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High or low doses of almitrine bismesylate in ARDS patients responding to inhaled NO and receiving norepinephrine?

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Abstract *Objective*: To evaluate the effects on oxygenation and pulmonary haemodynamics of almitrine bismesylate (AB) 5 μg/kg per minute and 16 μg/kg per minute in ARDS patients responding to and receiving inhaled NO (iNO) and presenting septic shock requiring norepinephrine, while no difference was observed in a previous trial including iNO responders and nonresponders.
Design: Prospective, cohort study.
Setting: Adult medico-surgical intensive care unit of a university hospital.
Patients: Fifteen patients with ARDS receiving and responding to iNO (10 ppm) and presenting septic shock requiring norepinephrine (mean 0.5 ± 0.45 μg/kg per minute, range 0.08– 2.08).
Interventions: The protocol consisted of two consecutive phases in a fixed order: continuous intravenous infusion of AB 5 μg/kg per minute for 30 min, and continuous intravenous infusion of AB 16 μg/kg per minute for 30 min.
Measurements and main results: AB 5 μg/kg per minute significantly increased PaO_2/FiO_2 ($P < 0.05$) compared with iNO alone [160 (range 77–450) mmHg vs 122 (range 70–225) mmHg]. AB 16 μg/kg per minute produced a greater increase of PaO_2/FiO_2 ($P < 0.05$) when compared with 5 μg/kg per minute [227 (range 84–501) mmHg]. AB did not improve shunt at any dose regimen. AB produced an increase in mean pulmonary arterial pressure (MPAP) from 22 ± 5 to 25 ± 4 mmHg ($P < 0.03$). MPAP did not significantly increase between the two doses. Pulmonary vascular resistances and other haemodynamic and respiratory parameters were not affected by almitrine bismesylate.
Conclusions: These results suggest that it is possible to obtain a further improvement in oxygenation by increasing AB infusion rate in ARDS patients iNO responders receiving norepinephrine. Due to the potential deleterious effects of AB, this strategy should be used in the most severely hypoxaemic patients.

Keywords ARDS · Almitrine · Nitric oxide · Oxygenation · Norepinephrine · Septic shock

Introduction

One therapeutic approach for hypoxaemia related to acute respiratory distress syndrome (ARDS) consists of diverting blood flow from poorly to well-ventilated areas of the lung. In the late 1980s, intravenous administration of almitrine bismesylate, a selective pulmonary vasoconstrictor, was shown to increase arterial oxygenation in patients with ARDS [1]. Low dosage is probably important to reducing toxicity [1, 2] and, in this regard, it should be underlined that 2–4 μg/kg per minute almitrine bismesylate was recently shown to be the optimal dose regimen [3, 4].

Inhalation of nitric oxide (NO), a selective pulmonary vasodilator, was shown to have the same beneficial effects on oxygenation as almitrine bismesylate [5]. However, recent studies failed to demonstrate a significant decrease in mortality after treatment with inhaled NO [6, 7, 8, 9]. Inhaled NO and almitrine bismesylate have been shown to have cumulative effects on oxygenation [10, 11], suggesting that such a pharmacological approach may be a safe therapeutic option to rapidly reduce ventilation requirements and FiO_2 below a toxic level [3, 12]. Since the influence of the association of inhaled NO and almitrine on outcome has not yet been evaluated, it still could be a part of a strategy using more recent strategies such as reduced tidal volume [13] or prone positioning [14].

We recently reported that norepinephrine, a vasopressor frequently used in ARDS patients with septic shock, hinders the beneficial effects of almitrine bismesylate (associated or not with inhaled NO) on oxygenation [15, 16]. One hypothesis concerning the lack of efficiency of almitrine bismesylate when patients concomitantly received norepinephrine was that the dose regimen of almitrine bismesylate was too high (16 μg/kg per minute), inducing a diffuse non-selective pulmonary vasoconstriction. However, we did not observe any difference between a high- (16 μg/kg per minute) and a low- (5 μg/kg per minute) dose regimen of almitrine bismesylate [15]. This latter result was obtained in ARDS patients under norepinephrine and receiving inhaled NO [15] without taking into account the response to inhaled NO as an inclusion criteria. Moreover, a lack of power cannot be excluded. Indeed, these results were obtained in an additive trial including only ten patients not screened for their response to inhaled NO. Therefore, we hypothesized that a different response to two different doses of almitrine bismesylate could be observed specifically in inhaled NO responders receiving norepinephrine.

To test this hypothesis, we conducted a new prospective study in order to compare the effects of two doses of almitrine bismesylate (5 μg/kg per minute vs 16 μg/kg per minute) on oxygenation and hemodynamics in patients with ARDS responders to and receiving inhaled NO (10 ppm) and presenting septic shock requiring norepinephrine.

Materials and methods

Patients

During a 15-month period, 15 patients (mean age: 59 ± 11 years) with ARDS [mean Lung Injury Score (LIS): 2.95 ± 0.5] diagnosed upon or after admission to the medico-surgical intensive care unit (ICU) of Saint Marguerite University Hospital in Marseille, France, were prospectively included in this study after obtaining written informed consent from the next of kin. Study design was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Marseille and conducted according to the principles established in Helsinki. Clinical characteristics of the patient population are summarized in Table 1. Indications for admission to the ICU were multiple trauma in seven patients, major surgery in three, and acute medical illness in five. Adult respiratory distress syndrome was defined according to the recommendations of the American-European Consensus Conference [17]. The etiology of ARDS was lung contusion in six patients, community-acquired pneumonia in four, aspiration pneumonia in two, nosocomial bronchopneumonia in one, and mediastinitis in two. Mean SAPS II score at the time of admission was 39 ± 20. All patients were sedated and paralyzed by continuous infusion of sufentanil, midazolam, and vecuronium bromide, and ventilated using conventional volume-controlled mechanical ventilation (Mallinckrodt Puritan Bennett 7200 series, Carlsbad, Calif., USA). Respiratory and hemodynamic status had been stable for 6 h prior to inclusion. Tidal volume and respiratory rate were adjusted to maintain minute ventilation constant throughout study. The selection of appropriate PEEP was performed by increasing PEEP in steps of 2 cmH2O. A blood gas analysis was performed after a 30-min period of stabilization of SpO_2. Finally, the lower level of PEEP giving the greater improvement of oxygenation was chosen. When no improvement was found while increasing PEEP, the level was set at 8 cmH2O. The levels of PEEP and FiO_2 were maintained constant throughout study. To detect changes induced by inhalation of NO, FiO_2 was monitored continuously using an O_2 analyzer (NOX 4000, Sérès, Aix-en-Provence, France) and adjusted accordingly.

All patients were treated with norepinephrine for septic shock [18] characterized by systolic arterial pressure below 90 mmHg despite fluid expansion. No other vasopressor (epinephrine, dopamine, phenylephrine) was administered during the study period. Four patients received dobutamine (9 ± 3 μg/kg per minute). All patients had plasma lactate level < 2 mmol/l and normal liver function tests after haemodynamic optimization with fluid expansion and norepinephrine infusion. Overall mortality during the study was 33 % (5/15). Cause of death was septic shock in two patients, multiple organ failure in two, and intractable hypoxemia in one patient.

Measurements

A radial artery catheter (Seldicath, Plastimed, Saint-Leu-la-Forêt, France) and a pulmonary artery catheter (Baxter Healthcare Corporation, Irvine, Calif., USA) were placed in all patients. The pulmonary artery catheter was inserted percutaneously through the right jugular or left axillary vein and positioned with the distal port in the pulmonary artery and proximal port in the right atrium

Table 1 Characteristics of the population (*NBP* nosocomial bronchopneumonia, *CAP* community-acquired pneumonia)

Pat. No	Age (yrs)	Sex	Cause of ARDS	SAPS II	PaO_2/FiO_2	PaO_2/FiO_2	PaO_2/FiO_2	Norepinephrine	Dobutamine	Outcome
					under NO	NO+Alm 5	NO+Alm 16	(μg/kg/min)	(μg/kg/min)	
1	42	M	Lung contusion	49	130	430	436	0.13		Alive
2	67	M	Lung contusion	45	100	130	214	0.16	5	Alive
3	44	M	Gastric aspiration	29	137	228	238	0.55		Alive
4	54	M	Gastric aspiration	44	120	159	253	0.19		Dead
5	70	M	Mediastinitis	35	115	160	281	0.16		Alive
6	50	F	NBP	35	87.5	78	84	0.26		Dead
7	68	M	Lung contusion	77	225	284	300	0.50		Alive
8	73	M	Lung contusion	91	70	77	95	0.35	10	Dead
9	66	M	Lung contusion	35	130	237	207	1.33		Alive
10	69	M	CAP	39	126	133	110	2.08	10	Dead
11	65	M	Mediastinitis	27	145	198	227	0.08		Alive
12	38	M	Lung contusion	12	103	251	280	0.11		Alive
13	66	M	CAP	29	122	110	117	0.40		Dead
14	52	F	CAP	18	125	450	501	0.11		Alive
15	64	M	CAP	29	115	111	157	0.30	5	Alive
Mean	59			39	121	202	233	0.5		
SD	11			20	35	114	119	0.45		
Median					122	160	227			

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 end-expiration. The supine zero reference level was the mid-axilla. Cardiac output was measured by thermodilution after injection of three boluses of 10-ml glucose solution at 6–10 °C via a closed system (Co-set, Baxter Healthcare Corporation, Irvine, Calif., USA) at end-inspiration. Injection temperature was measured by a thermistor located at the proximal port of the right atrial lumen. Study data corresponds to the mean of three measurements. Cardiac index (CI), venous admixture (Q_{VA}/Q_T), and pulmonary vascular resistance (PVRI) were calculated using conventional formulas. Systemic and pulmonary arterial blood samples were withdrawn simultaneously within 3 min after measurement of cardiac output. Arterial pH, PaO_2, and $PaCO_2$ were measured using a blood gas analyzer (278-blood gas system, Ciba Corning, Medfield, Mass., USA). Arterial and mixed venous oxygen saturation (SaO_2 and SvO_2) were measured using a calibrated hemoximeter (270-CO-oxymeter, Ciba Corning, Medfield, Mass., USA). Measured respiratory parameters were exhaled tidal volume, peak inspiratory pressure, mean inspiratory pressure, and respiratory rate. Respiratory dynamic compliance was calculated by dividing tidal volume by peak inspiratory pressure minus positive end-expiratory pressure. The rate of administration of vasoactive agents and fluids was maintained constant throughout the study.

Nitric oxide administration

Nitric oxide in nitrogen at a concentration of 450 parts per million (ppm) (Air Liquide, Meudon, France) was delivered continuously via the inspiratory limb of the ventilator immediately downstream from the humidifier. Intratracheal gas was sampled by continuous aspiration through the endotracheal tube (suction flow: 1 l/min) so as to allow continuous monitoring of inspiratory, expiratory, and mean nitric oxide and NO_2 concentrations using a chemiluminescence apparatus (NOX 4000, Aix-en-Provence, France). A flowmeter delivering flows within a range of 1–999 ml/min (Air Liquide, Meudon, France) was set to achieve the desired inspiratory tracheal concentration. Inhaled NO was introduced when PaO_2/FiO_2 was lower than 150 mmHg. Upon inclusion, patients had been receiving inhaled NO for periods ranging from 1 h to 5 days. All patients included in the present study were inhaled NO responders (improvement in $PaO_2 > 20\,\%$).

Protocol

Baseline measurements were performed under iNO 10 ppm. Because of the severity of ARDS and the consequences of an abrupt withdrawal of inhaled NO [19], baseline measurements without iNO were not performed. Therefore, the protocol consisted of two consecutive 30-min hemodynamic and blood gas measurements in a set order, i.e., after addition of a constant intravenous infusion of almitrine bismesylate 5 μg/kg per minute (Vectarion, Euthérapie, Neuilly, France) and after the addition of a constant intravenous infusion of almitrine bismesylate 16 μg/kg per minute. Because of the prolonged half-life of almitrine bismesylate [20], drug infusion rate was not randomized.

Statistical analysis

All statistical tests were performed by an experienced statistician (X. Thirion). Data were expressed as mean ± SD for parametric data or median (range) for non-parametric data. Statistical calculation was performed using the SPSS 9.0 package (SPSS, Chicago, Ill., USA). Distribution was checked. When distribution was normal, a one-way analysis of variance was used to evaluate the effects of almitrine bismesylate. For intra-group changes, Friedman's test or Dunnett's *t*-test for multiple comparisons were applied to compare the variations with control values. A patient was considered as a responder to addition of almitrine bismesylate when the increase of the PaO_2/FiO_2 ratio was at least 20 % over baseline (inhaled NO alone).

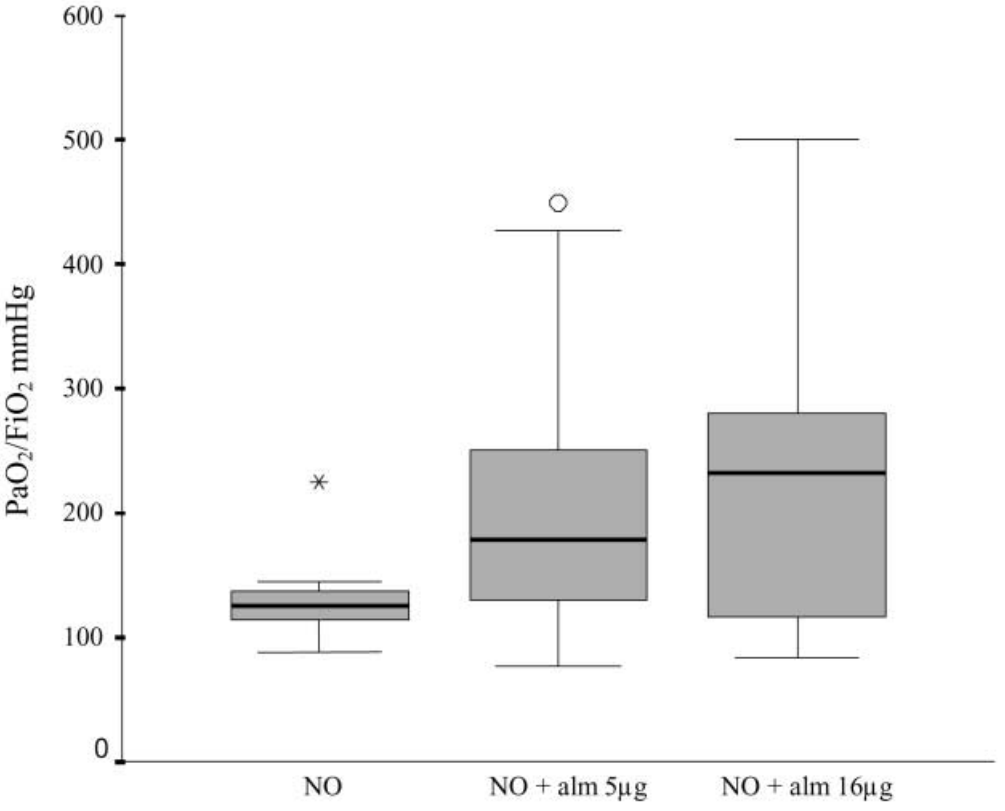

Fig. 1 Evolution of PaO_2/FiO_2. Each box plot represents the median, 25th, and 75th percentiles and largest and smallest values that are not outliers. Outliers (cases with values between 1.5 and 3 box-lengths from the upper or lower edge of the box) are presented as *open circles*. Extremes (cases with values more than 3 box-lengths from the upper or lower edge of the box) are presented as a *cross*. NO 10 ppm + almitrine 16 μg/kg per minute vs NO, $P < 0.02$; NO 10 ppm + almitrine 5 μg/kg per minute vs NO, $P < 0.05$; NO 10 ppm + almitrine 16 μg/kg per minute vs NO + almitrine 5 μg/kg per minute, $P < 0.05$ by Friedman's test

Results

Mean respiratory parameters at the time of inclusion were as follows: exhaled tidal volume: 8.5 ± 1.5 ml/kg; respiratory rate: 20 ± 2 cycles/min; PEEP 11.8 ± 2.0 cmH_2O; FiO_2: 0.75 ± 0.12; and peak inspiratory pressure: 33 ± 3 cmH_2O. The mean dose regimen of norepinephrine was 0.5 ± 0.45 μg/kg per minute (range 0.08–2.08 μg/kg per minute).

Evolution of $PaO_2/FiO2$

At the time of inclusion ARDS was assessed as severe, i.e., LIS greater than 2.5 in all patients with a mean PaO_2/FiO_2 ratio of 121 ± 35 mmHg with inhaled NO. After administration of almitrine bismesylate at a dose of 5 μg/kg per minute, median PaO_2/FiO_2 was 160 (77–450) mmHg. After 16 μg/kg per minute of almitrine bismesylate in association with inhaled NO, median PaO_2/FiO_2 was 227 (84–501) mmHg. A Friedman test comparing these three measurements demonstrated a significant improvement in oxygenation under almitrine bismesylate ($P < 0.02$). A dose regimen of 16 μg/kg per minute of almitrine bismesylate produced a greater increase of PaO_2/FiO_2 ($P < 0.05$) as compared with 5 μg/kg per minute (Fig. 1). Individual data are detailed in Fig. 2. Using an increase of at least 20% as the cutoff for defining a responder, ten patients (66%) responded to 5 μg/kg per minute almitrine bismesylate and 11 patients (73%) to 16 μg/kg per minute. In the seven more hypoxaemic patients ($PaO_2/FiO_2 < 120$ mmHg under NO alone), the high dose of almitrine produced a further improvement in PaO_2/FiO_2 (> 20%) in five patients as compared with low dose. Clinical characteristics and norepinephrine dose regimen were not different between almitrine bismesylate responders and non-responders. There was no correlation between norepinephrine infusion rate and increase in PaO_2 in the responder group. Four of five non-responders died, while only one of ten responders died.

Effects on hemodynamic and respiratory parameters

One-way ANOVA showed that administration of almitrine bismesylate led to a significant increase in MPAP ($P < 0.03$) (Table 2). The increase in MPAP observed with 16 μg/kg per minute was not significantly higher than that observed with 5 μg/kg per minute. Almitrine bismesylate did not increase PVRI or any of the other hemodynamic and respiratory parameters.

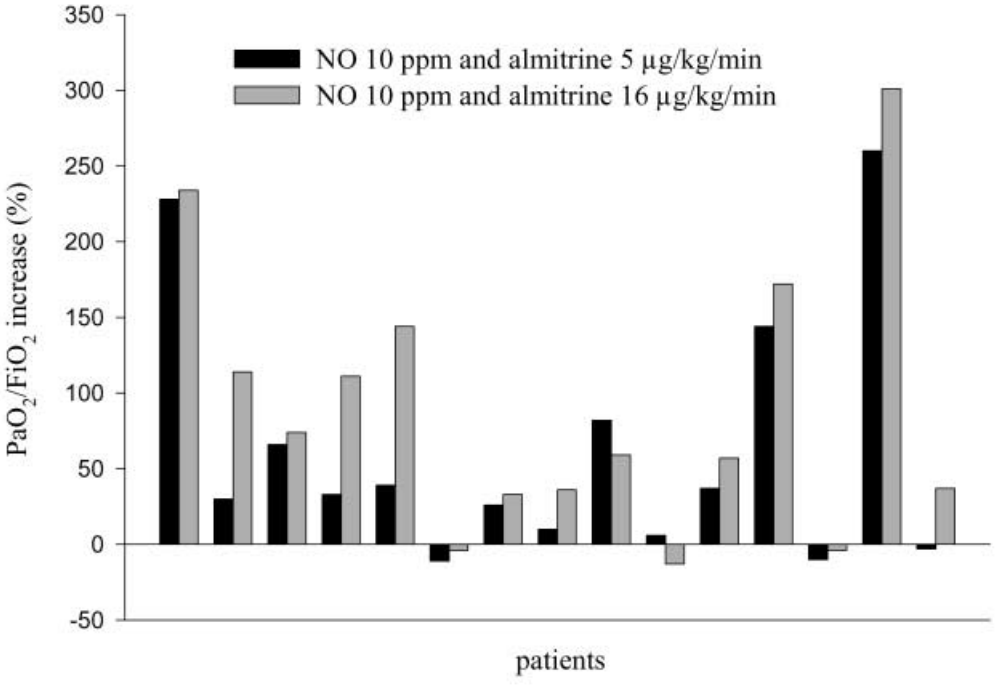

Fig. 2 respective potencies of inhaled NO with almitrine (5 µg/kg per minute and 16 µg/kg per minute) for increasing PaO_2/FiO_2 as compared with inhaled NO alone. Data are expressed in percentage

Discussion

The present study shows that intravenously administered almitrine bismesylate improved PaO_2 in ARDS patients iNO responders receiving concomitantly inhaled NO and norepinephrine (for septic shock). Moreover, this improvement was significantly greater using a dose of 16 µg/kg per minute rather than 5 µg/kg per minute. There was no significant difference between the two regimens with regard to the number of responders (11 vs 10). However, since the higher dose led to a greater response, the inspired fraction of oxygen could be lowered sooner in most cases. This could be an advantage by decreasing the potential risk of oxygen toxicity.

The present study aimed to fine-tune our previously published results [15] showing that a low dose and a high dose of almitrine bismesylate administrated to ARDS patients receiving norepinephrine and inhaled NO (whether they were iNO responders or not) produced the same effect on oxygenation. In the present study we found that a high dose of almitrine bismesylate is able to induce a greater improvement in oxygenation than a low dose in a population of ARDS patients with sepsis (all iNO responders) receiving norepinephrine and inhaled NO. The differences observed between the two studies could also be explained by a lack of power of our previous report [15]. Indeed, only ten patients were included in an additional trial [15], while 41 patients have been included in the main part of the study [15]. We have previously demonstrated that almitrine bismesylate (16 µg/kg per minute) not associated with inhaled NO was unable to improve significantly oxygen-

Table 2 Respiratory and haemodynamic parameters (*CI* cardiac index, *HR* heart rate, *MPAP* mean pulmonary arterial pressure, *MAP* mean arterial pressure, *Paop* pulmonary arterial occlusion pressure, *PVRI* pulmonary vascular resistances index, *RAP* right atrial pressure)

	NO (10 ppm)	NO+Almitrine (5 µg/kg/min)	NO+Almitrine (16 µg/kg/min)	ANOVA
$PaCO_2$ (mmHg)	45 ± 8	45 ± 9	45 ± 9	NS
SvO_2 (%)	73 ± 7	74 ± 8	75 ± 7	NS
MPAP (mmHg)	22 ± 5	25 ± 4†	27 ± 6†	< 0.05
MAP (mmHg)	71 ± 9	78 ± 15	84 ± 16	NS
HR (beats/min)	93 ± 22	92 ± 23	94 ± 24	NS
Paop (mmHg)	11 ± 3	11 ± 5	12 ± 5	NS
RAP (mmHg)	7 ± 4	9 ± 5	10 ± 5	NS
CI (L/min/m^2)	4.0 ± 1.0	3.9 ± 1.0	4.0 ± 1.1	NS
PVRI (dyne·sec/cm^5/m^2)	255 ± 97	304 ± 108	292 ± 106	NS
QVA/QT (%)	38 ± 12	35 ± 12	39 ± 13	NS

Comparison versus NO 10 ppm by Dunnett test: †$P < 0.01$

ation in ARDS patients receiving norepinephrine [15, 16]. In our previously published study [15], it was noted that almitrine bismesylate did not induce an improvement in oxygenation when combined with inhaled NO when the patients concomitantly received norepinephrine. As we have demonstrated that this result was not caused by an excessive amount of almitrine bismesylate [15], another hypothesis was that (as suggested by the distribution of the values of PaO_2/FiO_2 presented in Fig. 2 [15]) inhaled NO could restore the efficiency of almitrine bismesylate only in iNO responders by counteracting the non-specific diffuse vasoconstriction related to norepinephrine, and finally facilitating the redistribution of blood flow towards well-ventilated pulmonary areas. The results of the present study supported this latter hypothesis.

Our results are different from those of Gallart et al. [3] who reported a maximal increase of PaO_2/FiO_2 with 2 μg/kg per minute almitrine bismesylate in patients with sepsis with ARDS treated with inhaled NO. Several differences between the two studies could explain this discrepancy. Unlike Gallart et al. [3] in whose study all but two patients were postoperative or multiple trauma patients, we had only two surgical patients. Moreover in the present study, norepinephrine was used strictly as a vasoactive agent.

Despite sepsis and NO inhalation, most of the patients presented a slight increase of RVPI prior to almitrine infusion. Indeed, hypoxia is responsible for a local inhibition of NO synthase inducible during sepsis [21]. Moreover, norepinephrine administration potentiates this increase. The lack of increase in RVPI between the two doses could be explained in part by the large distribution of PVRI and in part by the small variations of the three components taken into account in the calculation of this parameter. Indeed, the small increase in PAOP and cardiac index between the two regimens could have lessened the weight of the increase of MPAP in the calculation of PVRI. Despite an increase in PaO_2, almitrine did not improve shunt. This can be explained, first, by a lack of power of the study, second, because of the possible variations of the components of this parameter, and finally because of the difficulty in showing an improvement in oxygen content in highly saturated hemoglobin.

Almitrine bismesylate has previously been found to have beneficial effects on oxygenation in ARDS patients [1, 10, 11]. Gotschall et al. [22] suggested that almitrine bismesylate potentates hypoxic constriction at low doses (< 20 μg/kg per minute) but causes diffuse pulmonary vasoconstriction rendering vessels unresponsive to hypoxia at high doses. Russell et al. [23] also reported dose-dependent effects of almitrine. These findings in isolated perfused lungs may not be comparable to patients treated in a clinical setting under different conditions and dose regimens.

In the present study, two regimens of almitrine bismesylate were used, i.e., 16 μg/kg per minute and 5 μg/kg per minute. Sixteen μg/kg per minute is the usual dose regimen for clinical studies using short-term infusion whereas 5 μg/kg per minute is the preferred regimen to limit the long-term and probably dose-dependent effects of almitrine bismesylate in critically ill patients [2, 24]. Prolonged administration of almitrine bismesylate has been implicated in reversible peripheral neuropathies in patients with COPD [25, 26]. This complication is often associated with plasma levels > 400 ng/ml [23]. In a group of 17 ARDS patients, Gallart et al. [1] reported plasma levels > 400 ng/ml in all but one patient (16/17) receiving 16 μg/kg per minute of almitrine bismesylate as opposed to only one patient receiving 4 μg/kg per minute, suggesting that the lower dose regimen is safe for acute administration. In eight of 25 ARDS patients, B'chir et al. [2] observed increased plasma lactate concentrations associated with impaired hepatic function within the first 24 h of intravenous administration of 2–8 μg/kg per minute almitrine bismesylate. The amount of almitrine bismesylate administered in the first 24 h was greater in patients showing high lactate levels than those showing low lactate levels. Because of the short period of the protocol in our study, plasma lactate level and liver function tests were not evaluated.

We found that the lack of response to almitrine seems to be a factor of poor prognosis. However the present study was not designed to evaluate the effect of almitrine on outcome. Moreover, the small number of patients included in the present study precludes any interpretation of this result.

In conclusion, intravenously administered almitrine bismesylate markedly improved arterial oxygenation in ARDS patients with sepsis receiving norepinephrine and responding to inhaled NO. A greater increase in PaO_2/FiO_2 was achieved using an infusion rate of 16 μg/kg per minute than 5 μg/kg per minute without any deleterious effect on cardiac output. A high-dose regimen of almitrine is not necessary in all ARDS patients under norepinephrine, but it is often able to produce a further improvement in oxygenation in the more hypoxaemic patients. Although oxygenation improvement may not be the best criteria to evaluate the efficacy of treatments in ARDS patients, it is still important to evaluate therapeutic combinations that could permit us to decrease FiO_2 and ventilation requirements. Further study will need to evaluate the potential toxicity of long-term use of this high-dose regimen of almitrine bismesylate and to verify whether this therapeutic favorably impacts on outcome.

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