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## Inhaled Nitric Oxide, Almitrine Infusion, or Their Coadministration as a Treatment of Severe Hypoxemic Focal Lung Lesions

Didier Payen, M.D., Ph.D.,\* Jane Muret, M.D.,† Sadek Beloucif, M.D., Ph.D.,† Claire Gatecel, M.D.,‡  
Nathalie Kermarrec, M.D.,‡ Nathalie Guinard, M.D.,‡ Joaquim Mateo, M.D.‡

**Background:** The partition of pulmonary blood flow between normal and shunting zones is an important determinant of oxygen tension in arterial blood ( $\text{Pa}_{\text{O}_2}$ ). The authors hypothesized that the combination of inhaled nitric oxide (iNO) and almitrine infusion might have additional effects related to their pharmacologic properties to improve  $\text{Pa}_{\text{O}_2}$ . Such a combination was tested in patients with hypoxia caused by focal lung lesions, distinct from the acute respiratory distress syndrome.

**Methods:** Fifteen patients with hypoxic focal lung lesions despite optimal therapy were included and successively treated with (1) 5 ppm iNO, (2) low-dose almitrine infusion ( $5.5 \pm 1.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) during iNO, and (3) almitrine infusion alone (with NO turned off). Then iNO was reintroduced and we studied the effect of the coadministration in reducing the fractional concentration of oxygen in inspired gas ( $\text{Fi}_{\text{O}_2}$ ) and positive end-expiratory pressure (PEEP) levels. Changes in blood gases and pulmonary and systemic hemodynamics were measured.

**Results:** Systemic hemodynamic variables remained stable in all protocol conditions. Use of iNO improved arterial oxygenation and decreased intrapulmonary shunt. Almitrine similarly improved  $\text{Pa}_{\text{O}_2}$  but increased pulmonary artery pressure and right atrial pressure. Coadministration of iNO and almitrine improved  $\text{Pa}_{\text{O}_2}$  compared with each drug alone and with control. All patients responded (that is, they had at least a +30% increase in  $\text{Pa}_{\text{O}_2}$ ) to this coadministration. When the drug combination was continued,  $\text{Fi}_{\text{O}_2}$  and PEEP could be reduced over 8 h. The hospital mortality rate was 33% and unrelated to hypoxia.

**Conclusions:** In hypoxemic focal lung lesions, iNO or low-dose almitrine markedly improved  $\text{Pa}_{\text{O}_2}$  to a similar extent. Furthermore, the coadministration amplified the  $\text{Pa}_{\text{O}_2}$  increase at a level that allowed reductions in  $\text{Fi}_{\text{O}_2}$  and PEEP levels. (Key words: Pulmonary blood flow partition; pulmonary vascular tone; ventilatory settings.)

SEVERE hypoxia remains a challenging situation to treat in intensive care units. Despite different causes, radiologic extension, and pulmonary  $\text{V}_A/\text{Q}$  mismatching mechanisms, the severity of impaired gas exchange is commonly assessed by the ratio of oxygen tension in arterial blood ( $\text{Pa}_{\text{O}_2}$ ) to the fractional concentration of oxygen in inspired gas ( $\text{Fi}_{\text{O}_2}$ ), calculated intrapulmonary shunt, or both.<sup>1</sup> As an example, a similar hypoxia might be observed in patients with acute respiratory distress syndrome (ARDS; diffuse lesions) and with limited pulmonary lesions, because similar fractions of pulmonary blood flow perfuses hypoxic zones. Consequently, it is not the extension of the lesions but the partition of flow toward the hypoxic zones that determines the final  $\text{Pa}_{\text{O}_2}$  level.<sup>2</sup>

As a result, the therapeutic strategy might be different, because the benefit of alveolar recruitment in injured zones may be deleterious for the remaining normal zones. The pharmacologic manipulation of the flow component of the  $\text{V}_A/\text{Q}$  equation offers the interesting possibility of reducing hypoxia while limiting undesirable complications of mechanical ventilation.<sup>3-5</sup> Such a concept has been established by the use of inhaled NO (iNO) as a means to correct hypoxia in ARDS.<sup>6</sup> The iNO-induced redistribution of pulmonary blood flow toward nonshunting zones improves arterial  $\text{Pa}_{\text{O}_2}$  in relation to regional pulmonary vasodilatation.<sup>7</sup> One can then hypothesize that the mechanism by which NO improves  $\text{Pa}_{\text{O}_2}$  might be amplified if the regional vascular conductance gradient between aerated and shunting zones is increased. Since publication of the initial report showing the benefit of the coadministration of intravenous almi-

\* Professor and Chairman, Department of Anesthesiology and Critical Care Medicine.

† Associate Professor.

‡ Assistant Professor.

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Address reprint requests to Dr. Payen: Department of Anesthesiology and Critical Care Medicine, Lariboisière University Hospital, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France. Address electronic mail to: didier.payen@hol.fr



trine bismesylate and iNO in ARDS patients in term of  $\text{PaO}_2$  improvement,<sup>8</sup> some studies concerning mainly ARDS patients have shown the potentialization of the effects of iNO by intravenous almitrine.<sup>9,10</sup> Almitrine seems to be particularly suitable, because it has been shown to reinforce,<sup>11</sup> or to restore,<sup>12</sup> hypoxic pulmonary vasoconstriction (HPV), but controversies exist related to the dose ranging<sup>13,14</sup> and to its efficacy. We hypothesized that such a pharmacologic association might also be efficient to treat hypoxia related to non-diffuse and limited lung lesions. In this case, hypoxia results mainly from a high proportion of blood flow perfusing these limited zones, suggesting a large  $\text{PaO}_2$  benefit of a blood flow partition modification by iNO and almitrine. The current study concerned patients selected for severe hypoxemia related to limited pulmonary lesions or focal lung lesions (FLLs). Inhaled NO alone, intravenous almitrine, or both were tested in term of  $\text{PaO}_2$  and shunt improvement, the proportion of responders to nonresponders, and the ventilatory requirements as  $\text{FiO}_2$  and positive end-expiratory pressure (PEEP) levels.

## Materials and Methods

### Patients

Fifteen consecutive patients with severe hypoxic FLLs were included in the study in accordance with the recommendations of the Ethical National French Law and after obtaining informed consent from their closest relatives. The studied population was selected on the following criteria: (1) severe hypoxia ( $\text{PaO}_2 < 250$  mmHg with  $\text{FiO}_2 = 1$ ) after a 24-h optimal therapy strategy<sup>15</sup> that excluded NO or almitrine therapy; (2) FLL defined on chest radiograph and computed tomography images as follows. On the radiograph, the opacities or densities should involve at maximum two quadrants with no detectable abnormalities on the remaining parenchyma. Thoracic computed tomography scans were performed for all patients before inclusion to ensure the limitation of the lesions and to have information on the mechanism of these lesions, such as atelectasis, condensation, densities, or pleural effusion. Although computed tomography scans consisted of multiple sections, four fixed levels of sections were selected to assess the extent of the lesions by four blinded observers. When the limitation of the computed tomography images corresponded to  $< 50\%$  of the section surface measured by digital delineation, three-dimensional reconstruction of the thorax was

done. Then only the patients with a "volume" of lesions  $< 50\%$  of the total lung volume were included. Patients with hypoxia were excluded when (1) the lung lesions corresponded to diffuse lesions related to ARDS or pulmonary edema from a cardiogenic or noncardiogenic cause, and (2) they had been previously treated with iNO, almitrine, or both. Furthermore, the response in  $\text{PaO}_2$  during iNO or almitrine administration was not considered a selection criteria.

Although the diagnosis of lung infection remains difficult and controversial, all patients were studied to diagnose a possible infectious cause of the FLLs. We used the currently accepted criteria in our institution: a positive bacterial culture obtained by a plugged telescoping protected catheter introduced with fiberoptic fibroscopy<sup>16</sup> associated with pulmonary symptoms, classical physical findings, an increase in the leukocyte count, fever, and the absence of other causes of infection. When these criteria were not met, the FLL was considered not to be related to infection. All patients were mechanically ventilated with a Servo ventilator Siemens 900 C or 300 (Elema Siemens, Solna, Sweden). When a pharmacologic cardiovascular support (six patients) was needed, it was maintained at the same infusion rate during the protocol.

### Nitric Oxide Delivery

Nitric oxide was delivered continuously from a stock tank containing 225 parts per million (ppm) NO in  $\text{N}_2$  (Air Liquide Santé, Paris, France) by a non-rebreathing circuit within the inspiratory limb of the ventilator, before the Y piece. Five ppm of NO in  $\text{N}_2$  gas flow were administered according to the following equation:

$$\text{NO flow rate (L/min)} = \frac{5 \text{ (ppm)}}{225 \text{ (ppm)}} \times \text{Minute ventilation (L/min)}$$

NO delivery was monitored by minute ventilation and a chemoluminescence device (EchoPhysic, Massy, France). The methemoglobin level was determined daily.

### Measurements

Mean systemic arterial pressure ( $\text{Pao}$ ) was measured with a radial artery catheter, and in eight patients an oxymetric thermodilution pulmonary artery catheter (Abbott Laboratories, Chicago, IL) was inserted to measure cardiac index and the pulmonary arterial ( $\text{Ppa}$ ), right atrial, and pulmonary artery occlusion pressures. Pressure values were averaged over the respiratory cycle from paper recordings, except for pulmonary artery oc-



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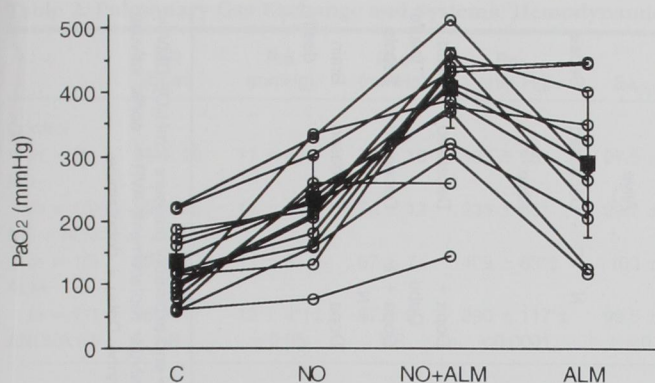


Fig. 1. Individual responses to nitric oxide, almitrine, and their coadministration.  $\circ\circ$  Individual values.  $\blacksquare\blacksquare$  Mean  $\pm$  SD.

clusion pressure, which was measured at end expiration. Indexed systemic and pulmonary vascular resistances (PVRI) were calculated using standard formulas. Arterial and mixed-venous blood gases were measured with standard blood gas electrodes (ABL 300; Radiometer, Copenhagen, Denmark), and total hemoglobin concentration, hemoglobin oxygen saturation, and methemoglobin levels were measured with spectrophotometry (OSM 2 Hemoximeter; Radiometer). Shunt ( $Q_s/Q_t$ ) was calculated from standard equations using the  $Fi_{O_2}$  measured by the ventilator sensor and oxygen contents. Ventilatory parameters were monitored continuously by a ventilatory module (E 2248 respiratory module; Siemens, Germany), providing instantaneous measurements of airway pressure and gas flow. The software allowed us to measure or calculate breath by breath, tidal volume, peak and mean airway pressures, flow rate, and quasi-static compliance. The later parameter corresponded to the slope of the pressure-volume relationship between the end of expiration and the end of the inspiratory plateau for the given tidal volume.

### Protocol

As a consequence of the mode of NO administration, the true alveolar oxygen fraction cannot be known. Because of the importance of small variations in  $Fi_{O_2}$  in the presence of low  $V_A/Q$  or shunting areas,<sup>17</sup> the control point was done on  $Fi_{O_2} = 1$  with an addition of  $N_2$  at the same gas flow rate that iNO would be later administered during NO inhalation (fig. 1). Therefore, modifications in blood gases were analyzed at a similar alveolar oxygen fraction ( $FA_{O_2}$ ) level throughout the protocol. After 30 min with  $N_2$  inhalation (control situation), the hemodynamic and gas exchange parameters were recorded. Then NO in  $N_2$  was administered and measure-

ments were repeated after 60 min of NO inhalation. Almitrine (Servier, Suresnes, France) was infused through a central catheter. The dose of almitrine was titrated to obtain the best  $Pa_{O_2}$  level,<sup>18</sup> and the measurements were performed 60 min after the infusion rate was stabilized. Because iNO seems to act as an "on-off" phenomenon,<sup>7</sup> the effect of almitrine alone was measured 60 min after iNO was discontinued and replaced by the same added gas flow of  $N_2$ . This last point failed to be obtained in four patients (#3, 7, 10, and 11) because of a risk of severe hypoxia or of protocol failure. After this part of the protocol was complete, iNO was reintroduced at the same flow rate, and the coadministration of NO and almitrine was continued to determine whether it could allow a gradual reduction in  $Fi_{O_2}$  while maintaining a  $Pa_{O_2} \geq 80$  mmHg and a oxygen saturation level  $\geq 0.96$ . When  $Fi_{O_2}$  could be reduced to 0.4, the PEEP level was also reduced step by step. Eight hours after NO was reintroduced, PEEP and  $Fi_{O_2}$  reductions were measured. Finally, the criteria for weaning almitrine was an oxygen saturation level  $\geq 0.96$ . Then, a day-per-day test of NO weaning was performed, and NO was discontinued when  $Pa_{O_2}$  was close to 300 mmHg at a  $Fi_{O_2}$  during 4 h after NO withdrawal.

### Statistical Analysis

Values are presented as mean  $\pm$  SD. The effects of iNO, almitrine, and their coadministration were analyzed by one-way analysis of variance for repeated measures. When the analysis of variance was significant, we used the criterion of Huynh and Feld<sup>19</sup> rather than the classical F value to test the significance, because the measurements were not strictly independent. The significance level was fixed at 5%. Baseline differences between infected and uninfected groups were tested using a Student's *t* test.

### Results

Patients characteristics, including causes of lung disease, outcome, and causes of death are summarized in table 1. None of these patients had previous pulmonary disease. Eleven of 15 patients were studied within the first week of mechanical ventilation, and they were initially ventilated for extrapulmonary reasons, such as head trauma or postsurgical necessity. The tidal volume used was  $430 \pm 96$  ml, and the respiratory rate was 20. Based on the given diagnostic criteria detailed in Materials and Methods, bacterial pneumonia was diagnosed in seven patients.



Table 1. Clinical Characteristics of the Patients at the Time of Inclusion in the Protocol

Patient Number*	Age/Sex	Comorbidity	Primary Diagnosis	Etiology	SAPS	MOF Score	Cqs	PEEP	Previous/Total DMV	Vasoactive Drugs	Outcome	Cause of Death
1	46/M	—	MVR and AVR	Bacterial pneumonia	17	3	—	8	14/29	Dopa + N	Alive	
2	25/M	—	Head and thoracic trauma	Bacterial pneumonia	13	4	53	9	1/12		Alive	
3	60/M	—	Head trauma	Bacteria	23	6	—	7	5/8		Deceased	Brain death
4	41/M	—	Thoracic trauma	Bacteria	12	3	41	8	7/17		Alive	
5	28/M	—	AVR	Bacterial pneumonia	15	4	33	11	32/43		Alive	
6	56/F	Diabetes	MVR and AVR	Bacterial pneumonia	10	4	29	7	8/65	Dopa + E	Alive	
7	28/m	—	Head trauma	Bacterial pneumonia	11	4	52	—	4/22		Alive	
8	49/F	—	Head and thoracic trauma	Pulmonary contusion	14	5	26	6	2/13		Alive	
9	46/M	Diabetes MI	CABG	Lobar atelectasia	6	2	41	10	2/12		Alive	
10	16/M	—	Thoracic trauma	Pulmonary contusion	14	6	22	—	4/12		Alive	
11	55/M	UAC	Post surgical abscess	Lobar atelectasia	11	6	45	5	2/12	N	Deceased	Sepsis
12	34/M	—	Head and thoracic trauma	Pulmonary contusion	9	4	48	8	9/24		Alive	
13	77/F	MI, HT, BC	CABG, AVR	Lobar atelectasia	12	6	39	10	11/12	Dopa + Dobu	Deceased	Heart failure
14	72/F	RP	Peritonitis	Lobar atelectasia	24	10	31	9	1/3	Dopa + E + N	Deceased	Sepsis
15	58/M	—	Head and thoracic trauma	Pulmonary contusion	17	4	30	5	1/28	Dopa	Deceased	Brain death
Mean ± SD	46 ± 18				14 ± 5	4.8 ± 2	38 ± 10	8 ± 2	7 ± 8/21 ± 16			

SAPS = Simplified Acute Physiology Score<sup>41</sup>; MOF = multiple organ failure score<sup>42</sup>; Cqs, quasi-static compliance (ml/cmH<sub>2</sub>O); PEEP = positive end expiratory pressure (cmH<sub>2</sub>O); DMV = duration of mechanical ventilation; CABG = coronary artery bypass grafting; MI = myocardial infarction; HT = hypertension; MVR = mitral valvular replacement; AVR = aortic valvular replacement; RP = rheumatoid polyarthritis; BC = breast cancer; UAC = upper airway cancer; D = dopamine; E = epinephrine; N = norepinephrine; Dobu = dobutamine. Patients 1 to 7: infectious focal lung lesion. Patients 8 to 15: noninfectious focal lung lesion.



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Table 2. Pulmonary Gas Exchange and Systemic Hemodynamic Measurements (n = 15)

	HR (bpm)	Pra (mmHg)	Pao (mmHg)	PaO <sub>2</sub> (mmHg)	SaO <sub>2</sub> (%)	CaO <sub>2</sub> (mlO <sub>2</sub> /[Hgl])	PaCO <sub>2</sub> (mmHg)	DO <sub>2</sub> I (ml O <sub>2</sub> /min/m <sup>2</sup> )	Ppi (cmH <sub>2</sub> O)	Cqs (ml/cmH <sub>2</sub> O)
Control (n = 5)	91 ± 19	11 ± 4	72 ± 10	135 ± 58	97.5 ± 2.6	12.8 ± 2	38 ± 5	412 ± 89	24.4 ± 2.7	38.9 ± 7
NO (n = 15)	90 ± 15	11 ± 4	74 ± 12	235 ± 65*	99.7 ± 0.5*	13.4 ± 1.9*	38 ± 6	435 ± 115	24.7 ± 2.7	36.3 ± 8.3
NO + ALM (n = 15)	89 ± 17	11 ± 3	67 ± 7	409 ± 63*†	100 ± 0*	13.9 ± 2*†	37 ± 6	462 ± 109*	24.6 ± 2.6	37.7 ± 8.2
ALM (n = 11)	95 ± 17	12 ± 4*†‡	67 ± 9	290 ± 117*†	99.5 ± 0.8*	13.5 ± 2.2*†	39.4 ± 7	455 ± 120*	24.6 ± 2.9	37.9 ± 8.9
ANOVA (P)	NS	<0.05	NS	<0.0001	<0.01	<0.0001	NS	<0.05	NS	NS

Values are mean ± SD. Almitrine point was obtained in 11 patients.

HR = heart rate; Pra = right atrial pressure; Pao = mean systemic arterial pressure; CaO<sub>2</sub> = arterial content in oxygen (mlO<sub>2</sub>/[Hgl]); DO<sub>2</sub>I, indexed oxygen delivery (ml O<sub>2</sub>/min/m<sup>2</sup>); Ppi = peak inspiratory pressure; Cqs = quasi-static compliance; NS = not significant.

\* *P* < 0.05 versus control.

† *P* < 0.05 versus NO.

‡ *P* < 0.05 versus NO + ALM.

Table 2 presents the pulmonary gas exchange and systemic hemodynamic measurements of the overall population (n = 15). Table 3 presents the right heart catheterization measurements, which concerned only eight patients. The last point under almitrine alone concerned 11 patients, as noted before. The four patients who did not complete the four points of the protocol study did not differ statistically from the rest of the patients. Almitrine was infused at a mean dose of  $5.5 \pm 1.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , ranging from 4 to 9  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .

At the control point (N<sub>2</sub>), a low PaO<sub>2</sub> level ( $135 \pm 58$  mmHg) was associated with a shunt of  $32.1 \pm 6.9\%$  and mild pulmonary hypertension ( $28 \pm 8$  mmHg) (figs. 1, 2A, and 2B).

Nitric oxide inhalation did not significantly influence the hemodynamic parameters. However, PaO<sub>2</sub> significantly increased, leading to a significant CaO<sub>2</sub> increase and calculated oxygen shunt reduction (figs. 1, 2A). The other parameters did not change, except oxygen saturation, venous oxygen saturation, and oxygen content (CaO<sub>2</sub>), which increased significantly (fig. 2B). No side effect in terms of methemoglobin (<1%) measured daily or NO<sub>2</sub> > 2 ppm was observed during NO inhalation.

The coadministration of NO and almitrine did not influence hemodynamic parameters compared with control point. The PaO<sub>2</sub> further increased (+274 mmHg from control point, and +174 mmHg from NO alone; figs. 1 and 2A), with a concomitant decrease in oxygen shunt

Table 3. Right Heart Catheterization Measurements (n = 8)

	Ppaop (mmHg)	Ppa (mmHg)	CI (L/min/m <sup>2</sup> )	SVRI (IU)	PVRI (IU)	PvO <sub>2</sub> (mmHg)	SvO <sub>2</sub> (%)	CvO <sub>2</sub> (ml %)	Qs/Qt (%)	DavO <sub>2</sub> (ml %)	VO <sub>2</sub> I (ml O <sub>2</sub> /min/m <sup>2</sup> )
Control (n = 15)	15 ± 6	28 ± 8	3.6 ± 0.9	18.6 ± 5.8	4 ± 1.2	39.5 ± 7	70.2 ± 6.9	9.2 ± 1.8	32.1 ± 6.9	3.8 ± 1	124 ± 20
NO (n = 15)	14 ± 5	25 ± 6	3.3 ± 1	19.6 ± 6.5	3.5 ± 1.2	41.4 ± 7.5	74.8 ± 4.9*	9.8 ± 1.4*	23 ± 4.2*	3.9 ± 1	124 ± 21
NO + ALM (n = 15)	14 ± 4	28 ± 6	3.4 ± 0.9	17.4 ± 4.3	4.4 ± 1	46.4 ± 8.1*†	79.5 ± 5.4*†	10.4 ± 1.6*†	13.7 ± 4.1*†	3.9 ± 1	122 ± 15
ALM (n = 11)	15 ± 3	32 ± 8†‡	3.5 ± 1.2	15.3 ± 4*†	4.9 ± 1.6*†	44.8 ± 6.3*	76.2 ± 6.9*	10.1 ± 2*	21.1 ± 8.1*†	3.8 ± 1	132 ± 41
ANOVA (P)	NS	<0.05	NS	<0.05	<0.05	<0.05	<0.005	<0.005	<0.0001	NS	NS

Values are mean ± SD. Almitrine point was obtained in 11 patients, six of them being monitored with a Swan-Ganz catheter.

Ppaop = pulmonary artery occlusive pressure; Ppa = mean pulmonary arterial pressure; CI = cardiac index; SVRI = indexed systemic vascular resistances; PVRI = indexed pulmonary vascular resistances; CvO<sub>2</sub> = venous content in oxygen; Qs/Qt = oxygen intrapulmonary shunt; DavO<sub>2</sub> = arterial venous difference in oxygen; VO<sub>2</sub>I = indexed oxygen consumption; NS = not significant.

\* *P* < 0.05 versus control.

† *P* < 0.05 versus NO.

‡ *P* < 0.05 versus NO + ALM.



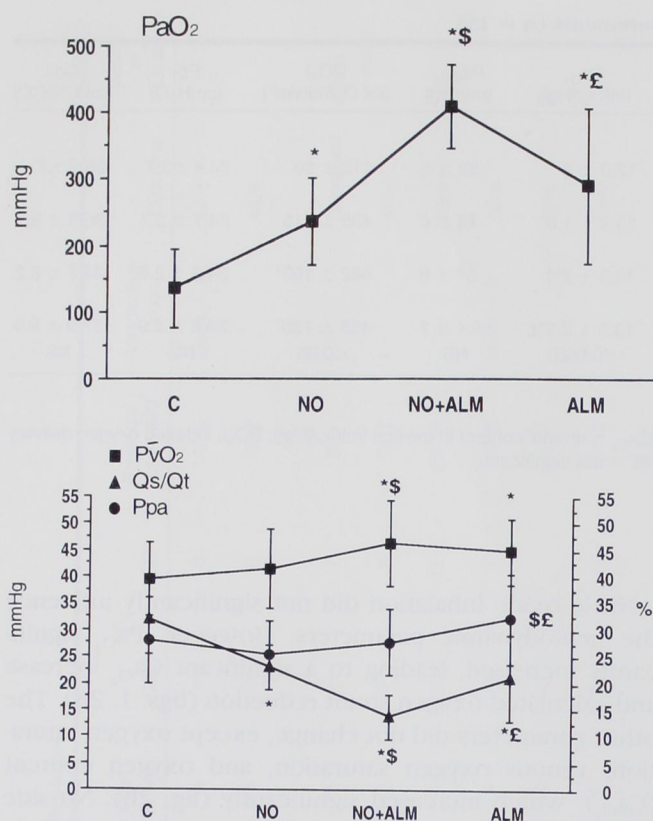


Fig. 2. (A) Mean  $\pm$  SD of  $\text{PaO}_2$  during protocol conditions. Analysis of variance + the Huynh-Feld test were used. \* $P < 0.05$  vs. control,  $P < 0.05$  vs. nitric oxide (NO), &  $P < 0.05$  vs. NO + almitrine (ALM). (B) Mean  $\pm$  SD of pulmonary arterial pressure, shunt, and oxygen pressure in mixed venous blood during protocol conditions. Analysis of variance + the Huynh-Feld test were used. \* $P < 0.05$  vs. Control,  $P < 0.05$  vs. NO, &  $P < 0.05$  vs. NO + ALM.

versus control point and iNO (fig. 2B). The oxygen pressure in mixed venous blood, venous oxygen saturation, and  $\text{CO}_2$  increased further compared with iNO alone (fig. 2B). Indexed oxygen delivery ( $\text{DO}_{2\text{I}}$ ) increased significantly without a change in indexed oxygen consumption.

After turning off NO and reintroducing  $\text{N}_2$ , almitrine alone increased right atrial pressure, Ppa, and PVRI compared with iNO alone and with baseline for right atrial pressure and PVRI, with no change in pulmonary blood flow (fig. 2B). Almitrine alone induced a significant decrease in indexed systemic vascular resistance compared with control and iNO. Compared with the coadministration,  $\text{PaO}_2$  decreased significantly at a level that did not differ from  $\text{PaO}_2$  obtained with NO alone (figs. 1 and 2A). Except for  $\text{DO}_{2\text{I}}$ , which increased from the control point, the other parameters such as oxygenation or pul-

monary mechanics did not differ between iNO and almitrine alone.

The comparison between infected and uninfected FLLs showed no difference for hemodynamic and pulmonary gas exchange data during the protocol conditions (data not shown).

Based on an arbitrary threshold of  $\text{PaO}_2$  increase of 30% from baseline, 12 of 15 patients (80%) responded to iNO. The same proportion has been observed with almitrine alone, but some of these patients did not respond to iNO. Sixty percent of the global population responded to both drugs given separately, whereas 100% responded to the coadministration (fig. 1).

Because all patients responded to the coadministration of iNO and almitrine infusion, this treatment was maintained  $4.9 \pm 3.1$  days (from 1 to 11) for NO inhalation and for  $2.5 \pm 1.7$  days (from 1 to 6) for intravenous almitrine. During the 8-h observation period,  $\text{FI}_{\text{O}_2}$  was dramatically reduced from 1 to  $0.39 \pm 0.06$  ( $P < 0.0001$ ) for all patients except one, who died at day 1, and PEEP was reduced from  $8 \pm 1.9$  to  $4 \pm 2.8$   $\text{cmH}_2\text{O}$  ( $P < 0.005$ ).

## Discussion

This study reports the effect of a combined therapy by NO inhalation and almitrine infusion on gas exchange and ventilation requirements in patients with FLLs. The improvement in  $\text{PaO}_2$  compared with baseline was higher (+ 203%) in the current study than the  $\text{PaO}_2$  increase observed in previous studies on coadministration in ARDS patients,<sup>9,10,20</sup> which were 120%, 48%, and 36%, respectively. Further, all the patients studied responded to the coadministration, a proportion that differs from the results reported by Wysocki *et al.*<sup>9</sup> These differences may result from several reasons. First, the previous studies concerned patients with ARDS but not FLLs. Despite similar basal intrapulmonary shunt, the pulmonary blood flows and the extension of the lesions were greater in the ARDS patients compared with our FLL patients.<sup>9,10,20</sup> Second, in several studies, only patients with positive NO response were selected.<sup>10</sup> Third, the pulmonary vascular reactivity in FLL might differ from the one observed in ARDS in terms of pulmonary vasoconstriction, including HPV.<sup>21-23</sup>

In the current study, the selected population did not fit with the ARDS definition<sup>24</sup> because radiologic densities were focal and thoracic compliance was reduced only slightly. Despite the use of a more conservative criteria



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for a "responder" definition in term of  $\text{Pa}_{\text{O}_2}$  improvement compared with previous studies,<sup>6,9,25-28</sup> all our patients responded to the coadministration of iNO and intravenous almitrine. Such a proportion was largely higher than those reported in nonselected ARDS patients treated by NO inhalation.<sup>9,18</sup> Finally, the death rate (33%) for the current study appears lower than those reported in ARDS patients<sup>15,29</sup> and was never related to hypoxia.

Because cardiac output or pulmonary blood flow did not change throughout the study, the level of Ppa can be analyzed in term of pulmonary vascular tone modifications because ventilatory settings were constant during the protocol period.

#### Nitric Oxide Inhalation

Nitric oxide inhalation at 5 ppm in FLLs induced an increase in  $\text{Pa}_{\text{O}_2}$  (+74%) associated with no significant change in Ppa, PVRI, and cardiac index, suggesting that iNO essentially modified the regional pulmonary blood flow partition. Such a regional partition of flow without Ppa and pulmonary blood flow modifications was shown previously in a rabbit model<sup>30</sup> of HPV. Based on the "antivasoconstrictive" effect of NO,<sup>7</sup> the NO-induced vasodilation in normal zones implies a certain degree of preexisting vasoconstriction unrelated to HPV, because patients were ventilated with  $\text{Fi}_{\text{O}_2} = 1$ . This concept was illustrated by Light,<sup>21</sup> who showed the presence of a pulmonary vasoconstriction nonexclusively related to HPV in a canine model of pneumonia. The author concluded that "regional flow redistribution in experimental pneumonia may be mediated by a vasoconstrictor compound or mechanism other than HPV." Such a pulmonary vasoconstriction in our study can be assessed by the elevated control PVRI, which suggests several mechanisms of vasoconstriction in addition to HPV.

#### Almitrine Infusion

The molecular mechanisms of action of almitrine on the pulmonary vessels remains debated. It is a lipophilic substance with a long terminal half-life in humans inducing a direct stimulation of chemoreceptors<sup>31</sup> and a direct pulmonary vasoconstrictive action.<sup>18</sup> For the current study, only the later property was essential because the patients were sedated and mechanically ventilated. In *in vitro* and *in vivo* animal experiments, almitrine mimicked,<sup>11</sup> enhanced,<sup>32</sup> or restored<sup>12</sup> HPV in a dose-dependent biphasic mode.<sup>13</sup> In clinical situations, almitrine was studied in ARDS patients secondary to shock or sepsis, in whom both shunt and  $\text{V}_\text{A}/\text{Q}$  mismatching ex-

plained severe hypoxia. Intravenous almitrine significantly improved  $\text{Pa}_{\text{O}_2}$  with negligible pulmonary and systemic hemodynamic changes.<sup>33,34</sup> The multiple inert gas technique showed that almitrine redistributed pulmonary blood flow from shunt areas to lung units with a normal  $\text{V}_\text{A}/\text{Q}$  ratio while pulmonary artery pressure increased. These changes returned to baseline 30 min after the drug infusion was stopped.<sup>33</sup>

In our study, almitrine alone improved  $\text{Pa}_{\text{O}_2}$  to a similar extent as NO, but it increased Ppa, right atrial pressure, and PVRI without any effect on pulmonary blood flow. Eighty percent of the patients responded to almitrine with a more spectacular  $\text{Pa}_{\text{O}_2}$  improvement (+115%) than observed in ARDS patients<sup>9,20</sup> (15% and 13%, respectively). Such a difference with ARDS patients may result from a more potent "steal" of shunting blood flow toward normal zones. However, the almitrine-induced Ppa increase at a constant flow may have limited the gain in  $\text{Pa}_{\text{O}_2}$  induced by almitrine because a Ppa increase has been shown to recruit pulmonary vessels, including those perfusing shunting zones.<sup>2</sup>

One study concerning patients with acute unilateral bacterial pneumonia compared the effects of lateral positioning and high-dose ( $16 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) almitrine infusion on  $\text{Pa}_{\text{O}_2}$ .<sup>35</sup> This study failed to observe any positive effect for almitrine, whereas an improvement in  $\text{Pa}_{\text{O}_2}$  was observed by positioning. Almitrine induced modest pulmonary hypertension that disappeared at  $\text{Fi}_{\text{O}_2}$  and  $\text{Pa}_{\text{O}_2}$  and oxygen shunt did not improve. Compared with our study, the dose used was larger, with potentially the same limitations as discussed before,<sup>13,14</sup> and the population concerned mainly alcoholic patients with pneumococcal infection, two situations that may both alter pulmonary vascular reactivity.<sup>28,36,37</sup>

#### Effects of Coadministration

In the current study with FLL patients, coadministration was the unique condition during which 100% of the patients had improved  $\text{Pa}_{\text{O}_2}$ . Furthermore, such a  $\text{Pa}_{\text{O}_2}$  improvement was statistically superior to those obtained with each drug alone, emphasizing the role of vascular control in arterial oxygenation. As expected, the combination of a vasodilatation of normal zones added to a predominant vasoconstriction of hypoxic zones acted synergistically to redistribute blood flow away from shunting zones and further improve  $\text{Pa}_{\text{O}_2}$ . In the study by Wysocki *et al.*,<sup>9</sup> coadministration improved  $\text{Pa}_{\text{O}_2}$  in only 40% of patients with severe ARDS, without increasing Ppa compared with the control point. The reasons for this variable response are not yet clear, but these authors



have suggested that patients who respond to iNO respond all the more to the coadministration. Based on these findings, Lu *et al.*<sup>10</sup> only included in a co-administration study six ARDS patients who were responders to NO (defined as a  $\text{PaO}_2$  increase  $>40\%$ ) and observed that the addition of a high dose ( $16 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) of almitrine to iNO amplified the  $\text{PaO}_2$  response.

The amplification of the effect of the coadministration on  $\text{PaO}_2$  compared with each drug given alone should be discussed. Based on the value of Ppa and pulmonary blood flow, the coadministration of iNO and almitrine did not induce any difference in pulmonary hemodynamic (Ppa and flow) compared with control. Despite this, the  $\text{PaO}_2$  level was dramatically improved ( $+201\%$ ) and may have resulted from different mechanisms. Compared with iNO alone, the coadministration probably amplified the regional gradient between regional vascular tone, diverting more blood toward normal zones. A similar mechanism may account for the difference with almitrine alone. In addition, the lower Ppa level during coadministration than during almitrine alone may have reduced the vascular recruitment, especially in hypoxic zones, thus improving the partition of flow.

From a practical perspective, such a drug combination appears suitable for several purposes. First, the prolongation of this combined therapy allowed us to reduce the  $\text{FiO}_2$  and also the PEEP level. The latter effect might be fruitful to limit the risk of normal lung overdistention.<sup>38</sup> However, the benefit of this therapy in terms of outcome would be modest because none of the patients died of severe hypoxia. Second, if hypoxia must be treated in the presence of compromised right ventricular function, this drug combination can be used. Furthermore, if the gain in  $\text{PaO}_2$  is large, as observed in the current study, the PEEP level can be reduced with a potential benefit for right ventricular function. Third, the  $\text{PaO}_2$  increase during coadministration was not a "cosmetic"<sup>39</sup> effect because it corresponded to the unique situation in which arterial oxygen content and oxygen delivery were statistically increased at a constant cardiac output. This effect might have a positive effect to limit the high pulmonary blood flow as a source of lung edema amplification and of gas exchange deterioration. Fourth, it was the unique protocol condition during which all patients improved their  $\text{PaO}_2$  by as much as 30% from control.

#### Study Limitations

Because the sequence of drug administration was not randomized, a potential role of preinhalation of NO on

the observed effect of almitrine alone cannot be eliminated. This particular design was chosen because NO response acts as an "on-off" phenomenon,<sup>40</sup> whereas almitrine has a long half-life clearance.<sup>18</sup>

Discontinuation of NO after the coadministration to study the effects of almitrine alone was not performed in 4 of 15 patients. Three of these four patients were considered "almitrine responders" because the increase in  $\text{PaO}_2$  with coadministration was much higher than the increase in  $\text{PaO}_2$  observed with NO alone; the remaining patient did not have further improvements in  $\text{PaO}_2$  with the coadministration compared with NO alone and was considered as an almitrine nonresponder.

In conclusion, this study shows that pharmacologic manipulation of pulmonary blood flow associating iNO and intravenous almitrine efficiently corrects severe arterial hypoxia in patients with FLLs. The coadministration of these drugs in hypoxic patients seems more frequently efficient and allowed us to reduce the ventilatory settings. Such a therapy should be added to the optimal strategy for treating acute lung injury.<sup>15</sup>

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