Intravenous Almitrine Combined with Inhaled Nitric Oxide for Acute Respiratory Distress Syndrome

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Inhaled nitric oxide (iNO), a selective pulmonary vasodilator and intravenously administered almitrine, a selective pulmonary vasoconstrictor, have been shown to increase Pa_{O_2} in patients with acute respiratory distress syndrome (ARDS). This prospective study was undertaken to assess the cardiopulmonary effects of combining both drugs. In 48 consecutive patients with early ARDS, cardiorespiratory parameters were measured at control, after iNO 5 ppm, after almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and after the combination of both drugs. In 30 patients, dose response to 2, 4, and 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine with and without NO was determined. Almitrine and lactate plasma concentrations were measured in 17 patients. Using pure O_2, Pa_{O_2} increased by 75 $\pm$ 8 mm Hg after iNO, by 101 $\pm$ 12 mm Hg after almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and by 175 $\pm$ 18 mm Hg after almitrine combined with iNO ($p < 0.001$). In 63% of the patients, Pa_{O_2} increased by more than 100% with the combination of both drugs. Mean pulmonary artery pressure ($\overline{Ppa}$) increased by 1.4 $\pm$ 0.2 mm Hg with almitrine 4 $\mu g/kg/min$ ($p < 0.001$) and decreased by 3.4 $\pm$ 0.4 mm Hg with iNO and by 1.5 $\pm$ 0.3 mm Hg with the combination ($p < 0.001$). The maximum increase in Pa_{O_2} was obtained at almitrine concentrations $\leq$ 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, whereas almitrine increased $\overline{Ppa}$ dose-dependently. Almitrine plasma concentrations also increased dose-dependently and returned to values close to zero after 12 h. In many patients with early ARDS, the combination of iNO 5 ppm and almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dramatically increases Pa_{O_2} without apparent deleterious effect allowing a rapid reduction in inspired fraction of O_2. The long-term consequences of this immediate beneficial effect remain to be determined. Gallart L, Lu Q, Puybasset L, Umamaheswara Rao GS, Coriat P, Rouby J-J, and The NO Almitrine Study Group. Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome.

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In acute respiratory distress syndrome (ARDS), the classic therapeutic approach for reversing hypoxemia is to apply a positive end-expiratory pressure (PEEP) during mechanical ventilation to recruit nonventilated alveolar territories that remain perfused. Because of the major reduction in aerated lung volume, high peak airway pressure and lung volutrauma may result from mechanical ventilation if minute ventilation is not substantially reduced (1, 2). Recently, a ventilatory strategy aimed at "keeping the lung open" with a concomitant reduction of tidal volume has been recommended to treat patients with ARDS (3). It results in "permissive hypercapnia," which carries its own risks (4).

Another therapeutic option is to redistribute pulmonary blood flow towards aerated lung areas through selective vasoconstriction of pulmonary vessels perfusing non-aerated lung areas or selective vasodilation of pulmonary vessels perfusing aerated lung areas. In the late eighties, intravenously administered almitrine, a selective pulmonary vasoconstrictor, was shown to increase arterial oxygenation via a redistribution of pulmonary blood flow from shunt areas to lung units with normal ventilation perfusion ratio (5). In the early nineties, similar beneficial effects were obtained by administering inhaled nitric oxide (iNO), a selective pulmonary vasodilator, in patients with ARDS (4, 6–8). Recently, 5 to 10 parts per million of iNO combined with 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine administered intravenously were shown to have additive effects on arterial oxygenation in patients with ARDS (9–11).

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The aims of this prospective study performed in patients with early ARDS and impaired oxygenation were (*1*) to quantify the respective effects on arterial oxygenation of iNO, almitrine and the combination of almitrine and iNO, (*2*) to determine the dose response and assess short-term toxicity of almitrine combined with iNO.

METHODS

Patients

The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of our institution. After obtaining written informed consent from the patient's next of kin, 48 consecutive and unselected patients with an ARDS dating from less than 72 h were included according to the following criteria: (*1*) extensive bilateral infiltrates on chest radiograph and computerized tomographic (CT) scan, (*2*) $Pa_{O_2} < 150$ mm Hg at an $F_{I_{O_2}}$ of 1 without PEEP. Patients with left ventricular dysfunction (pulmonary capillary wedge pressure [Ppcw] > 18 mm Hg and left ventricular ejection fraction < 50% as assessed by transesophageal echocardiography) were excluded. Septic shock was defined as sepsis with systolic blood pressure < 90 mm Hg along with the presence of perfusion abnormalities such as lactic acidosis and oliguria (12).

All patients were anesthetized and artificially ventilated in a volume-controlled mode and had in place arterial and thermistor Swan-Ganz catheters for cardiovascular monitoring. As previously described (13), all patients had a high resolution thoracic CT scan in order to assess the extension of nonaerated lung areas after PEEP administration.

Measurements

Arterial pressure, EKG, and cardiac filling pressures were continuously recorded on a Gould ES 1000 recorder (Gould Ltd, Ilford, UK) and measured at end-expiration. Cardiac output was measured using the thermodilution technique with simultaneous withdrawing of systemic and pulmonary arterial blood samples within 1 min. Pa_{O_2}, $P\bar{v}_{O_2}$, Pa_{CO_2} and pH were measured using a conventional analyzer (ILBGE; Instrumentation Laboratories, Paris, France), whereas hemoglobin and methemoglobin concentrations and arterial and mixed venous oxygen saturations were measured using an OSM3 hemoximeter (Radiometer Copenhagen, Neuilly-Plaisance, France). Arterial and mixed venous blood samples that showed hemoglobin concentrations differing by more than 0.1 g/100 ml were considered diluted and the highest hemoglobin concentration was used to calculate oxygen contents. Standard formulas were used to calculate cardiac index (CI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), pulmonary shunt ($\dot{Q}s/\dot{Q}T$), oxygen delivery (D_{O_2}), and oxygen consumption (V_{O_2}). Expired CO_2 was continuously recorded and measured using an infrared capnometer, and the ratio of alveolar deadspace to tidal volume (V_{DA}/V_T), was calculated as previoulsy described (11, 13). Respiratory pressure–volume (P–V) curves on inflation were obtained in each patient using the supersyringe method in order to determine opening pressure (Pop) and respiratory compliance (Crs) (14).

NO was sequentially administered from a cylinder containing NO 900 ppm in nitrogen (Air Liquide, Meudon, France) into the proximal inspiratory limb of the ventilator using a sequential device delivering stable and reproducible inspiratory NO concentrations (15). Inspiratory tracheal concentrations of NO and NO_2 were continuously measured using a fast-response chemiluminescence apparatus (NOX 4000 Sérès; NOX, Aix-en-provence, France) (11).

Almitrine plasma concentrations were determined by high performance liquid chromatography with detection by ultraviolet (HPLC-UV), developed by Servier (Courbevoie, France) and validated and performed by Biotec Centre (Orléans, France). The method is linear from 1 to 500 ng/ml. The mean accuracy is −7% and −14%, respectively for the repeatability (intraday assays) and reproducibility (interday assays). The coefficient of variation was, respectively, 19 and 17%. Catecholamine and lactic acid blood concentrations were determined at control (PEEP) and after the end of 1 h of almitrine infusion. As previously described (4), catecholamine plasma concentrations were determined using a radioenzymatic assay based on the enzymatic methylation of norepinephrine and epinephrine by catechol-*O*-methyltransferase in the presence of tritiated *S*-adenosyl-L-methionine (radiolabeled SAMe^{3}H; Amersham, Buckinghamshire, UK). Normal values were 200 to 300 pg/ml for norepinephrine (intra-assay variability, 4.2%, and interassay variability, 7.5%) and 25 to 55 pg/ml for epinephrine (intra-assay variability, 3.6%, and interassay variability, 10%). Lactic acid plasma concentrations were measured with Dimension (DuPont de Nemours, Les Ulis, France). The technique used is a modification of the Marbach and Weil method (16), which employs the oxidation of lactate to piruvate. Reference interval was 0.4 to 2 mmol/L. Coefficient of variation was between 4 and 8%. Quality control was supported by an independent laboratory (Bio-Rad, Paris, France).

Study Protocol

On the day of inclusion, the CT scan was performed and ventilatory settings were optimized. A PEEP of 10 cm H_2O, which was equal to or greater than the Pop that could be identified on the P–V curve of 25 patients, was applied to each patient. Tidal volume and respiratory

TABLE 1

EFFECTS OF ALMITRINE AND INHALED NITRIC OXIDE ON HEMODYNAMIC AND RESPIRATORY PARAMETERS: MECHANICAL VENTILATION WITH 100% O_2 AND POSITIVE END-EXPIRATORY PRESSURE OF 10 cm H_2O*

					Two-Way Analysis of Variance		
	Control	NO (*5 ppm*)	Almitrine ($4\ \mu g \cdot kg^{-1} \cdot min^{-1}$)	Almitrine + NO	Factor NO	Factor Almitrine	p Value Interaction
Pa_{O_2}, mm Hg	141 ± 10	215 ± 13	242 ± 15	310 ± 15	0.0001	0.0001	NS
$\dot{Q}s/\dot{Q}T$, %	38 ± 1	34 ± 1	33 ± 1	30 ± 1	0.0001	0.0001	NS
$S\bar{v}_{O_2}$, %	70 ± 1	73 ± 1	74 ± 1	76 ± 1	0.0001	0.0001	NS
D_{O_2}, ml · min^{-1} · m^{-2}	402 ± 20	397 ± 19	415 ± 2	421 ± 21	NS	NS	NS
$\dot{V}_{O_2}$, ml · min^{-1} · m^{-2}	103 ± 6	102 ± 5	105 ± 6	103 ± 6	NS	NS	NS
Pa_{CO_2}, mm Hg	44 ± 1	42 ± 1	42 ± 1	42 ± 1	0.0002	0.05	NS
V_{DA}/V_T, %	35 ± 1	32 ± 2	29 ± 2	28 ± 2	0.0008	0.0001	NS
$\overline{Ppa}$, mm Hg	24 ± 1	21.3 ± 1	26 ± 1	23 ± 1	0.0001	0.0006	NS
PVRI, dyn · s · cm^{-5} · m^2	404 ± 25	333 ± 21	443 ± 30	353 ± 19	0.0001	0.0007	NS
HR, beats/min	87 ± 3	83 ± 3	85 ± 3	85 ± 3	NS	NS	NS
$\overline{Pa}$, mm Hg	75 ± 3	75 ± 3	75 ± 2	74 ± 2	NS	NS	NS
CI, L · min^{-1} · m^{-2}	3.2 ± 0.2	3.1 ± 0.2	3.2 ± 0.2	3.3 ± 0.2	NS	NS	NS

Definition of abbreviations: CI = cardiac index; D_{O_2} = oxygen delivery; HR = heart rate; NO = nitric oxide; $\overline{Pa}$ = mean arterial pressure; $\overline{Ppa}$ = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; $\dot{Q}s/\dot{Q}T$ = pulmonary shunt; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation; $\dot{V}_{O_2}$ = oxygen consumption; V_{DA}/V_T = alveolar dead space to tidal volume ratio.

* Values are given as mean ± SEM. Right columns show the p value of two-way ANOVA for two within-factors (factor NO and factor almitrine). The absence of significant interaction indicates that the effect of iNO and almitrine are additive and not synergistic.

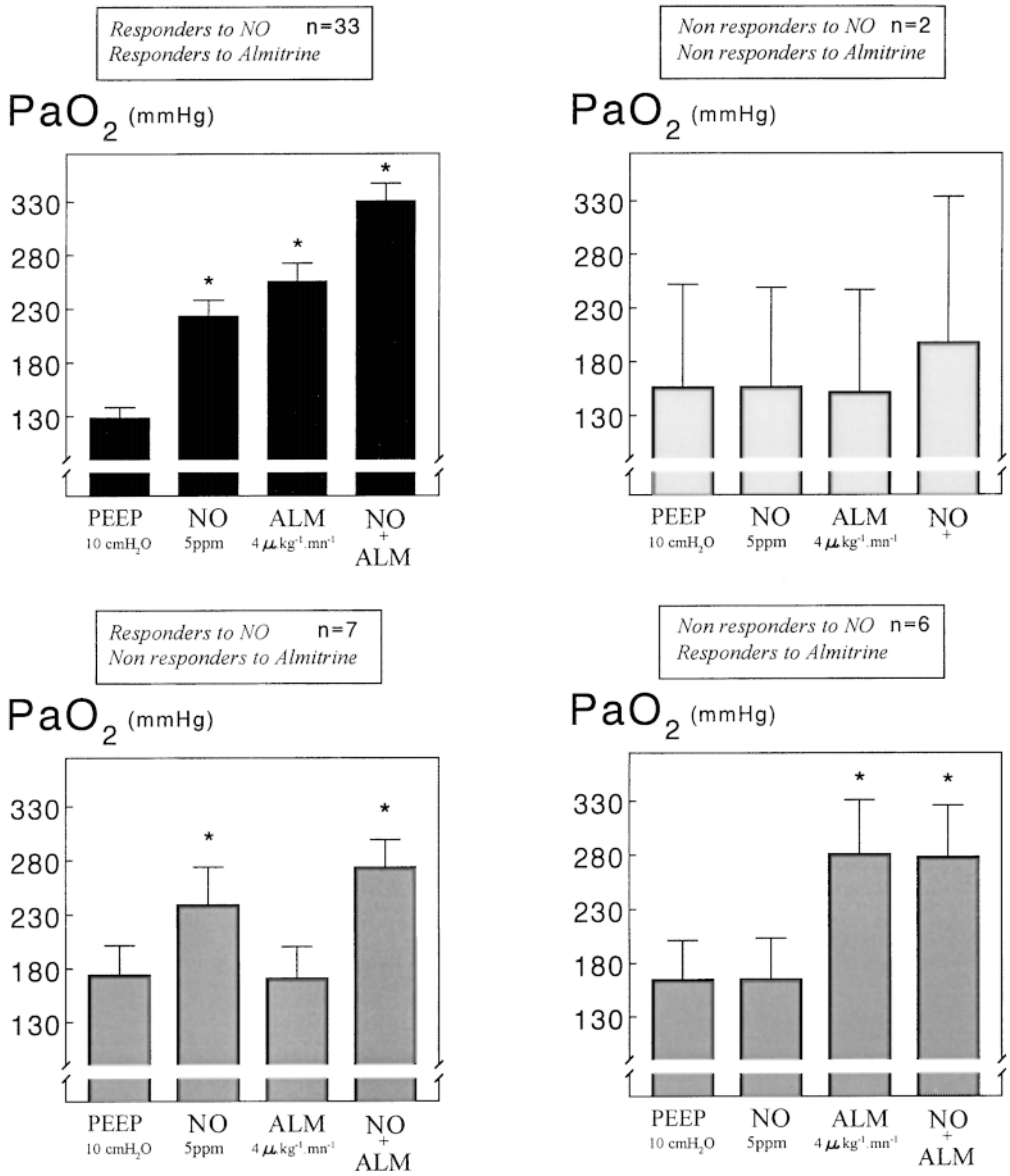

Figure 1. Mean changes in Pa_{O_2} in 48 patients with ARDS according to the response to almitrine, iNO, and the combination of both drugs (*$p < 0.05$ versus PEEP 10 cm H_2O).

rate were adjusted to maintain Pa_{CO_2} between 40 and 50 mm Hg while maintaining peak airway pressure below 35 cm H_2O (3). On the second day of the study, hemodynamic and respiratory parameters were recorded: (*1*) at control, (*2*) after administration of iNO 5 ppm for 15 min, (*3*) after administration of almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h, and (*4*) after administration of almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and iNO 5 ppm for 15 min. After this first part of the study was completed, almitrine and NO were stopped and the patients were ventilated until the next morning using PEEP and an $F_{I_{O_2}}$ required for maintaining an arterial oxygen saturation $\geq$ 90%. On the third day of the study, dose response to almitrine was studied in 30 patients. Cardiorespiratory parameters were measured after three doses of almitrine were administered for 1 h with and without iNO 5 ppm. Because of the long duration of action of almitrine, the three doses were administered in the same order: 2, 4, and 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$. For a given dose of almitrine, cardiorespiratory parameters were measured either without iNO or after 15 min of administration of iNO 5 ppm, the order of administration being randomized. Plasma concentrations of almitrine and lactate were measured at the end of each infusion period (n = 17) and 15 min, 1 h, 2 h, and 12 h after cessation of the 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion (n = 6). At control and after administration of almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h, catecholamine plasma concentrations were measured in eight patients.

At the end of the study, patients who had responded to both almitrine and iNO were continued on both therapies for a mean period of 4 $\pm$ 3 d; patients who had responded to iNO alone were treated with iNO 5 ppm; patients who had responded to almitrine alone were treated with 2 or 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, according to their dose response to almitrine, for a mean duration of 3 $\pm$ 3 d. Patients who had not responded to any of the therapies did not subsequently received iNO or almitrine. Periodically, almitrine and iNO were interrupted in order to assess their effect on arterial oxygenation. They were definitively stopped when an arterial oxygen saturation could be maintained above 90% solely with a PEEP of 10 cm H_2O and an $F_{I_{O_2}} \leq 0.4$.

Statistical Analysis

Hemodynamic and respiratory parameters at control and after administration of iNO, almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the combination of both drugs were compared by a two-way analysis of variance for two within-factors, factor iNO and factor almitrine. The presence or the lack of a significant interaction between the two factors allowed us to

test whether NO and almitrine act synergistically or additively. Univariate and multivariate analysis were performed to identify factors predicting the response to almitrine and iNO. The following parameters were tested : control values of Pa_{O_2}, Pa_{CO_2}, $\overline{Ppa}$, PVRI, $\dot{Q}s/\dot{Q}T$, V_{DA}/V_T, Crs, extension of lung hyperdensities, morphologic aspects of the thoracic CT scan (nondependent diffuse patchy hyperdensities versus bilateral consolidation of lower lobe), and presence or absence of septic shock. Dose response to almitrine was tested by a one-way analysis of variance for repeated measures (2, 4, and 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The influence of septic shock and iNO 5 ppm on dose response to almitrine was analyzed by a three-way analysis of variance for one grouping factor, factor shock and two within-factors, factor "dose of almitrine" and factor "iNO". All statistics were performed using Statview 4.0.2 and SuperANOVA softwares (Abacus Concepts Inc. Berkeley, CA). All data are presented as mean ± SEM, and a p value < 0.05 was considered as significant.

RESULTS

Forty-two male and six female patients (56 ± 2 yr of age) were included in the study. ARDS complicated major surgical procedures (n = 32), multiple trauma (n = 14), and medical diseases (n = 2) and was caused by acute bronchopneumonia

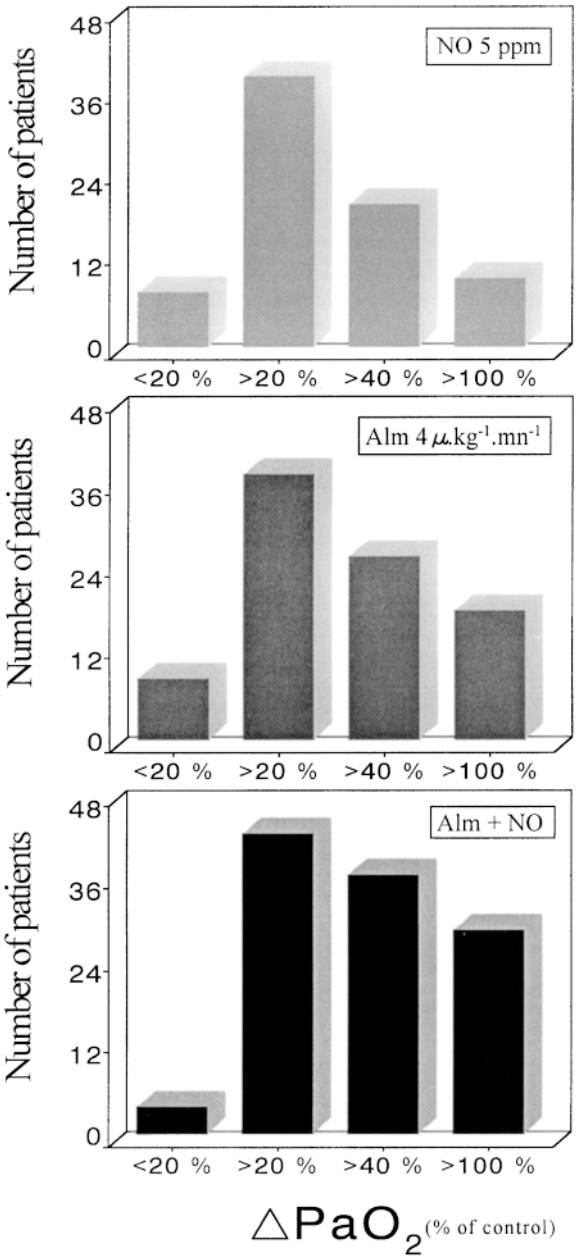

Figure 2. Respective potencies of iNO, almitrine, and the combination of both drugs for increasing Pa_{O_2} 20, 40, and 100% above control values in 48 patients with ARDS. The *y*-axis indicates the number of patients showing increases in Pa_{O_2} as defined on the *x*-axis. The *x*-axis indicates the cut-off value of the percentage increase in Pa_{O_2}. At 40 and 100% cutoff levels, almitrine combined with iNO was superior to almitrine alone, which was itself superior to iNO alone.

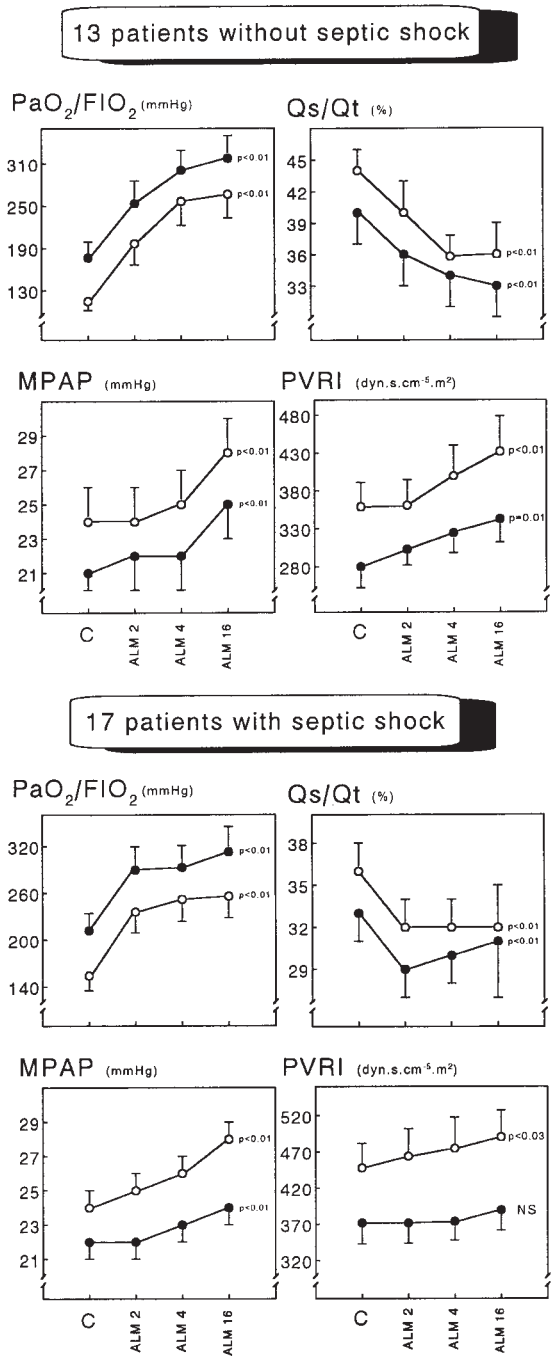

Figure 3. Dose response to almitrine in 30 patients with ARDS without (n = 13) and with (n = 17) septic shock, in the absence (*open circles*) or presence (*closed circles*) of iNO 5 ppm.

(n = 30), septic shock (n = 8), aspiration of gastric content (n = 4), pulmonary contusion (n = 4), and cardiopulmonary bypass (n = 2). Lung injury severity score (17) was 2.9 ± 0.1. Using pure O_2 and a PEEP of 10 cm H_2O, patients had a Pa_{O_2} of 141 ± 10 mm Hg, a V_{DA}/V_T of 35 ± 1%, a $\overline{Ppa}$ of 26 ± 1 mm Hg, a Crs of 51 ± 4 ml/cm H_2O and a percentage of nonaerated lung areas assessed with a high resolution CT scan of 45 ± 2%. Twenty-two patients had septic shock and were treated with norepinephrine. Twenty-five of the 48 patients included died (52%).

As shown in Table 1, almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and iNO increased Pa_{O_2} and $S\bar{v}_{O_2}$ and decreased $\dot{Q}S/\dot{Q}T$, Pa_{CO_2}, and V_{DA}/V_T significantly. When iNO and almitrine were combined, additive effects were observed. When defining a positive response as an increase in Pa_{O_2} of at least 20% from the control value, 69% of the patients responded to iNO and almitrine, 15% to iNO, but not to almitrine, 12% to almitrine but not to iNO, and 4% did not respond to either drug (Figure 1). As represented in Figure 2, almitrine was superior to NO alone for inducing increases in $Pa_{O_2} > 40\%$ of the control values. Increases ⩾ 100% were observed in 63% of the patients receiving the combination, in 45% of the patients receiving almitrine alone, and in only 25% of the patients receiving iNO alone ($p < 0.001$). In the 33 patients who responded to almitrine and iNO, both drugs were continued after the cessation of the study allowing to reduce $F_{I_{O_2}}$ below 0.6 in each of them.

Inhalation of NO resulted in a significant decrease in $\overline{Ppa}$ and PVRI, whereas almitrine slightly but significantly increased both parameters. The combination of iNO and almitrine resulted in a slight but significant decrease in $\overline{Ppa}$ and PVRI ($p < 0.001$). All other hemodynamic and respiratory parameters remained unchanged. None of the parameters tested as factors predicting the response to almitrine appeared statistically significant using the univariate analysis. In contrast, iNO-induced increase in Pa_{O_2} correlated well with the control values of $\overline{Ppa}$ ($p = 0.002$) and PVRI ($p = 0.002$).

As shown in Figure 3, the maximum increase in $Pa_{O_2}/F_{I_{O_2}}$ and decrease in $\dot{Q}S/\dot{Q}T$ were observed at almitrine concentrations of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in patients with septic shock and at concentrations of 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in patients without septic shock ($p < 0.001$). Dose response on $\overline{Ppa}$ and PVRI were similar in patients with and without septic shock. In both groups, $\overline{Ppa}$ and PVRI increased dose-dependently. The addition of iNO induced an additional increase in Pa_{O_2} and decrease in $\dot{Q}S/\dot{Q}T$, limited almitrine-induced increase in $\overline{Ppa}$ and PVRI but did not modify the dose response to almitrine. Almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ had no effect on plasma concentrations of norepinephrine (660 ± 306 versus 501 ± 151 pg/ml, n = 8), epinephrine (84 ± 29 versus 143 ± 73 pg/ml, n = 8) and lactate (Figure 4). As shown in Figure 5, almitrine plasma concentrations increased dose-dependently, were not different in patients with and without septic shock, and returned to values close to zero within 12 h after the cessation of almitrine infusion.

DISCUSSION

When combining iNO, a selective pulmonary vasodilator of ventilated lung areas, with intravenous almitrine, a selective pulmonary vasoconstrictor of nonventilated lung areas, an increase in arterial oxygenation was observed in patients with ARDS and persisting impaired arterial oxygenation despite optimization of ventilatory settings. The increase in Pa_{O_2} was

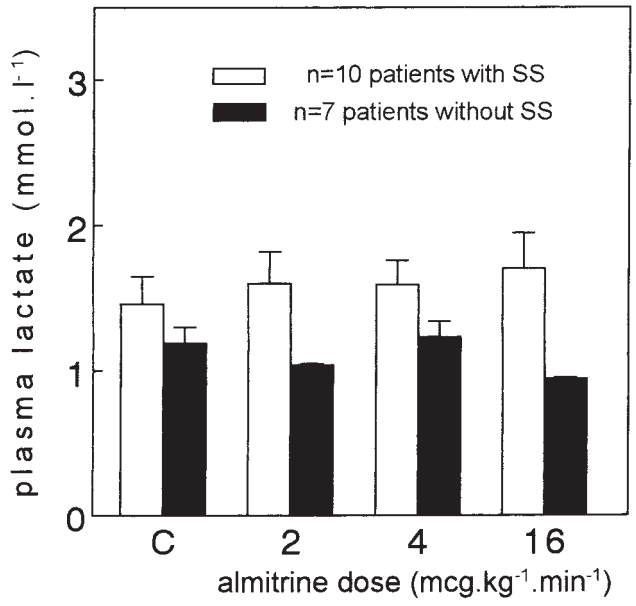

Figure 4. Mean changes in plasma lactate in 10 patients with ARDS and without septic shock (SS) and in seven patients with ARDS and septic shock after increasing doses of almitrine.

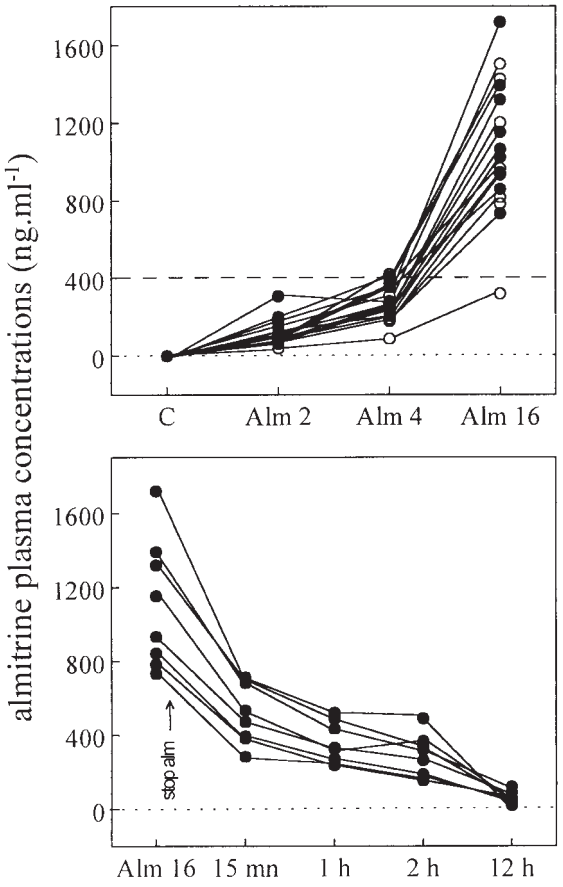

Figure 5. Almitrine plasma concentrations at increasing doses of almitrine (2, 4, and 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in 17 patients with ARDS. *Top panel* shows patients with septic shock (*open circles*) and patients without septic shock (*closed circles*). *Bottom panel* shows almitrine plasma concentrations measured in six patients without septic shock after discontinuation of a 1-h perfusion of almitrine at a dose of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

of a far greater magnitude than the one resulting from the administration of iNO or almitrine alone. Almitrine 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was superior to iNO 5 ppm for inducing an increase in $Pa_{O_2} > 40\%$ of control values and the combination of both drugs more than doubled the Pa_{O_2} in 63% of the patients. As a consequence, the inspired fraction of oxygen could be rapidly lowered below 0.6 in most of the patients, thereby limiting the risk of oxygen toxicity. The design of the present study did not allow us to assess whether this beneficial effect was sustained over time. These immediate beneficial effects were obtained with iNO concentrations and almitrine doses much lower than those previously recommended.

In the first study demonstrating the beneficial effects of almitrine on arterial oxygenation in patients with ARDS (5), the group of Rodriguez-Roisin used 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$, a concentration that, subsequently served as a reference for many investigators (9, 10, 18–20). In the present study, the maximal effect on arterial oxygenation was obtained for almitrine concentrations fourfold lower in patients without septic shock and eightfold lower in patients with septic shock. Similarly, in the first study reporting the beneficial effect of iNO on arterial oxygenation and pulmonary shunt in patients with ARDS (6), the group of Falke used concentrations of 18 and 36 ppm, referring to dose-response studies performed in experimental animals (21, 22). Further studies performed in patients with ARDS demonstrated that the maximal effect was observed at concentrations around 5 ppm (7, 11, 23, 24) and that the dose-response was not modified by the concomitant administration of almitrine (11).

Acute toxicity of iNO appears more related to the formation of nitrogen dioxide (NO_2) (23, 25, 26) than to methemoglobin accumulation in the blood (27). The concentration of 5 ppm that was used in the present study was shown to be associated with NO_2 concentrations inferior to the toxic threshold of 0.5 ppm (7, 11). One of the acute deleterious effect of almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ consists of an increase in pulmonary arterial pressure (5, 9, 11), which may generate additional leak of plasma towards the alveolar space in patients with ARDS. By using almitrine concentration $\leqslant 4\ \mu g \cdot kg^{-1} \cdot min^{-1}$ in combination with iNO, $\overline{Ppa}$ slightly but significantly decreased, thereby suppressing the risk of increasing pulmonary edema formation. Experimental studies have suggested that almitrine may inhibit oxidative phosphorylation and induce tissular hypoxemia (28). In the present study, plasma lactates remained unchanged after almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$, even in patients with septic shock and increased basal concentration of lactates, suggesting that almitrine does not worsen tissular hypoxia. Administration of almitrine over several months can be associated with the occurrence of peripheral neuropathy (29). Measurement of plasma concentrations of almitrine in patients with chronic obstructive pulmonary disease suffering from almitrine-induced peripheral neuropathy demonstrated plasma levels $\geqslant$ 400 ng/ml (30). In the present study, almitrine plasma concentrations $\geqslant$ 400 ng/ml were observed in all patients receiving 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and in only one patient receiving 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Although the significance of almitrine plasma concentrations might be different in acute or prolonged administration, these pharmacokinetic results strongly suggest that a dose of 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is safe in terms of acute toxicity.

By dilating constricted pulmonary veins and, to a lesser degree, constricted pulmonary arteries perfusing ventilated lung areas, iNO decreases pulmonary shunt by diverting pulmonary blood flow away from nonventilated regions and reduces the alveolar dead space to tidal volume ratio by increasing the perfusion of ventilated lung areas (4, 7, 11, 13, 15, 24, 31). In addition, it could also reduce the pulmonary transvascular albumin flux by decreasing capillary microvascular pressure (32). The present study confirms that at the early phase of ARDS, the response to iNO is related to the basal increase in $\overline{Ppa}$ and pulmonary vascular resistance (13, 23, 33). Several recent studies have shown that the beneficial effect of iNO on arterial oxygenation is not prolonged over time, lasting less than 72 h (31, 34, 35). In addition, the reduction of the $F_{I_{O_2}}$ resulting from the improvement in arterial oxygenation is of small clinical relevance (35). As a consequence, the interest for inhaled NO could decline in the future because of the lack of long-lasting effect on arterial oxygenation.

The beneficial effect of almitrine alone is related to a selective pulmonary vasoconstriction of precapillary pulmonary arteries perfusing lung areas exposed to a hypoxic challenge (36, 37). At doses $< 4\ \mu g \cdot kg^{-1} \cdot min^{-1}$, almitrine reinforces hypoxic pulmonary vasoconstriction, whereas at doses $\geqslant 4\ \mu g \cdot kg^{-1} \cdot min^{-1}$, it constricts the entire pulmonary vascular bed and may even partly impair hypoxic pulmonary vasoconstriction (18). These dose effects may explain the inconstancy of the beneficial effect of almitrine reported in humans (9, 20) and in experimental animals (19). The basal status of hypoxic pulmonary vasoconstriction appears as a factor influencing the response to almitrine: the more deficient the hypoxic pulmonary vasoconstriction, the greater the almitrine-induced constrictor effect in lung areas exposed to hypoxia (38). In patients with ARDS and sepsis, hypoxic pulmonary vasoconstriction may be impaired by vasodilating substances released from the activated pulmonary endothelium such as prostaglandin E1, prostacyclin, or endogenous NO (39). In such situations, pulmonary vessels exposed to hypoxia may become particularly sensitive to almitrine, explaining that maximal effects on arterial oxygenation and pulmonary shunt were obtained in patients with septic shock at lower almitrine concentrations than in patients without septic shock. By decreasing the perfusion of nonventilated lung areas, almitrine decreases pulmonary shunt and indirectly reduces alveolar dead space to tidal volume ratio by increasing the perfusion of ventilated lung areas (5). Almitrine may also induce slight but significant increases in heart rate and cardiac output in experimental animals (37). In the present study, both parameters and circulating catecholamines remained unchanged after almitrine administration, suggesting the lack of any systemic effects. Although it was easy to identify factors influencing the effects of iNO, we were unable to determine factors predicting the response to almitrine. An important limitation for using almitrine is the fact that the drug is commercially available in a limited number of European countries. In North America, it has not been approved for treating patients with COPD or ARDS. As a consequence, it still has to be considered as an experimental treatment and cannot be routinely used in the treatment of ARDS until controlled randomized studies demonstrate a long-lasting effect of almitrine alone or in combination with iNO on arterial oxygenation and a beneficial influence on the outcome of ARDS.

The resulting effects of combining almitrine and iNO are likely related to the respective vascular effect of each drug on aerated and nonaerated lung compartments and explain why additive and not synergistic respiratory effects were observed. It has recently been shown that an impaired hypoxic pulmonary vasoconstriction in nonaerated lung areas decreases the cardiopulmonary response to iNO (40). The present study confirms that when reinforcing hypoxic pulmonary vasoconstriction by small doses of almitrine, the NO-induced increase in arterial oxygenation can be markedly enhanced.

In conclusion, in 63% of patients with early ARDS and im-

paired oxygenation, the combination of iNO and almitrine more than doubled Pa_{O_2}. This beneficial effect was obtained without any apparent detrimental effect, suggesting that such a pharmacologic approach may be a safe therapeutic option to rapidly reduce $F_{I_{O_2}}$ below the toxic threshold of 0.6. Further controlled randomized studies are required to assess whether this immediate and spectacular improvement in arterial oxygenation continues over time and has any impact on the evolution of ARDS.

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