspiratory time expressed as a fraction of total time (Ti%), NO concentration within the inspired gas mixture (C_I) is given by the formula:

$$C_I = [C_b \cdot \dot{V}_{NO} \cdot Ti\%] / \dot{V}_{tot}$$

where $\dot{V}_{NO}$ is the NO flow rate delivered continuously using a calibrated nitrogen flowmeter (Minibloc D56, CFPO, Meudon la Fôret, France) and V_{tot} the sum of ($\dot{V}_{NO} \cdot Ti\%$) and inspired minute ventilation delivered by the ventilator ($\dot{V}$). For instance: $C_b = 225$ ppm, $\dot{V}_{NO} = 1$ l/min, Ti% = 30% and $\dot{V} = 12$ l/min gives a $C_I = 5.6$ ppm. In two patients we were able to record the concentrations of NO and of the oxidative derivatives of NO (NO_x) including NO_2 and NO_3 under constant administration of 10 ppm NO, as calculated by the above formula. Gas was aspirated continuously via a thin catheter placed at the carina and analyzed using the chemiluminescence technique (NO_x 2000, Seres, Aix en Provence, France). Due to the site of sampling, the gas sampled was a mixture of the inspired gases after passage in the endotracheal tube and the trachea, and of the expired gases. Measurements were obtained after a period of stabilization and were found to be constant over a 1 h period. In the two patients the same measurements were repeated over several days and did not show any significant change. NO concentrations were always in the range 1.45–2 ppm and NO_x concentrations never exceeded 0.2 ppm. These measurements suggest that although it is difficult to determine the precise concentration of NO reaching the alveolar level, it probably never exceeded the calculated level. Moreover, in gas sampled at the carina, no toxic concentration of NO_x was found.

On the basis of previous studies [2, 8, 9] we choose here to study the effect of inhaling 5–10 ppm of NO. Methemoglobin saturation (OSM 3 hemoximeter, Copenhagen, Denmark) was measured before and at the end of the procedure in 5 patients.

Methods

All patients were sedated, paralyzed and had a pulmonary artery catheter and a radial or femoral artery catheter as routine management for pressure monitoring, cardiac output measurement and blood gas sampling.

Volume-controlled mechanical ventilation settings as well as vasopressor and fluid administration rates remained constant over the study. For each patient 5 conditions were obtained in the following sequences: i) baseline, ii) NO during 30 min, iii) discontinuation of NO to return to baseline conditions (30 min), iv) administration of ALM (Vectarion, Eutherapie, Neuilly, France) at 0.5 mg/kg during 30 min, v) administration of ALM at 0.5 mg/kg during 30 min in association with NO.

For each condition, mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary wedge pressure (PWP) and right atrial pressure (RAP) were measured at end expiration with disposable transducers. Cardiac output was measured in triplicate using the thermodilution technique and cardiac index (CI) was calculated. Arterial and mixed venous partial pressure of oxygen (PaO_2, $P\bar{v}O_2$), of carbon dioxide ($PaCO_2$, $P\bar{v}CO_2$) and arterial and mixed venous hemoglobin saturation in oxygen (SaO_2, $S\bar{v}O_2$) were measured (ABL 510, Radiometer, Copenhagen, Denmark). Venous admixture (Q_{VA}/Q_T) was derived from the standard shunt equation:

$$Q_{VA}/Q_T: 0.003(PAO_2 - PaO_2)/0.003(PaO_2 - P\bar{v}O_2) + CaO_2 - C\bar{v}O_2)$$

where CaO_2, $C\bar{v}O_2$ were oxygen content in arterial and mixed venous and PaO_2 the alveolar pressure in oxygen ($PAO_2 = (P_{bar} - P_{H_2O}) \cdot FIO_2 - PaCO_2/0.8$).

Table 2. Changes in gas exchange and hemodynamic variables among baseline, inhaled nitric oxide, discontinuation of nitric oxide, infusion of almitrine and association of inhaled nitric oxide with almitrine in 17 hypoxemic patients with ARDS

	Baseline	NO	Off NO	ALM	NO + ALM
Heart rate (beats/min)	118 ± 18	117 ± 20	118 ± 19	121 ± 17	119 ± 17
MAP (mmHg)	73 ± 15	71 ± 13	70 ± 14	72 ± 17	70 ± 13
PWP (mmHg)	10 ± 2	10 ± 2	10 ± 3	11 ± 3	10 ± 2
MPAP (mmHg)	30 ± 5	26 ± 5 ##	28 ± 5	31 ± 5**	27 ± 5*
RAP (mmHg)	9 ± 3	9 ± 2	9 ± 2	9 ± 3	9 ± 2
Cardiac index (l/min/m^2)	5.2 ± 1.4	5.2 ± 1.4	5.3 ± 1.7	5.3 ± 1.6	5.2 ± 1.3
pH	7.26 ± 0.14	7.28 ± 0.12	7.26 ± 0.12	7.26 ± 0.13	7.28 ± 0.11
$PaCO_2$ (mmHg)	65 ± 23	61 ± 19	66 ± 23	67 ± 23	62 ± 19
PaO_2/FIO_2 (mmHg)	88 ± 30	98 ± 37	92 ± 25	106 ± 43	130 ± 56 ## **
Q_{VA}/QT (%)	47 ± 7	43 ± 9	45 ± 7	43 ± 9	39 ± 10 #

Abbreviations: NO, inhaled nitric oxide; off NO, discontinuation of nitric oxide; ALM, intravenous almitrine bismesylate; NO + ALM, inhaled nitric oxide associated with intravenous almitrine bismesylate; MAP, mean arterial pressure; PWP, pulmonary wedge pressure; MPAP, mean pulmonary arterial pressure; RAP, right arterial pressure; Q_{VA}/QT, venous admixture; #, $p<0.05$ and ##, $p<0.01$ for the comparison with baseline values; *, $p<0.05$ for the comparison with values on ALM and **, $p<0.01$ for the comparison with values on NO using an analysis of variance for repeated measures (ANOVA) and a least-significant difference test if the F-ratio reached a $p<0.05$ level

Results are presented as mean ± SD. Comparisons between values obtained under the 5 conditions (Baseline, NO, off NO, ALM, NO + ALM) were made by analysis of variance for repeated measures (ANOVA) with a least-significant difference test if the F-ratio reached a $p<0.05$ level [10]. p-values are for two-tailed comparisons and were considered significant if <0.05. STATGRAPHICS software package (Statistical graphics corporation) was used for statistical analysis.

This investigation was approved by the Henri Mondor hospital Comité de Protection des Personnes dans la Recherche Biomédicale and informed consent was obtained from each patient's next of kin.

Results

Results are shown in Table 2. At baseline patients were severely hypoxemic and the concept of permissive hypercapnia was used with the aim of reducing the risk of barotrauma associated with mechanical ventilation [4].

The PaO_2/FIO_2 ratio increased from 88 ± 30 to 98 ± 37 mmHg (NS) with NO alone, from 92 ± 25 to 106 ± 43 mmHg (NS) with ALM alone, and from 92 ± 25 to 130 ± 56 mmHg ($p<0.01$) with NO + ALM. The PaO_2/FIO_2 ratio was significantly higher with NO + ALM than with NO alone (131 ± 58 versus 98 ± 37 mmHg, $p<0.05$). In a subgroup of 7 patients in which the PaO_2/FIO_2 ratio increased by at least 10 mmHg with NO (NO-responders), the additive effect of NO + ALM was amplified (Fig. 1): the PaO_2/FIO_2 ratio increased from 87 ± 30 to 128 ± 39 mmHg ($p<0.05$) with NO alone, from 93 ± 20 to 111 ± 43 mmHg (NS) with ALM alone and from 93 ± 20 to 169 ± 51 mmHg ($p<0.01$) with NO + ALM. Again the PaO_2/FIO_2 ratio with NO + ALM was significantly higher than with NO alone (169 ± 51 versus 128 ± 39 mmHg, $p<0.05$). By contrast, in the group of 10 patients in which the PaO_2/FIO_2 ratio did not increase (or by less than 10 mmHg) with NO (NO-non-responders), ALM with or without NO did not improve the PaO_2/FIO_2 ratio (Fig. 2).

In the whole group, venous admixture decreased from 47 ± 7 to 43 ± 9% (NS) with NO alone, from 45 ± 7 to 43 ± 9% (NS) with ALM alone and from 45 ± 7 to 39 ± 10% ($p<0.05$) with NO + ALM.

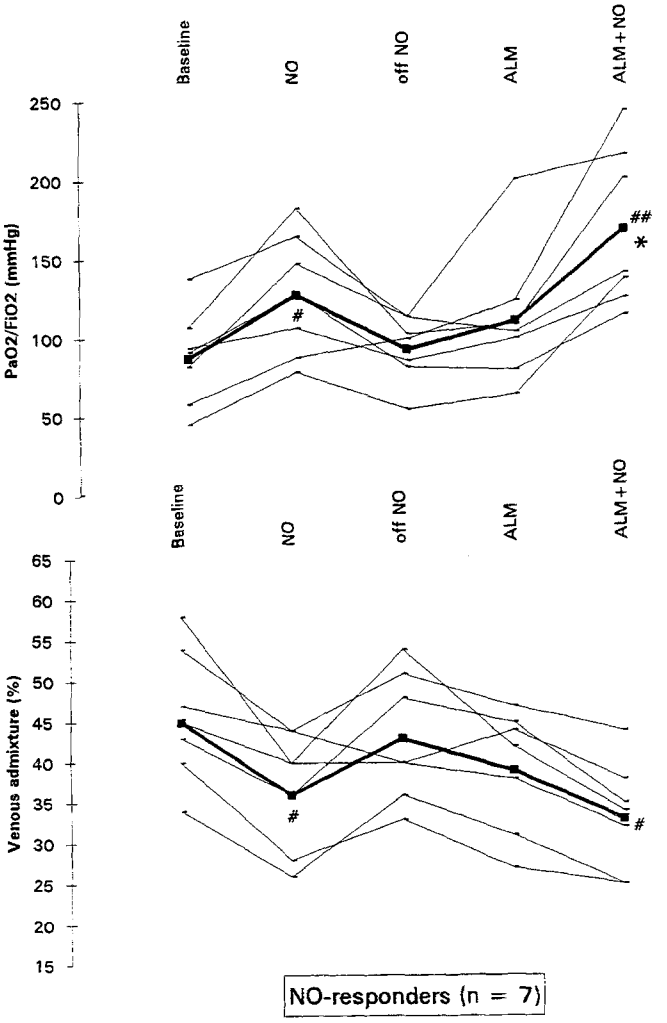

Fig. 1. Individual variations for the PaO_2/FIO_2 ratio and venous admixture between baseline, inhalation of nitric oxide (*NO*), discontinuation of nitric oxide (*off NO*), perfusion of almitrine bismesylate (*ALM*) and inhalation of nitric oxide associated with perfusion of almitrine bismesylate (*NO + ALM*) in 7 ARDS patients in which the PaO_2/FIO_2 ratio increased by at least 10 mmHg with NO (NO-responders). *Solid lines* and *squares* indicate variation of the means. #: $p<0.05$ and ##: $p<0.01$ versus baseline; *: $p<0.05$ versus NO alone

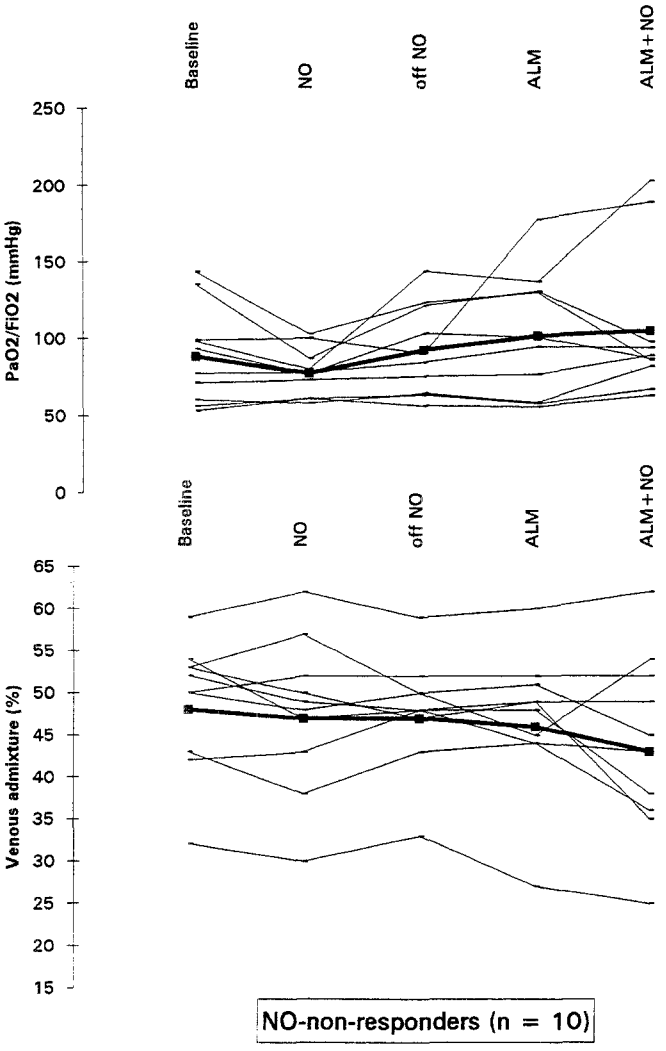

Fig. 2. Individual variations for the PaO_2/FIO_2 ratio and venous admixture between baseline, inhalation of nitric oxide (*NO*), discontinuation of nitric oxide (*off NO*), perfusion of almitrine bismesylate (*ALM*) and inhalation of nitric oxide associated with perfusion of almitrine bismesylate (*NO+ALM*) in 10 ARDS patients in which the PaO_2/FIO_2 ratio did not increase (or by less than 10 mmHg) with NO (NO-non-responders). *Solid lines* and *squares* indicate variation of the means. There is no statistical difference between each situation for the PaO_2/FIO_2 ratio and the venous admixture

MPAP decreased from 30±5 to 26±5 mmHg ($p < 0.01$) with NO alone, increased slightly from 28±5 to 31±5 mmHg (NS) with ALM alone and decreased to 27±5 mmHg ($p < 0.05$) when NO was added to ALM. No systemic effect (MAP, CI) of both drugs alone or in association was noted (Table 2). Methemoglobin levels measured in 5 patients did not increase during the study and remained below 2%.

Discussion

Our results demonstrate that: i) NO and almitrine bismesylate may have an additive effect, resulting here in a 41% increase in the PaO_2/FIO_2 ratio and a 10% decrease in venous admixture; ii) the effect of NO on gas exchange may be variable from patient to patient – 7 of our patients increased the PaO_2/FIO_2 ratio by at least 10 mmHg (NO-responders) while 10 did not (NO-non-responders); iii) the additive effect of NO+ALM was observed predominantly in NO responders with a 81% increase in the PaO_2/FIO_2 ratio and a 23% decrease in venous admixture; iv) the association of NO and ALM keeps the benefit of NO to reduce pulmonary hypertension.

Nitric oxide (NO), known as the endothelium-derived relaxing factor, is synthetized by the vascular endothelium to act as a local vasodilator [11]. The effect of NO on the pulmonary circulation has been studied extensively [12–16] and a beneficial effect on gas exchange of inhaled NO has been described recently in patients with hypoxemia resulting from ARDS [2]. Because the vasodilating effect of inhaled NO should be limited to the ventilated regions of the lungs, NO is thought to improve the perfusion of ventilated regions, thus reducing intrapulmonary shunting and improving arterial oxygenation [2].

In the present study, NO alone described a small and non-significant effect with an increase in the PaO_2/FIO_2 ratio (+10%) and a decrease in venous admixture (−8%) to a lesser extent than obtained by Rossaint and coworkers [2]. Differences between our results and those from the latter study [2] may be due in part to the patients studied. In the report of Rossaint and coworkers [2], ARDS was related to lung contusion and aspiration pneumonia and a high survival rate was reported (80%). ARDS was related to sepsis and pneumonia (Table 1) and a low survival rate (35%) was observed in our study, strongly suggesting that our patients were not comparable to those of Rossaint and coworkers [2]. Gas exchange was also not comparable because several patients were on extracorporeal oxygenation before NO was started in the study of Rossaint and coworkers [2]. Because of the potential toxicity of NO, we used lower doses of NO (5–10 ppm) than used by Rossaint and coworkers (18 and 36 ppm) [2]. However, in a recent preliminary study [9], low doses of NO (10 ppm) improved significantly the PaO_2/FIO_2 ratio in patients with ARDS. The optimal dose for NO inhalational therapy is not yet available but may be patient-related or severity of the ARDS-related. Most recent reports suggest, however, that doses lower than 1 ppm may be sufficient to increase PaO_2 [17]. Therefore, although the doses of inhaled NO may not have been optimal in some of our patients, it is unlikely that the dosage used here was insufficient for improving oxygenation.

Two patterns of response were observed when NO was added to the inhaled mixture: 7 of 17 patients (NO-responders) improved the PaO_2/FIO_2 ratio by a mean of 25%, while 10 of the 17 patients did not (NO-non-responders). Baseline values for the PaO_2/FIO_2 ratio (87±30 versus 88±31 mmHg), venous admixture (45±8 versus 48±7%), MPAP (29±7 versus 30±4 mmHg), pulmonary vascular resistance index (326±124 versus 323±133 dynes.s.cm^{-5}.m^{-2}) and lung injury score (3.0±0.2 versus 3.2±0.2) were comparable between the NO-responders and the NO-non-responders. $PaCO_2$ tended to be higher in NO-non-responders (71±25 versus

57 ± 18, $p = 0.28$ using a Wilcoxon rank-sum test for non paired data [18]) which could suggest a greater severity in term of lung damage in the non-responders group.

Almitrine bismesylate (ALM) is a peripheral chemoreceptor stimulant that has been reported to improve oxygenation in ventilated patients with ARDS [3]. It has been hypothesized that improvement in gas exchange resulted from enhancement of hypoxic pulmonary vasoconstriction. Because the vasoconstrictor effect of almitrine should be predominant in the non-ventilated regions of the lung, almitrine should improve the matching between ventilation and perfusion of the lung. In the present study, by contrast with the report of Reyes and coworkers [3] and despite the same dosage (0.5 mg/kg administered for 30 min), we did not observe a significant effect of ALM alone. However, in the latter report [3] patients were less severely hypoxemic (mean PaO_2: 78 ± 15 mmHg with a mean FIO_2: 0.61 ± 0.07, mean shunt: $29 \pm 9\%$) than our patients (Table 1) and it has been shown in experimental studies that ALM may not enhance hypoxic pulmonary vasoconstriction when vigorous hypoxic vasoconstriction is already present [19], as it was probably the case in our patients. Moreover, the pulmonary vascular effect of ALM may not work predominantly in the more hypoxic regions of the lung and the effect of ALM on gas exchange may be uncertain [20]. This may also explain that almitrine did not improve oxygenation during unilateral bacterial pneumonia [21].

Because ARDS combines well ventilated regions (in which NO may act as a vasodilator) and non-ventilated regions (in which almitrine may enhance hypoxic vasoconstriction), we hypothesized that the association of inhaled NO with intravenous almitrine may improve arterial oxygenation to a greater extent than each drug alone. In the present study, the PaO_2/FIO_2 ratio was significantly higher with NO+ALM than with NO alone, suggesting an additive effect of NO and almitrine. The additive effect was predominantly observed in the 7 NO-responders with a 81% increase in the PaO_2/FIO_2 ratio and a 23% decrease in venous admixture (Fig. 1). We did not perform multiple inert gas elimination technique (MIGET) [22] to precisely elucidate the physiologic mechanism by which both drugs in association improved oxygenation. However, as recently suggested [23], NO+ALM might optimize the matching of ventilation and perfusion, suggesting a NO-regulated effect on ALM induced pulmonary vasoconstriction. Because of the long plasma half-life (40 h) of almitrine bismesylate [19] we did not randomize the sequence of therapeutic interventions and thus we can not definitively exclude a possible time effect of ALM [24]. However, despite the long plasma half-life of almitrine, rapid effect (30 min) of almitrine on gas exchange has been reported by Reyes and coworkers [3].

Lastly, ALM alone may increase pulmonary arterial pressure [3] with the risk of jeopardizing right ventricular function. In our patients, mean pulmonary artery pressure rose from 28 ± 5 mmHg to 31 ± 5 mmHg during infusion with ALM alone and was significantly higher than with NO alone (31 ± 5 versus 26 ± 5 mmHg, $p < 0.01$). NO in association with ALM induced a 13% decrease in mean pulmonary arterial pressure ($p < 0.05$) by comparison with ALM alone. In addition to the effects on gas exchange, the association of NO and ALM keeps the benefit of NO to reduce pulmonary hypertension.

As reported by others [2, 8, 9, 12–16] we did not observe any systemic effect of NO alone or in association with almitrine (Table 2) confirming the specific effect of both medications on the pulmonary vascularisation.

Also reported previously [2, 8, 12–16] methemoglobin did not increase during treatment and in the 2 patients in which the oxidative derivatives of NO were measured by chemiluminescence, concentrations never exceeded 0.2 ppm which is far below the level of toxicity [12]. However, a potential toxicity exists with both ALM and NO. Peripheral neuropathy has been reported after prolonged therapy with ALM [25] while short-term administration of ALM in patients with ARDS has been considered safe [3, 26]. Derivative oxidatives of NO (NO_2 and NO_3) are highly toxic for the lung in doses of 5 ppm [12]. Although several studies [2, 9, 14–16] did not detect toxic levels of NO_2 when NO was inhaled during mechanical ventilation, the toxicity of NO as a long-term therapy is not known.

Although the precise physiologic mechanism by which both drugs in association improved oxygenation are unknown, our results might be of practical significance in severely hypoxemic patients (Table 1). Most of our patients were ventilated with 100% FIO_2 ($n = 14$), with positive end expiratory pressure above 5 cmH_2O ($n = 15$) and despite sedation, paralysis and careful hemodynamic monitoring, none had a PaO_2/FIO_2 ratio above 150 mmHg and only 5 had a PaO_2/FIO_2 ratio above 100 mmHg. Most of these patients had ARDS related to pneumonia or associated with sepsis and had more than 2 organ failures [6]. These patients had severe and life-threatening hypoxemia and NO+ALM may be helpful as a short-term therapy for improving gas exchange. Moreover all of these patients were ventilated with a potentially toxic level of FIO_2 (>70%) and NO+ALM may be useful for reducing the level of FIO_2. Consequently the potential toxicity of both medications need to be weighed against the potential toxicity of high level of inspired O_2 fractions.

In conclusion, we found here that the combination of the two treatments (NO and ALM) had additive effects to increase oxygenation while decreasing pulmonary artery pressure in severely hypoxemic patients with ARDS. This effect is amplified and may be predicted in patients in whom NO improved gas exchange by at least 10 mmHg (NO-responders). This combination may be helpful as a short-term therapy, but further studies are needed before considering NO+ALM as a long-term therapy in patients with ARDS. Further studies are also needed to delineate which patients may have significant improvement with NO+ALM.

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