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Inhaled NO and almitrine bismesylate in patients with acute respiratory distress syndrome: effect of noradrenalin

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ABSTRACT: The combination of inhaled nitric oxide with almitrine bismesylate has been proposed for the management of acute respiratory distress syndrome in order to divert pulmonary blood flow away from poorly ventilated toward well-ventilated areas. The aims of this prospective and comparative study were to: 1) confirm the beneficial effects on oxygenation of this association; 2) evaluate the haemodynamic effects of this association; and 3) evaluate the influence of noradrenaline (a nonspecific vasoconstrictor) on the modification of gas exchange related to inhaled NO and/or almitrine bismesylate.

Forty-one sedated paralysed and ventilated patients were investigated. Haemodynamic and blood gas measurements were performed in a fixed order: baseline; inhalation of NO for 30 min.; intravenous infusion of almitrine bismesylate; and concomitant administration of inhaled NO and almitrine bismesylate.

Inhaled NO and almitrine bismesylate increased arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) ($p<0.001$). The association of inhaled NO with almitrine bismesylate resulted in a dramatic improvement in $P_{a,O_2}/F_{I,O_2}$ ($p<0.0001$ *versus* almitrine bismesylate, $p<0.05$ *versus* inhaled NO). In patients receiving noradrenalin (n=19), almitrine bismesylate had no effect on oxygenation.

The present study confirmed that the combination of inhaled NO with almitrine bismesylate improved oxygenation, and demonstrated that almitrine bismesylate has no effect on oxygenation in patients receiving noradrenalin.

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Despite the use of new therapeutic agents, acute respiratory distress syndrome (ARDS)-related mortality remains high [1, 2]. Inhaled nitric oxide has been widely used since the beginning of the 1990s but recent studies have been unable to demonstrate a significant decrease in mortality related to its use [3, 4]. Certain methodological considerations could possibly explain, in part, this lack of positive impact on outcome. However, it could be useful to find some therapeutic associations that would enhance the beneficial effects of inhaled NO on oxygenation. It has been found that the association of the prone position with inhaled NO can enhance arterial oxygen tension P_{a,O_2} [5]. A pharmacological approach consisting of diverting pulmonary blood flow away from poorly-ventilated toward well-ventilated areas in which inhaled NO can exert its vasodilating action would appear to be attractive. Several vasoactive agents have been proposed, *i.e.* the use of a systemic and pulmonary vasoconstrictor (phenylephrine) [6] or the use of a specific pulmonary vasoconstrictor (almitrine bismesylate) [7, 8]. Noradrenalin (NA) is extensively used in the intensive care unit (ICU) [9], especially in septic shock, which is frequently associated with ARDS. Therefore, the aims of this prospective study were to: 1) confirm the beneficial effects on oxygenation of the association of inhaled NO with almitrine bismesylate; 2) evaluate the haemodynamic effects of this association with special emphasis on right ventricular function; and 3) evaluate the influence of NA (a nonspecific vasoconstrictor) on the modification of gas exchange related to inhaled NO and/or almitrine bismesylate.

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Materials and methods

Patients

During a 24-month period, 41 patients (mean±SD age 55±17 yrs) with ARDS (mean Lung Injury Score 3.05±0.4) diagnosed on or after admission to the medicosurgical ICU 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. ARDS was defined according to the recommendations of the American-European Consensus Conference [10]. Among the 41 patients enrolled in the study, 12 were admitted to the ICU after multiple trauma, nine with

postoperative complications following major surgery and 20 for an acute medical illness. ARDS was related to nosocomial bronchopneumonia (14 patients), lung contusion (nine patients), community-acquired pneumonia (six patients), aspiration pneumonia (five patients), peritonitis (four patients) or acute pancreatitis (three patients). On admission, the mean Simplified Acute Physiology Score (SAPS) II was 41±18. All patients were sedated and paralysed with a continuous infusion of sufentanil, midazolam and vecuronium bromide, and lungs were ventilated using conventional volume-controlled mechanical ventilation (Mallinckrodt Puritan Bennett 7200 series; Mallinckrodt Puritan Bennett Carlsbad, CA, USA). Respiratory parameters at the time of inclusion in the study were as follows: exhaled tidal volume 509±89 mL; respiratory frequency 22±4 cycles·min^{-1}; positive end-expiratory pressure (PEEP) 11±2 cmH_2O; inspiratory oxygen fraction (F_{I,O_2}) 0.75±0.16; and peak inspiratory pressure 33±6 cmH_2O. The duration of mechanical ventilation preceding the study was 5±4 days. All of the patients had been stable (respiratory status and haemodynamic condition) for ≥6 h preceding inclusion. For each patient, tidal volume and respiratory frequency were adjusted to maintain minute ventilation constant throughout the study period. The level of PEEP was maintained constant throughout the study period. In order to detect changes in F_{I,O_2} induced by inhalation of NO, F_{I,O_2} was monitored continuously using an oxygen analyser (NOX 4000; Sérès, Aix-en-Provence, France) and subsequently adjusted in order to keep F_{I,O_2} constant throughout the study period. Nineteen of the 41 patients received NA (mean 0.60±0.62 μg·kg^{-1}·min^{-1}; range, 0.03–2.09 μg·kg^{-1}) for septic shock [11] with systolic arterial pressure <90 mmHg despite fluid expansion. Eleven of the 22 patients who did not receive NA presented with sepsis [11] at the time of the study. The mortality of the entire population included in the study was 51%. The characteristics of the patients receiving or not receiving NA are summarized in table 1. No major difference was observed between the two groups on inclusion.

Table 1. – Characteristics of the patients receiving or not receiving noradrenalin (NA)

	No NA	NA	p-value
Patients n	22	19	
SAPS II on admission	36.5±16.5	46.6±18.4	0.07
APACHE III on admission	65.1±26.5	88.2±31.3	0.01
Lung Injury Score*	3.03±0.40	3.08±0.31	NS
Age yrs	51.9±18.5	58.7±14.8	NS
Minute ventilation L·min^{-1}*	11.1±2.4	10.9±1.9	NS
Tidal volume mL*	502±106	517±67	NS
Respiratory frequency cycles·min^{-1}*	22.4±4.1	21.3±3.6	NS
PEEP cmH_2O*	11.0±2.0	11.0±1.5	NS
F_{I,O_2}	0.73±0.15	0.77±0.16	NS
$P_{a,O_2}/F_{I,O_2}$ mmHg*	83.3±33.4	84.9±45.6	NS
Peak inspiratory pressure cmH_2O*	32.6±6.2	33.0±6.1	NS
Mortality %	45	63	NS

Data are presented as mean±SD. SAPS II: Simplified Active Physiology Score II; APACHE III: Acute Physiology and Chronic Health Evaluation III; PEEP: positive end-expiratory pressure; F_{I,O_2}: inspiratory oxygen fraction; P_{a,O_2}: arterial oxygen tension. (1 mmHg=0.133 kPa.)

Measurements

All patients had a radial artery catheter (Seldicath; Plastimed, Saint Leu la Foret, France) and a pulmonary artery catheter equipped with a fast-response thermistor (model 93 A-434H-7.5F; Baxter Healthcare Corporation, Irvine, CA, USA), which 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 in the right atrium, just above the tricuspid valve. Systolic arterial pressure, diastolic arterial pressure, systolic pulmonary arterial pressure, diastolic pulmonary arterial pressure, pulmonary artery occlusion pressure (PAOP) and right atrial pressure (RAP) were measured at endexpiration. The supine zero reference level was the midaxilla. Right ventricular end-diastolic (RVEDVI) and end-systolic volume index (RVESVI) were calculated from the right ventricular ejection fraction (RVEF) and the stroke volume. RVEF and cardiac output were measured by means of thermodilution using three boluses of 10 mL glucose solution at 6–10°C, injected *via* a closed system (Co-set; Baxter Healthcare Corporation) 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 using a thermistor located at the proximal port of the right atrial lumen. The mean of three measurements is reported. RVEF was evaluated using an algorithm based on an exponential curve analysis using a computer (Edwards Cardiac Output computer REF-1; Baxter Healthcare Corporation) as previously described and validated [12]. Patients with cardiac dysrythmias were not included. Cardiac index (CI), oxygen delivery index (DO_2I), oxygen consumption index, oxygen extraction ratio, right and left ventricular stroke work index, venous admixture ($\dot{Q}va/\dot{Q}t$) and systemic (SVRI) and pulmonary vascular resistances index (PVRI) were calculated using standard formulae. Systemic and pulmonary arterial blood samples were simultaneously withdrawn within 3 min of measurement of cardiac output. Arterial pH, P_{a,O_2}, venous oxygen tension (P_{v,O_2}), and arterial carbon dioxide tension (P_{a,CO_2}) were measured using a blood gas analyser (278-blood gas system; Ciba Corning, Medfield, MA, USA). Haemoglobin concentration, arterial (S_{a,O_2}) and mixed venous oxygen saturations (S_{v,O_2}) and methaemoglobin levels were measured using a calibrated haemoximeter (270-CO-oxymeter; Ciba Corning). The following respiratory parameters were recorded: exhaled tidal volume, peak inspiratory pressure, mean inspiratory pressure and respiratory frequency. Respiratory dynamic compliance was calculated as tidal volume/(peak inspiratory pressure - PEEP). Vasoactive agents and fluid administration rates remained constant throughout the study.

Nitric oxide administration

NO 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 humidifier *via* a flowmeter delivering flows within the range 1–999 mL·min^{-1} (Air Liquide). Intratracheal gas was sampled using continuous aspiration through the endotracheal tube (aspirative flow 1 L·min^{-1}), permitting inspiratory,

expiratory and mean concentrations of NO and nitrogen dioxide to be continuously determined using a chemiluminescence apparatus (NOX 4000; Seres, Aix-en-Provence, France). The flowmeter was set to reach the desired inspiratory tracheal concentration.

Protocol

The duration of the study was ~3 h for each patient. The protocol consisted of four consecutive phases, performed in the two groups (19 patients receiving NA and 22 patients not receiving NA). Haemodynamic and blood gas measurements were performed in a fixed order: baseline after 1 h of steady-state conventional mechanical ventilation; after inhalation of 10 ppm NO for 30 min; after 30 min of constant intravenous infusion of almitrine bismesylate (Vectarion®, Euthérapie, Neuilly, France) (16 $\mu g \cdot kg^{-1} \cdot min^{-1}$); and after 2 h of concomitant administration of inhaled 10 ppm NO and constant intravenous infusion of almitrine bismesylate (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). It was decided not to randomize the sequence of therapeutic interventions because of the prolonged half-life of almitrine bismesylate [13].

Statistical methods

All the statistical analyses were performed by an experienced statistician (X. Thirion). Data are expressed as mean±SD). Statistical calculations were performed using the SPSS 8.0 package (SPSS, Inc., Chicago, IL, USA). Statistically significant differences were analysed by means of parametric (general factorial analysis of variance) or nonparametric (Friedman multiple comparison test) tests as required. For intragroup changes, the Friedman test or Dunnett's t-test for multiple comparisons was applied to compare the various time points with control values. When normal distribution was present, comparison between two times (or two groups) was performed by means of Student's t-test for paired samples or the Mann-Whitney U-test in the case of nonparametric data. A patient was considered as a responder to NO inhalation and/or almitrine bismesylate when an increase in $P_{a,O_2}/F_{I,O_2}$ ratio of ≥20% was observed compared with baseline. Differences in the number of responders were analysed using Fisher's exact test. A p-value <0.05 indicated significance.

Results

Effects of inhaled nitric oxide and almitrine bismesylate on haemodynamic parameters

Although inhaled NO and almitrine bismesylate resulted in significant but opposed effects on mean pulmonary artery pressure (MPAP), PVRI and RVEF, no significant interaction was found (table 2). Except for an increase in cardiac frequency and CI under almitrine bismesylate, the other haemodynamic parameters were not or only marginally affected by both treatments (table 2).

Effects of inhaled nitric oxide and almitrine bismesylate on gas exchange

Although the effects of inhaled NO and almitrine bismesylate were moderate on P_{a,CO_2} (table 2), oxygenation was considerably modified by these two treatments (p<0.001). As presented in figure 1, $P_{a,O_2}/F_{I,O_2}$ increased from a median of 9.7 kPa (73 mmHg) (range 5.5–23.8 kPa (41–179 mmHg)) at baseline to a median of 11.6 kPa (87 mmHg) (range 5.9–57.2 kPa (44–430 mmHg)) when the patients received inhaled NO (p<0.0001). The increase in $P_{a,O_2}/F_{I,O_2}$ was also significant under almitrine bismesylate (median 12.0 kPa (90 mmHg), range 5.5–43.2 kPa (41–325 mmHg), p<0.05 *versus* baseline). Friedman analysis showed that inhaled NO induced greater improvement in oxygenation than did almitrine bismesylate

Table 2. – Haemodynamic and respiratory changes induced by nitric oxide and almitrine bismesylate

	Measurement				ANOVA		
	Baseline	NO 10 ppm	Almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Almitrine 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and NO 10 ppm	NO	Almitrine	NO+ almitrine
P_{a,CO_2} mmHg	44±9	43±9^{+}	45±9	44±9	0.004	0.007	NS
S_{v,O_2} %	72±7	76±7‡	74±8	76±8‡	0.0001	NS	NS
MPAP mmHg	29±7	26±7‡	32±8‡	29±7	0.0001	0.0001	NS
CI $L \cdot min^{-1} \cdot m^{-2}$	4.0±1.3	4.1±1.3	4.3±1.5	4.3±1.6^{+}	NS	0.001	NS
RVEF %	38±8	39±7	35±8	38±8	0.05	0.002	NS
f_C $beats \cdot min^{-1}$	96±21	94±18	103±21$^{\#}$	99±21	NS	0.0001	NS
PAOP mmHg	12.8±4.4	12±4.7	13.6±5.3	13±5	NS	NS	NS
RAP mmHg	8±4	7.4±3.9	8.4±3.9	8±3.4	NS	NS	NS
PVRI $dynes \cdot s \cdot cm^{-5} \cdot m^2$	421±205	357±146$^{\#}$	454±231	408±234	0.0001	0.002	NS
Q_{va}/Q_t %	41±12	38±14	41±13	35±14‡	0.0001	NS	NS
RVEDVI $mL \cdot m^{-2}$	112±24	113±28	120±34	116±27	NS	0.05	NS
RVESVI $mL \cdot m^{-2}$	69±20	70±21	78±24$^{\#}$	73±21	NS	0.001	NS
$D_{O_2}I$ $mL \cdot min^{-1} \cdot m^{-2}$	504±153	523±161	491±173	561±196‡	0.0001	NS	0.007

Data are presented as mean±SD. P_{a,CO_2}: arterial carbon dioxide tension; S_{v,O_2}: venous oxygen saturation; MPAP: mean pulmonary artery pressure; CI: cardiac index; RVEF: right ventricular ejection fraction; f_C: cardiac frequency; PAOP: pulmonary artery occlusion pressure; RAP: right atrial pressure; PVRI: pulmonary vascular resistances index; Q_{va}/Q_t: venous admixture; RVEDVI: right ventricular end-diastolic volume index; RVESVI: right ventricular end-systolic volume index; $D_{O_2}I$: oxygen delivery index. $^{+}$: p<0.02, $^{\#}$: p<0.005, ‡: p<0.0001 *versus* baseline (two-sided Dunnett *post hoc* test). (1 mmHg=0.133 kPa.)

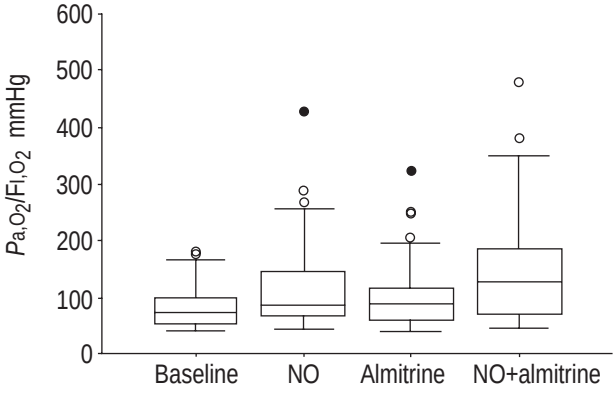

Fig. 1. – Effect of inhaled nitric oxide and/or almitrine bismesylate in all patients (n=41). Median arterial oxygen tension (P_{a,O_2})/ inspiratory oxygen fraction (F_{I,O_2}) (25th, 50th and 75th percentiles) are shown and the vertical bars represent the largest and smallest values that are not outliers. ○: outliers (cases with values 1.5–3 box-lengths from the upper or lower edge of the box); ●: extremes outliers (cases with values >3 box-lengths from the upper or lower edge of the box) (1 mmHg=0.133 kPa.)

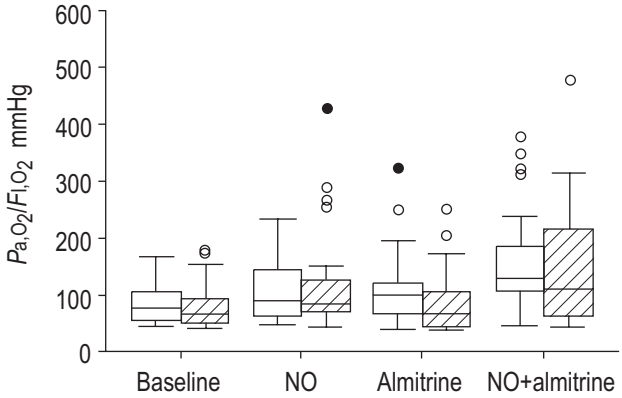

Fig. 2. – Effect of inhaled nitric oxide and/or almitrine bismesylate on arterial oxygen tension (P_{a,O_2})/ inspiratory oxygen fraction (F_{I,O_2}) in patients receiving noradrenalin (n=19; ▨) and in patients not receiving noradrenalin (n=22; □). Median $P_{a,O_2}/F_{I,O_2}$ (25th, 50th and 75th percentiles) are shown and the vertical bars represent the largest and smallest values that are not outliers. ○: outliers (cases with values 1.5–3 box-lengths from the upper or lower edge of the box); ●: extremes outliers (cases with values >3 box-lengths from the upper or lower edge of the box).

(p<0.02). The number of responders was not different when using either inhaled NO or almitrine bismesylate (24 with inhaled NO, 14 with almitrine bismesylate). The association of inhaled NO and almitrine bismesylate resulted in a dramatic improvement in $P_{a,O_2}/F_{I,O_2}$ (median 17.2 kPa 129 mmHg), range 6.1–63.7 kPa 46–479 mmHg) p<0.0001 *versus* both baseline and almitrine bismesylate, p<0.05 *versus* inhaled NO). Thirty-two responders to the combination of inhaled NO and almitrine bismesylate were identified (p<0.02 *versus* almitrine bismesylate). Two-thirds of both NO nonresponders (11 of 17) and almitrine bismesylate nonresponders (18 of 27) presented an increase in $P_{a,O_2}/F_{I,O_2}$ of ≥20% when the two therapeutics were combined. The decrease in Q_{va}/Q_t, was mainly related to inhaled NO. Concerning oxygen delivery, a potentiation between inhaled NO and almitrine bismesylate was observed.

Influence of noradrenalin on the oxygenation effects of inhaled nitric oxide and almitrine bismesylate

The influence of NA on the oxygenation effects of inhaled NO and almitrine bismesylate is illustrated in figure 2. Nineteen patients received NA for an associated septic shock. In these patients, almitrine bismesylate had no effect on oxygenation when given alone, whereas, in patients not receiving NA (n=22), almitrine bismesylate induced an increase in $P_{a,O_2}/F_{I,O_2}$ comparable to that observed with inhaled NO. In this subgroup of patients not receiving NA, the increase in $P_{a,O_2}/F_{I,O_2}$ observed when patients received the combination of almitrine bismesylate and NO was greater than that when patients received either inhaled NO (p<0.02) or almitrine bismesylate (p<0.0001). Conversely, in patients receiving NA, the combination of inhaled NO with almitrine bismesylate induced a significant increase in $P_{a,O_2}/F_{I,O_2}$ only when compared with that obtained while patients received almitrine bismesylate (p<0.0001). When the effects of NA on the variation in $P_{a,O_2}/F_{I,O_2}$ (between the baseline value and that obtained under inhaled NO, almitrine bismesylate, or the combination of inhaled NO and almitrine bismesylate) were examined, only the variation under almitrine bismesylate was affected (increase in $P_{a,O_2}/F_{I,O_2}$ of 39.5±56.3% in patients not receiving NA *versus* 5.9±19.9% in patients receiving NA; p<0.02). Moreover, although NA had no effect on the proportion of responders to inhaled NO or to the combination of almitrine bismesylate and NO, it significantly decreased the number of responders to almitrine bismesylate (one of 19 in patients receiving NA *versus* 13 of 22 in patients not receiving NA; p<0.0001). As shown in table 3, the main haemodynamic characteristics of the two groups of patients did not explain the lack of an increase in $P_{a,O_2}/F_{I,O_2}$ under almitrine bismesylate in patients receiving NA.

One hypothesis concerning the lack of efficiency of almitrine bismesylate when patients received NA was that the dose regimen was too high (16 $\mu g \cdot kg^{-1} \cdot min^{-1}$), inducing diffuse nonselective pulmonary vasoconstriction. Therefore, an additional trial was performed in 10 ARDS patients (not included in the first trial of 41 patients) receiving NA and inhaled NO, comparing the $P_{a,O_2}/F_{I,O_2}$ ratio under almitrine bismesylate at two different infusion rates, *i.e.* 2 h at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 30 min at 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$. No significant difference in $P_{a,O_2}/F_{I,O_2}$ was found when patients received almitrine bismesylate at 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (median 19.4 kPa (146 mmHg), range 10.1–57.7 kPa (76–434 mmHg)) as compared with almitrine bismesylate at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (median 17.3 kPa (130 mmHg), range 9.4–56.8 kPa (71–427 mmHg)). No significant difference in MPAP was observed when patients received 5 or 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine bismesylate (25±5 mmHg and 26±6 mmHg, respectively). Other pulmonary haemodynamic parameters remained unchanged (RAP, CI, PVRI; data not shown).

Discussion

This study shows that the combination of almitrine bismesylate with inhaled NO can markedly improve oxygenation in patients with ARDS. The effect of the combination

Table 3. – Haemodynamic changes induced by almitrine bismesylate in patients receiving or not receiving noradrenalin (NA)

	Measurement	No NA	NA	ANOVA
Patients n		22	19	
PVRI	Baseline	382±242	466±144	NS
dynes·s·cm^{-5}·m^{2}	Almitrine*	438±255	472±206	NS
MPAP mmHg	Baseline	26±7	32±5	0.002
	Almitrine	29±7	36±7	0.005
CI L·min^{-1}·m^{-2}	Baseline	4.2±1.6	3.9±0.9	NS
	Almitrine*	4.3±1.7	4.2±1.3	NS
RVEF %	Baseline	41±8	35±7	0.02
	Almitrine*	37±9	36±7	NS
PAOP mmHg	Baseline	11±4	13±4	0.03
	Almitrine*	12±4	14±6	0.01
RAP mmHg	Baseline	8±5	9±3	NS
	Almitrine*	7±4	10±3	NS

Data are presented as mean±SD. *: 16 mg·kg^{-1}·min^{-1}. ANOVA: analysis of variance; PVRI: pulmonary vascular resistances index; MPAP: mean pulmonary artery pressure; CI: cardiac index; RVEF: right ventricular ejection fraction; PAOP: pulmonary artery occlusion pressure; RAP: right atrial pressure.

of these two therapeutic agents on arterial oxygenation was better than that obtained with NO or almitrine bismesylate alone.

Almitrine bismesylate is a peripheral chemoreceptor agonist, which stimulates ventilation [14]. After almitrine bismesylate administration, a shift in blood flow distribution to better-oxygenated lung areas with higher ventilation/perfusion ratios (V'/Q') has been observed [15]. The effects of almitrine bismesylate have also been observed in isolated lung, suggesting a direct action on pulmonary tissue [16]. Almitrine bismesylate has been found effective in patients with ARDS [7, 8, 17]. The vasodilating effect of NO on the pulmonary circulation has been extensively studied. This effect is limited to the ventilated regions of the lung, thus improving the perfusion of ventilated regions, causing a reduction in intrapulmonary shunting and improving arterial oxygenation. The improvement in oxygenation with the combination of inhaled NO and almitrine bismesylate has been shown in ARDS patients [17–19], in hypoxaemic patients with focal lung lesions [20] and during one-lung ventilation in patients undergoing thoracic procedures [21]. The enhancement of hypoxic pulmonary vasoconstriction by almitrine bismesylate is also strongly suggested by the decrease in blood flow to low V'/Q' hypoxic lung regions demonstrated in mechanically ventilated COPD patients [22]. The mechanisms by which almitrine bismesylate increases inhaled NO-induced improvement in arterial oxygenation are not precisely known and can only be speculative. For example, using the multiple inert gas elimination technique, REYES *et al.* [17] found a redistribution of pulmonary blood flow from shunt areas to lung units of normal V'/Q', while pulmonary artery pressure increased. WYSOCKI *et al.* [7] did not find a significant effect of almitrine bismesylate used alone. However, their patients were more hypoxaemic than those included in the present study. Thus, it has been experimentally shown that almitrine bismesylate may not enhance hypoxic pulmonary vasoconstriction when vigorous vasoconstriction is already present [23].

The current study demonstrates that the addition of inhaled NO and almitrine bismesylate totally reverses the almitrine bismesylate-induced increase in MPAP and in PVRI. This suggests that when inhaled NO was added, the vasoconstriction related to ARDS, almitrine and/or NA was reversed in pulmonary vessels perfusing ventilated alveoli but not in nonventilated areas. This effect enhanced the redistribution of pulmonary blood flow toward well-ventilated lung regions. As a consequence, P_{a,O_2} significantly increased.

It was observed that 78% of the patients responded to the association of inhaled NO with almitrine bismesylate. WYSOCKI *et al.* [7] suggested that patients who do not respond to NO also do not respond to the combination almitrine bismesylate/NO. It was not possible to confirm these results. In the present study, two-thirds of the almitrine bismesylate nonresponders were considered responders when inhaled NO was introduced.

Reversible peripheral neuropathy has been reported after prolonged administration of almitrine bismesylate to patients with chronic obstructive pulmonary disease [24]. Although no serious side-effects have been described, the lowest possible dose of almitrine bismesylate should be administered to critically ill patients. The minimum dose at which almitrine bismesylate improves arterial oxygenation is not known in ARDS patients, but a recent study suggested that 4 μg·kg^{-1}·min^{-1} is sufficient to induce an improvement in oxygenation [25]. The two dose regimens for almitrine bismesylate were chosen for the following reasons: 16 μg·kg^{-1}·min^{-1} is the dose regimen that has been used in clinical studies using short-duration infusions, whereas 5 μg·kg^{-1}·min^{-1} is a dose regimen which could limit the adverse effects (neurological, hepatic) of almitrine bismesylate and which could be used for long-term administration. However, the effect of almitrine bismesylate on pulmonary vascular tone in hypoxic conditions remains controversial and seems to be species- and dose-related. In *in vivo* studies in dogs and in isolated lung studies, the effect of almitrine bismesylate on hypoxic pulmonary vasoconstriction has been described as enhancement [16, 26, 27] or inhibition. However, it is not realistic to compare isolated perfused lungs with patients. Furthermore, the dose regimens are probably different from those in a clinical setting. Moreover, ARDS is a heterogeneous parenchymal process, whereas hypoxia is induced in such animal models by the administration of hypoxic gases.

In the present study, it was noted that only 5% of the patients under NA responded to administration of almitrine bismesylate. In a previous study [28], it was reported that the improvement in oxygenation related to the administration of inhaled NO was not influenced by NA. The present results are different from those of GALLART *et al.* [29] who reported that almitrine bismesylate induced a significant increase in P_{a,O_2} when given to patients presenting septic shock. Some differences could explain the discrepancies between this latter study and the present work. Whereas, in the study of GALLART *et al.* [29], all but two patients were postoperative patients or multiple trauma patients, half of the present patients were medical. Only NA was used as vasoactive agent in the present study, whereas in the study of GALLART *et al.* [29] the number of patients under NA and the dose of NA were not stated. However, the main difference is probably the

baseline value of $P_{a,O_2}/F_{I,O_2}$, which was ~20.0 kPa (150 mmHg) in the study of GALLART *et al.* [29], whereas in the present work it was 11.2±6.1 kPa (84±46 mmHg). Pulmonary haemodynamics showed that MPAP was also very different at baseline. However, the increase in MPAP after the introduction of almitrine bismesylate was comparable between the two studies (3.2 to 4 mmHg). Therefore, the main factor that could explain the differences between the present work and the study of GALLART *et al.* [29] is probably the level of hypoxic pulmonary vasoconstriction at baseline, which is probably more elevated in the present work. This lack of effect of almitrine bismesylate on gas exchange when patients received a concomitant continuous infusion of NA suggests nonspecific pulmonary vasoconstriction that does not occur predominantly in most hypoxic regions and thus does not divert pulmonary blood flow toward better oxygenated areas. Another explanation is that NA itself favourably redistributes blood flow in a fashion comparable to almitrine bismesylate, and the addition of almitrine bismesylate confers no additional benefit. However, a study was recently performed that did not support this hypothesis [30].

In conclusion, the combination of inhaled nitric oxided with almitrine bismesylate markedly improved arterial oxygenation, probably by inducing vasodilation of normally-ventilated areas (nitric oxide effects and further constriction of shunting zones (almitrine bismesylate effects). Although nitric oxide inhalation alone significantly increased arterial oxygen tension, the enhancement of pulmonary vasoconstriction with almitrine bismesylate amplified this improvement in arterial oxygen tension and allowed the inspiratory oxygen fraction and positive end-expiratory pressure required for adequate gas exchange to be reduced, thus preventing ventilator-associated lung injuries. On the contrary, it was noted that almitrine bismesylate did not induce an increase in arterial oxygen tension when administered to patients receiving noradrenalin. No deleterious effect was observed in right ventricular function of almitrine bismesylate, noradrenalin, or the combination of these two vasoconstrictors. However, the potential toxicity of almitrine bismesylate implies great caution in its use. However, additional studies are needed in order to demonstrate a significant impact on outcome in acute respiratory distress syndrome patients.

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References

1. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome. 1983–1993. *JAMA* 1995; 273: 306–309.
2. Lewandowski K, Metz J, Deutschmann C, *et al*. Incidence, severity, and mortality of acute respiratory failure in Berlin, Germany. *Am J Respir Crit Care Med* 1995; 151: 1121–1125.
3. Dellinger RP, Zimmerman JL, Taylor RW, *et al*. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. *Crit Care Med* 1998; 26: 15–23.
4. Troncy E, Collet JP, Shapiro S, *et al*. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. *Am J Respir Crit Care Med* 1998; 157: 1483–1488.
5. Papazian L, Bregeon F, Gaillat F, *et al*. Respective and combined effects of prone position and inhaled nitric oxide in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 157: 580–585.
6. Doering EB, Hanson CW, Reily DJ, Marshall C, Marshall BE. Improvement in oxygenation by phenylephrine and nitric oxide in patients with adult respiratory distress syndrome. *Anesthesiology* 1997; 87: 18–25.
7. Wysocki M, Delclaux C, Roupie E, *et al*. Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome. *Intensive Care Med* 1994; 20: 254–259.
8. Lu Q, Mourgeon E, Law-Koune JD, *et al*. Dose-response curves of inhaled nitric oxide with and without intravenous almitrine in nitric oxide-responding patients with acute respiratory distress syndrome. *Anesthesiology* 1995; 83: 929–943.
9. Martin C, Perrin G, Saux P, Papazian L, Gouin F. Effects of norepinephrine on right ventricular function in septic shock patients. *Intensive Care Med* 1994; 20: 444–447.
10. Bernard GP, Artigas A, Brigham KL, *et al*. The American-European consensus conference on ARDS. *Am J Respir Crit Care Med* 1994; 149: 818–824.
11. Members of the American College of Chest Physicians/Society of Critical Care Medicine. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20: 864–874.
12. Dhainaut R, Brunet F, Monsallier JF, *et al*. Bedside evaluation of right ventricular performance using a rapid computerized thermodilution method. *Crit Care Med* 1987; 15: 148–152.
13. Bury T, Jeannot JP, Ansquer JC, Radermecker M. Dose-response and pharmacokinetic study with almitrine bismesylate after single oral administrations in COPD patients. *Eur Respir J* 1989; 2: 49–55.
14. Laubie M, Dior F. A pharmacological study of the respiratory stimulant action of S2620. *J Pharmacol* 1972; 3: 363–374.
15. Hervé PH, Musset MD, Simonneau MD, Wagner W, Duroux P. Almitrine decreases the distensibility of the large pulmonary arteries in man. *Chest* 1983; 94: 1119–1120.
16. Falus F, Herget J, Hampl V. Almitrine in low dose potentiates vasoconstrictor responses of isolated rat lungs to moderate hypoxia. *Eur Respir J* 1991; 4: 688–693.
17. Reyes A, Roca J, Rodriguez-Roisin R, Torres A, Ussetti P, Wagner PD. Effect of almitrine on ventilation-perfusion distribution in adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 137: 1062–1067.
18. Gillart T, Bazin JE, Cosserant B, *et al*. Combined nitric oxide inhalation, prone positioning and almitrine infusion improve oxygenation in severe ARDS. *Can J Anaesth* 1998; 45: 402–409.
19. Jolliet P, Bulpa P, Ritz M, Ricou B, Lopez J, Chevrolet JC. Additive beneficial effects of the prone position, nitric oxide, and almitrine bismesylate on gas exchange and oxygen transport in the acute respiratory distress syndrome. *Crit Care Med* 1997; 25: 786–794.
20. Payen D, Muret J, Beloucif S, *et al*. Inhaled nitric oxide, almitrine infusion, or their coadmini strati on as a treatment of severe hypoxemic focal lung lesions. *Anesthesiology* 1998; 89: 1157–1165.

21. Moutafis M, Liu N, Dalibon N, *et al*. The effects of inhaled nitric oxide and its combination with intravenous almitrine on P_{a,O_2} during one-lung ventilation in patients undergoing thoracoscopic procedures. *Anesth Analg* 1997; 85: 1130–1135.
22. Castaing Y, Manier G, Guenard H. Improvement in ventilation-perfusion relationships by almitrine in patients with chronic obstructive pulmonary disease during mechanical ventilation. *Am Rev Respir Dis* 1986; 134: 910–916.
23. Naeije R, Lejeune P, Vachiery JL, *et al*. Restored hypoxic pulmonary vasoconstriction by peripheral chemoreceptor agonists in dogs. *Am Rev Respir Dis* 1990; 142: 789–795.
24. Howard P. Hypoxia, almitrine and peripheral neuropathy. *Thorax* 1989; 44: 247–250.
25. Mourgeon EM, Law-Koune JD, Abdennour L, Lu Q, Coriat P, Rouby JJ. Dose-response of almitrine combined with NO in patients with ARDS. *Am J Respir Crit Care Med* 1996; 153: A595 (abstract).
26. Nakanishi S, Hiramoto T, Ahmed N, Nishimoto Y. Almitrine enhances in low dose the reactivity of pulmonary vessels to hypoxia. *Respir Physiol* 1988; 74: 139–150.
27. Romaldini H, Rodriguez-Roisin R, Wagner PD, West JB. Enhancement of hypoxic pulmonary vasoconstriction by almitrine in the dog. *Am Rev Respir Dis* 1983; 128: 288–293.
28. Papazian L, Brégeon F, Gaillat F, *et al*. Does norepinephrine modify the effects of inhaled nitric oxide in septic patients with acute respiratory distress syndrome? *Anesthesiology* 1998; 89: 1089–1098.
29. Gallart L, Lu Q, Puybasset L, Umamaheswara Rao GS, Coriat P, Rouby JJ. Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. The NO Almitrine Study Group. *Am J Respir Crit Care Med* 1998; 158: 1770–1777.
30. Papazian L, Brégeon F, Gaillat F, *et al*. Effects of nitric oxide and almitrine on hemodynamics and gas exchange of patients presenting ARDS. *Am J Respir Crit Care Med* 1998; 157: A682 (abstract).