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Effect of almitrine bismesylate on pulmonary vasoreactivity to hypoxia in chronic obstructive pulmonary disease

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Effect of almitrine bismesylate on pulmonary vasoreactivity to hypoxia in chronic obstructive pulmonary disease. A.Y. Saadjian, F.F. Philip-Jöet, A. Barret, S. Levy, A.G. Arnaud. ©ERS Journals Ltd 1994.

ABSTRACT: The aim of this double-blind, placebo-controlled study was to determine whether acute administration of almitrine enhances hypoxic pulmonary vasoconstriction in patients with chronic obstructive pulmonary disease (COPD).

Haemodynamics and blood gases were studied at various inspiratory fractional concentrations of oxygen (F_{IO_2}): 0.15, 0.21, 0.30 and 1.0, randomly administered for 20 min periods under constant infusion of either placebo or almitrine (8 μg·kg^{-1}·min^{-1}) in 20 patients with COPD.

The almitrine group exhibited a significant increase in mean pulmonary artery pressure, pulmonary vascular resistance and arterial oxygen tension (Pa_{O_2}) at F_{IO_2} 0.15, 0.21 and 0.30. During hypoxia, the increase in mean pulmonary pressure and pulmonary vascular resistance was three times greater in the almitrine group than the placebo group. No significant difference in cardiac output and systemic haemodynamics was found.

These results suggest that almitrine at the dose used, enhances pulmonary vasoconstriction in COPD patients.

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Almitrine bismesylate (Laboratoire Euthérapie, Neuilly sur Seine, France) is a potent peripheral chemoreceptor agonist, of which the beneficial effects on blood gases in patients with chronic obstructive pulmonary disease (COPD) are well-documented [1, 2]. Since arterial oxygen tension (Pa_{O_2}) generally increases more than arterial carbon dioxide tension (Pa_{CO_2}) decreases, it has been assumed that this improvement results from better ventilation/perfusion ($\dot{V}_A/\dot{Q}$) matching, due to an increase in either ventilation or local pulmonary vasoconstriction [3]. No improvement has been observed in the distribution of ventilation after administration of almitrine in normal subjects [4, 5], or COPD patients [6]. On the other hand, almitrine has been shown to enhance hypoxic pulmonary vasoconstriction (HPV) in normal subjects and result in a shift of blood flow to better oxygenated lung areas [5]. Higher $\dot{V}_A/\dot{Q}$ ratios have been reported after administration of almitrine in COPD patients breathing spontaneously with a constant minute ventilation [7], as well as in patients under controlled mechanical ventilation [8]. Likewise, it has recently been shown in isolated rat lungs that almitrine at low but not high doses potentiates the vasoconstrictor response to hypoxia [9]. More recently, we observed that the almitrine-induced increase in pulmonary artery pressure and Pa_{O_2} could be abolished by the vasodilator nifedipine [10].

The aim of the present study was to evaluate the effect of a single dose of almitrine on pulmonary vasoconstriction in COPD patients breathing various fractional inspiratory concentrations of oxygen (F_{IO_2}).

Patients and methods

Twenty patients with pulmonary hypertension secondary to chronic bronchitis (mean pulmonary artery pressure >20 mmHg), and functional tests documenting serious respiratory impairment (forced expiratory volume in one second (FEV_1) 20–40% predicted volume) were studied (table 1). All patients were smokers or ex-smokers and had dyspnoea and fatigue after minimal or moderate exertion, but were clinically stable and had been free from bronchopulmonary infection, acute respiratory distress, or right ventricular failure for at least 2 months prior to the study. Vasodilators, long-acting theophylline, β_2-agonists, almitrine, diuretics, or digitalis were suspended three days prior to the investigation, and oxygen therapy, when indicated (two patients in each group), 2 h before. All patients were in sinus rhythm, with no clinical, electrocardiographic, X-ray or echographic evidence of left ventricular dysfunction. The investigational protocol was approved by our institutional Ethics Committee. Informed consent was obtained from all patients.

Table 1. – Patients characteristics in the two groups

Variables	Placebo group	Almitrine group
Sex M/F	9/1	9/1
Age yrs	61±5	60±3
Weight kg	64±3	65±6
Height cm	166±2	166±3
FEV_1 % pred	33±4	36±5
FEV_1/VC % pred	39±10	40±4
MPAP mmHg	25±1	27±2
Pa_{O_2} kPa	8.8±0.4	8.8±0.5
Pa_{CO_2} kPa	5.3±0.3	5.3±0.3
TLC % pred	86±13	87±14
RV/TLC %	57±3	61±6

Data are presented as mean±SEM. FEV_1: forced expiratory volume in one second; VC: vital capacity; MPAP: mean pulmnary artery pressure; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; TLC: total lung capacity (helium); RV: residual volume.

Study procedure

Right heart catheterization was performed in the supine position through a femoral vein, using a 7 F flow-directed balloon-tipped thermodilution catheter (Spectramed, Oxnard, CA, USA). Systemic arterial pressure measurements and arterial blood sampling were achieved through a 4 F teflon cannula in the femoral artery. Intravascular pressures were measured relative to atmospheric pressure with a zero reference point at the midaxillary line. Pressure values were obtained by averaging measurements of three successive respiratory cycles. Cardiac output (CO) was determined by the thermodilution technique (Spectramed device) and expressed as the mean of four consecutive determinations varying <10%. Pa_{O_2}, Pa_{CO_2}, mixed venous oxygen tension ($P\bar{v}_{O_2}$), and pH were determined with a Radiometer BMS 3 MK2 blood gas analyser (Copenhagen, Denmark), and arterial oxygen saturation (Sa_{O_2}) with a Radiometer OS M2. Haemoglobin levels (Hb) were measured with a Technicon M 6000 (Technicon Instruments Corp., Tarrytown, NY, USA).

Derived haemodynamic variables were calculated as follows: 1) cardiac index (CI) ($l \cdot min^{-1} \cdot m^2$) = CO/body surface area; 2) stroke volume (SV) (ml) = CO/heart rate (HR); and 3) pulmonary vascular resistances (PVR) ($dynes \cdot cm^{-5} \cdot s^{-1}$) = mean pulmonary artery pressure (MPAP) - pulmonary artery wedge pressure (PWP) × 80/CO.

Study design

In a randomized, double-blind study, an intravenous infusion of almitrine was compared with a placebo infusion at four F_{IO_2} levels. Baseline determinations were performed at F_{IO_2} 0.21(room air), 30 min after catheter insertion, when HR, vascular pressures, and respiratory rate were stable. The patients were then randomly distributed into two groups of 10 patients: one receiving a constant intravenous infusion of almitrine at the dose of 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ through an infusion pump, and the other group the solvent (a malic acid solution in saline) under the same conditions. During infusion, gas mixtures consisting of 15% O_2 in nitrogen (F_{IO_2} 0.15), 21% O_2 (F_{IO_2} 0.21) in nitrogen, 30% O_2 in nitrogen (F_{IO_2} 0.30) and pure O_2 (F_{IO_2} 1.0) were randomly administered through a face mask (with a balloon and two lateral valves, Respiron MHC O9, Europe Medical, Bourg en Bresse, France). Haemodynamics and blood gases were measured after 20 min of inhalation of each mixture. In addition, arterial blood samples were collected, centrifuged and frozen, pending determination of almitrine plasma concentration by gas chromatography.

Statistical analysis

All values are expressed as means (±SEM). The statistical analysis consisted in a three-factor (group, treatment and F_{IO_2}) analysis of variance, with repeated measures on the last two factors. When the F ratios were greater than the tabulated p=0.05 critical value, Student tests were performed to compare means obtained at different F_{IO_2} in the same group of patients. The almitrine group was considered to be different from the placebo group when the interaction term (group by treatment by F_{IO_2}) reached significance.

Results

There was no difference between the two groups with respect to sex, age, body weight, height and respiratory function (table 1). No complications or side-effects were observed. Almitrine plasma levels were stable throughout the study: mean plasma concentration was 325±9 $ng \cdot ml^{-1}$. No almitrine was detected in the control group.

Haemodynamic data

In both groups, HR and CI decreased as F_{IO_2} increased. SV remained constant. Compared to control values, HR was slightly higher during hypoxia in the almitrine group. Although the interaction term was significant ($p<0.05$), no statistical difference was found between the two groups.

Mean systemic arterial pressure (MAP) and PWP were unaffected by changes in F_{IO_2}. No difference was found between the two groups with regard to CI, SV, MAP (table 2) or PWP (table 3).

Major changes were observed in pulmonary haemodynamics (table 3). During hypoxia (F_{IO_2} 0.15), MPAP increased relative to control values in all patients. This increase was small (<3 mmHg) in five patients in the placebo group, and in only one in the almitrine group (fig. 1). During hypoxia, the increase in MPAP was three times greater in the almitrine than in the placebo group (4 *versus* 13 mmHg). In both groups, increasing F_{IO_2} resulted in a significant reduction in pulmonary hypertension, although MPAP remained significantly

Table 2. – Systemic haemodynamic variables according to F_{IO_2}

Variables	F_{IO_2}	Placebo group		Almitrine group		Comparison	
	level	Mean±SEM	p-value*	Mean±SEM	p-value*	p-value**	Interaction
HR	Control	82±4		83±3		NS	
b·min^{-1}	0.15	83±3	NS	89±13	<0.005	NS	
	0.21	80±3	NS	84±3	NS	NS	<0.05
	0.30	77±3	<0.01	81±3	NS	NS	
	1.0	76±3	<0.005	76±3	<0.001	NS	
MAP	Control	110±6		105±9		NS	
mmHg	0.15	110±9	NS	118±12	NS	NS	
	0.21	110±9	NS	115±12	NS	NS	NS
	0.30	111±7	NS	111±12	NS	NS	
	1.0	107±8	NS	112±12	NS	NS	
CI	Control	2.5±0.2		2.8±0.1		NS	
l·min^{-1}·m^2	0.15	2.7±0.2	NS	3.0±0.1	<0.05	NS	
	0.21	2.5±0.2	NS	2.7±0.1	NS	NS	NS
	0.30	2.4±0.2	NS	2.6±0.1	<0.01	NS	
	1.0	2.2±0.1	<0.002	2.5±0.1	<0.001	NS	
SV	Control	53±5		59±4		NS	
ml	0.15	56±5	NS	59±4	NS	NS	
	0.21	54±5	NS	59±4	NS	NS	NS
	0.30	53±4	NS	55±4	NS	NS	
	1.0	51±5	NS	57±4	NS	NS	

F_{IO_2}: fractional inspiratory oxygen; HR: heart rate; MAP: mean systemic arterial pressure; CI: cardiac index; SV: stroke volume; NS: nonsignificant. *: control *versus* F_{IO_2} 0.15, 0.21, 0.30 and 1.0, respectively; **: placebo *versus* almitrine.

Table 3. – Pulmonary haemodynamic variables according to F_{IO_2}

Variables	F_{IO_2}	Placebo group		Almitrine group		Comparison	
	level	Mean±SEM	p-value*	Mean±SEM	p-value*	p-value**	Interaction
PASP	Control	38±3		39±2		NS	
mmHg	0.15	42±3	<0.05	59±4	<0.0002	<0.005	
	0.21	38±3	NS	48±2	<0.001	<0.01	<0.0001
	0.30	35±2	<0.005	44±2	<0.02	<0.02	
	1.0	33±2	<0.002	40±2	NS	<0.05	
PADP	Control	17±1		19±2		NS	
mmHg	0.15	19±2	NS	27±1	<0.0001	<0.001	
	0.21	17±1	NS	23±1	<0.0001	<0.002	<0.0001
	0.30	16±1	NS	22±1	<0.002	<0.005	
	1.0	15±1	<0.05	19±1	NS	<0.05	
MPAP	Control	25±1		27±1		NS	
mmHg	0.15	29±2	<0.02	40±2	<0.0001	<0.001	
	0.21	25±1	NS	34±1	<0.0002	<0.001	<0.0001
	0.30	23±1	<0.002	31±1	<0.05	<0.001	
	1.0	22±1	<0.0005	27±1	NS	<0.005	
PWP	Control	12±1		12±1		NS	
mmHg	0.15	12±1	NS	12±1	NS	NS	
	0.21	11±1	NS	12±1	NS	NS	NS
	0.30	10±1	NS	12±1	NS	NS	
	1.0	10±1	NS	11±1	NS	NS	
PVR	Control	235±18		260±25		NS	
dynes·cm^{-5}·s^{-1}	0.15	283±27	<0.05	438±32	<0.002	<0.01	
	0.21	245±17	NS	386±32	<0.0005	<0.0002	<0.0001
	0.30	235±17	NS	386±32	<0.0005	<0.002	
	1.0	220±19	NS	316±22	<0.01	<0.005	

F_{IO_2}: fractional inspiratory oxygen; PASP: pulmonary artery systolic pressure; PADP: pulmonary artery diastolic pressure; MPAP: mean pulmonary artery pressure; PWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; *: control *versus* F_{IO_2} 0.15, 0.21, 0.30 and 1.0, respectively; **: placebo *versus* almitrine. NS: nonsignificant.

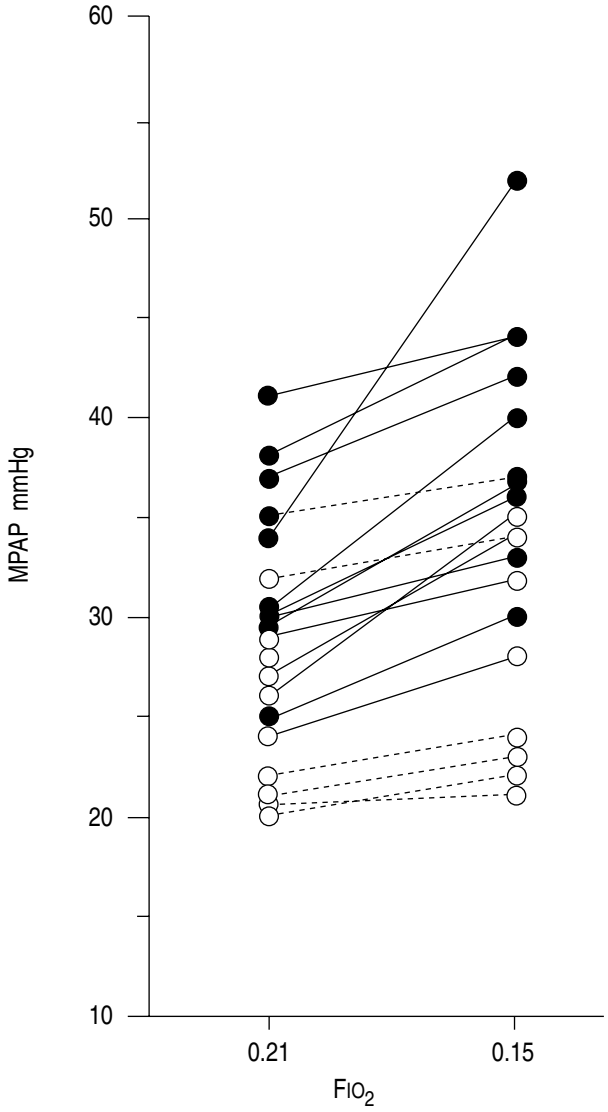

Fig. 1. – Individual variations of mean pulmonary artery pressure (MPAP) during hypoxia (F_{IO_2} 0.15).—○—: patients receiving placebo; —●— : patients receiving almitrine; ——— : patients with a small hypertensive response (<3 mmHg). F_{IO_2}: fraction of inspired oxygen.

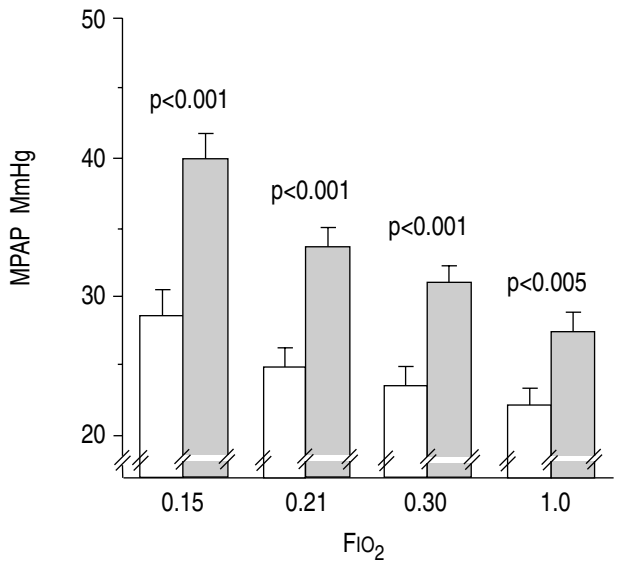

Fig. 2. – Variation of mean pulmonary artery pressure (MPAP) according to F_{IO_2} level. Data are presented as mean±SEM. □: placebo; ▭ : almitrine. For abbreviations see legend to figure 1.

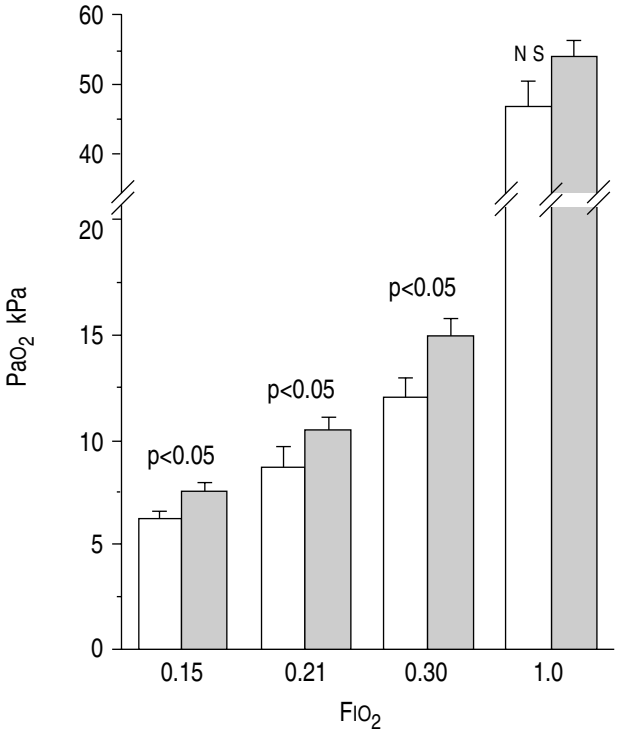

Fig. 3. – Variation of Pa_{O_2} according to F_{IO_2} level in the almitrine and placebo groups. Data are presented as mean±SEM. NS: nonsignificant; Pa_{O_2}: arterial oxygen tension. □ : placebo; ▭ : almitrine. For further abbreviations see legend to figure 1.

higher in the almitrine group (fig. 2 and table 3). During hypoxia, the increase in systolic pulmonary pressure was five times greater in the almitrine group than in the placebo group (+20 *versus* +4 mmHg). The increase in diastolic pulmonary pressure was lower.

At each F_{IO_2} level, PVR was significantly higher in the almitrine than the placebo group. During hypoxia, it was more than three times higher. The decrease in PVR during hyperoxia was also greater in the almitrine group.

Blood gases

At each F_{IO_2} level, Pa_{O_2} was higher in the almitrine group than in the placebo group. However, under pure oxygen, the difference was not statistically significant (fig. 3). Arterial pH was significantly higher in the almitrine group. Pa_{CO_2} was slightly lower in the almitrine group, although no statistical difference could be found. Within the almitrine group, Pa_{CO_2} was lower than the control value at each F_{IO_2}, except during pure oxygen (table 4). Sa_{O_2} was slightly higher in the almitrine group, but this difference was not statistically significant. $P\bar{v}_{O_2}$ was the same in both groups.

Table 4. – Blood gases according to F_{IO_2} in the two groups

Variables	F_{IO_2}	Placebo group		Almitrine group		Comparison	
	level	Mean±SEM	p-value*	Mean±SEM	p-value*	p-value**	Interaction
Pa_{O_2}	Control	8.8±0.4		8.8±0.5		NS	
kPa	0.15	6.3±0.3	<0.0001	7.5±0.4	<0.01	<0.05	
	0.21	8.7±0.9	NS	10.5±0.5	<0.01	<0.05	<0.05
	0.30	12±0.9	<0.0002	14.9±0.9	<0.001	<0.05	
	1.0	46.5±3.3	<0.0001	53.6±2.3	<0.0001	NS	
Pa_{CO_2}	Control	5.3±0.3		5.3±0.3		NS	
kPa	0.15	5±0.3	<0.05	4.5±0.3	<0.001	NS	
	0.21	5.3±0.3	NS	4.8±0.3	<0.01	NS	<0.001
	0.30	5.3±0.4	NS	5.1±0.3	<0.05	NS	
	1.0	5.7±0.4	<0.02	5.3±0.3	NS	NS	
$P\bar{v}_{O_2}$	Control	5.3±0.3		4.9±0.3		NS	
kPa	0.15	4.4±0.1	<0.05	4.3±0.3	<0.002	NS	
	0.21	5.2±0.3	NS	4.8±0.1	NS	NS	NS
	0.30	5.6±0.4	NS	5.3±0.4	NS	NS	
	1.0	6.7±0.5	<0.002	6.5±0.3	<0.0001	NS	
pHa	Control	7.39±0.01		7.39±0.01		NS	
	0.15	7.39±0.01	NS	7.44±0.01	<0.002	<0.01	
	0.21	7.39±0.03	NS	7.44±0.01	<0.01	<0.01	<0.01
	0.30	7.37±0.01	<0.0005	7.42±0.01	<0.05	<0.01	
	1.0	7.36±0.02	<0.005	7.41±0.01	NS	<0.05	
Sa_{O_2}	Control	92±1		91±2		NS	
%	0.15	81±2	<0.005	85±1	NS	NS	
	0.21	91±2	NS	94±1	<0.01	NS	NS
	0.30	95±1	<0.001	98±1	<0.002	NS	
	1.0	99±1	<0.001	99±1	<0.002	NS	
Almitrine	Control	0		0			
plasma level	0.15	0		318±14			
$ng \cdot ml^{-1}$	0.21	0		334±20			
	0.30	0		329±20			
	1.0	0		320±14			

$P\bar{v}_{O_2}$: mixed venous oxygen tension; pHa: arterial hydrogen ion concentration; Sa_{O_2}: arterial oxygen saturation. For further abbreviations see legends to tables 1 and 2. *: control *versus* F_{IO_2} 0.15, 0.21, 0.30 and 1.0, respectively; **: placebo *versus* almitrine.

Discussion

In the present randomized, double-blind, placebo-controlled trial, we investigated the effects of almitrine on pulmonary haemodynamics at different F_{IO_2} concentrations. All patients had COPD with pulmonary artery pressure values comparable to those reported previously in this condition [11, 12]. Almitrine was administered in a single dose. Mean plasma levels (325±9 $ng \cdot ml^{-1}$) (table 4) were the same as those obtained after 50 mg *per os* twice a day (between 214–387 $ng \cdot ml^{-1}$) which corresponds to the dose used in chronic studies in COPD patients [13]. At this dose, almitrine has little effect on ventilation [4, 5, 7, 14–16], although we did not measure this variable in the present study.

Almitrine is a peripheral chemoreceptor agonist [1, 2]. Improvement of hypoxia and hypercapnia observed at high doses was first attributed to the augmentation of alveolar ventilation. However, beneficial effects on blood gases have been observed when almitrine was administered at low doses, or when alveolar ventilation was unchanged or kept constant during mechanical ventilation [8]. A plausible explanation for this finding is an improvement of the ventilation/perfusion ratio. In the present study, almitrine enhanced pulmonary vasoconstriction in patients suffering from COPD. Relative to control values, the increase in MPAP and PVR during hypoxia, was more than three times higher in the almitrine group. Using a lower F_{IO_2} (0.125) on normal subjects, MÉLOT *et al*. [5] reported a similar increase in MPAP with a greater HPV. It is noteworthy that ABRAHAM *et al*. [17], who also observed high HPV in COPD patients submitted to F_{IO_2} 0.15, demonstrated that central blood volume plays a role in HPV. In our study, the enhancement of HPV was concomitent with an increase in Pa_{O_2} and a slight decrease in Pa_{CO_2}. The augmentation of Pa_{O_2} was greater than the reduction of Pa_{CO_2}. These findings are consistent with previous studies suggesting an improvement in $\dot{V}_A/\dot{Q}$ matching rather than an increase in overall ventilation [3, 7]. The decrease in Pa_{CO_2} between

F_{IO_2} 0.21 and 0.15 was similar in both groups, but compared to the control value the decrease in P_{ACO_2} was greater in the almitrine group. Lower P_{ACO_2} could be attributed to hyperventilation but, if so, one would expect to observe lower PVR unless lung volume increases.

Previous investigations concerning the effects of almitrine on HPV have yielded apparently contradictory findings. Low-dose almitrine (≤4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) enhanced HPV in normal lungs [5, 18–20], whilst higher doses blunted it [9, 21–23]. These discrepancies may be due to differences in species and experimental design. The same dose of almitrine could have different effects depending on whether the thorax is open or closed [9, 21, 22], and whether the lung is normal or diseased (COPD). In normal subjects, low doses of almitrine (4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) have been shown to increase basal pulmonary vascular tone [5]. In the present study, the same effect was observed in COPD patients at higher doses (8 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

The effects of almitrine on pulmonary circulation are not only dose-dependent but are also influenced by the reactivity of the pulmonary vessels to hypoxia. Differences in response to hypoxia have been observed in animals [24, 25], as well as in patients suffering from chronic bronchitis [26]. NAEIJE *et al*. [24] showed that low-dose almitrine (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) induced HPV in dogs with a naturally absent hypoxic pulmonary pressor response (non-responders) but had no effect in responders. They suggested that responders had a very strong pressor response to hypoxia, that could not be further enhanced. However, in the same study, a higher dose (4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) induced HPV in non-responders but inhibited HPV in responders. In our study, almitrine at the dose of 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, caused a notable enhancement of HPV in 9 out of 10 COPD patients. An elevation of the basal tone of the pulmonary vascular bed might explain this enhancement [27]. Using low doses of almitrine, FALUS *et al*. [9] did not find any increase in basal tone. However, it has been previously shown that in normal subjects [28], as well as in COPD patients [29], high-dose almitrine (16 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreases distensibility of large pulmonary vessels, resulting in an increase in systolic pulmonary artery pressure, which is consistent with our results. In our experience, almitrine appeared to increase pulmonary vascular tone since MPAP and PVR at F_{IO_2} 0.21, were much higher during almitrine infusion than during the control period, whereas CI remained constant. Likewise, the vasopressive response to hypoxia was more frequent and greater in the almitrine than placebo group.

The pressor effect of almitrine could result from stimulation of peripheral chemoreceptors. Several studies have shown that hypoxic stimulation of peripheral chemoreceptors inhibits HPV [30–33]. A direct effect on pulmonary vessels is also likely, since almitrine is still able to induce or enhance pulmonary vasoconstriction after chemoreceptor denervation [9, 18, 22, 23, 31, 34]. Furthermore, a vasodilating agent, such as nifedipine, acting on arterial wall cancels out the pulmonary vasoconstrictor effect of almitrine and abolishes its beneficial effect on P_{aO_2} [10].

Another aspect is the long-term effect of HPV. Although it preserves blood oxygenation, it increases right ventricular afterload and, therefore, may have deleterious consequences on right ventricular function. Thus, the question arises, whether chronic administration of almitrine has such consequences. In the 3 month study of MACNEE *et al*. [35], almitrine treatment was associated with an increase in MPAP. In a longer clinical study, PRÉFAUT and co-workers [36, 37] found an initial rise in pulmonary hypertension during the first two months of treatment, but this initial increase was no longer observed after one year. Several hypotheses have been proposed to explain the fact that long-term treatment is not accompanied by any significant change in pulmonary haemodynamics [37]. One is a difference in the plasma levels after acute and chronic administration. Interestingly, the mean almitrine plasma levels reported by WEITZENBLUM *et al*. [37] in their one year study were not very different from those of our acute study (285±38 $ng \cdot ml^{-1}$ *versus* 325±9 $ng \cdot ml^{-1}$). A second explanation is that during long-term almitrine administration, the vasoconstrictive effect of almitrine may be offset by the increase in P_{aO_2} [36, 37].

This hypothesis is not inconsistent with our finding that a single *i.v*. dose of almitrine results in an increase in MPAP and an enhancement of pulmonary vasoconstriction in patients suffering from COPD.

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