

Almitrine in low dose potentiates vasoconstrictor responses of isolated rat lungs to moderate hypoxia

F. Falus*, J. Herget, V. Hampl

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ABSTRACT: To test whether the effect of almitrine on hypoxic pulmonary vasoconstriction was dose-dependent, two series of experiments were performed on isolated rat lungs perfused with constant flow of blood.

In the first series, the effects of different doses of almitrine on perfusion pressure were measured. Baseline perfusion pressure was not changed by solvent or by $0.25 \mu\text{g}\cdot\text{ml}^{-1}$ almitrine, but it was increased by 0.5 and $2.0 \mu\text{g}\cdot\text{ml}^{-1}$ almitrine. The increase in perfusion pressure in response to 10 min ventilation with hypoxic gas mixture (5% O_2) was significantly ($p < 0.05$) higher after $0.25 \mu\text{g}\cdot\text{ml}^{-1}$ almitrine (12.0 ± 0.8 torr) than before addition of the drug (5.43 ± 1.8 torr). Responses to hypoxia were insignificant after higher doses (0.5 and $2.0 \mu\text{g}\cdot\text{ml}^{-1}$) of almitrine.

In the second series of experiments the responses to varying degrees of hypoxia were measured after administration of one dose of almitrine ($0.25 \mu\text{g}\cdot\text{ml}^{-1}$). Almitrine, compared to solvent alone, significantly altered the shape of the dose-response curve to hypoxia. Increases in perfusion pressure in response to moderate degrees of hypoxia were potentiated (10% O_2 : 8.7 ± 1.8 torr after almitrine, 2.1 ± 0.6 torr after solvent, $p < 0.05$), whereas responses to severe hypoxia (3% O_2) were not changed by almitrine. Reactivity to angiotensin II was decreased by $0.25 \mu\text{g}\cdot\text{ml}^{-1}$ almitrine.

We conclude that almitrine in low but not in high dose augments pulmonary vasoconstriction induced by mild degrees of hypoxia.

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Almitrine improves the arterial blood oxygenation in patients with respiratory failure even when they are artificially ventilated [1]. This finding suggests that almitrine not only stimulates peripheral chemoreceptors [2], but may also improve the matching of lung blood perfusion to ventilation [3]. Constriction of small pulmonary arteries in hypoventilated areas is an important factor which regulates the relationship of the lung ventilation to the lung perfusion [4]. Hence, it is possible that almitrine may potentiate hypoxic pulmonary vasoconstriction in hypoventilated parts of lungs. Studies on the effect of almitrine on the magnitude of hypoxic pulmonary vasoconstriction show contradictory results [5, 6]. The studies, however, differed in the experimental protocols and doses of almitrine.

The present study tests whether the effect of almitrine on hypoxic pulmonary vasoconstriction is dose-dependent. Using isolated rat lungs, two experiments were performed. In experiment A the vasoconstrictor response to one degree of hypoxia (5% O_2) was elicited following administration of different doses of almitrine. In experiment B the influence of one dose of almitrine, chosen in experiment A as the most potent (0.25

$\mu\text{g}\cdot\text{ml}^{-1}$), on responses to several degrees of hypoxia was measured. In addition, reactivity to angiotensin II was estimated in order to differentiate between nonspecific effect of almitrine on basal tone of lung vessels and a specific influence on hypoxic pulmonary vasoconstriction.

Methods

The experimental preparation used was the isolated perfused rat lung [7, 8]. Adult (250-350 g) male Wistar SPF rats were anaesthetized with thiopental ($100 \text{ mg}\cdot\text{kg}^{-1}$ BW, *i.p.*). Under positive pressure ventilation, their chest was opened and 0.15-0.25 ml of saline containing $1,000 \text{ IU}\cdot\text{ml}^{-1}$ heparin was injected into the left ventricle. The pulmonary artery and left ventricle were cannulated and the aorta ligated. Lungs were removed from the chest and suspended in a humid chamber at 38°C . The preparation was perfused with a constant flow ($0.04 \text{ ml}\cdot\text{min}^{-1}\cdot\text{g}$ of BW) of recirculating blood (approximately 15 ml) obtained by a cardiac puncture of 2-3 rat blood donors anaesthetized with ether.

Lungs were ventilated at 65 breaths·min⁻¹. Peak inspiratory and expiratory pressures were, respectively, 9 and 2.5 cmH₂O. All gas mixtures used for ventilation contained 5% CO₂ and were balanced with N₂. In all experiments, lungs were first allowed 15 min to stabilize whilst ventilated with 21% O₂. The lungs were then challenged twice with 10 min periods of hypoxia (3% O₂), each followed by 10 min of normoxic ventilation, to establish the reproducible and stable hypoxic reactivity [9]. As the flow rate, outflow pressure and ventilation were constant, all changes in perfusion pressure reflected changes in pulmonary vascular resistance.

A neutral solution of almitrine was used. Two milligrams of powder almitrine (Servier, France) were heated in 0.2 ml of ethyl alcohol and then mixed with 20 ml of solution of polyethyleneglycol in water (1:1). Fresh solution was prepared for each experiment.

Experiment A

In experiment A four equal hypoxic challenges (5% O₂, 10 min) were used in 10 min intervals to elicit hypoxic pulmonary vasoconstriction. Five minutes before the second, third and fourth challenge, respectively, 0.25, 0.5 and 2.0 µg·ml⁻¹ almitrine was added to the perfusate. Control lungs were treated similarly with corresponding amounts of solvent.

Additional experiment was performed to see whether the effect of low dose of almitrine was time-dependent. The experimental protocol was similar to that in experiment A. One dose of almitrine (0.25 µg·ml⁻¹) was added to the perfusate after the first 5% O₂ challenge. The next three 5% O₂ challenges were not followed by any dose of almitrine. They were separated by 10 min intervals of 21% O₂ ventilation.

Experiment B

At the beginning of each experiment of the B series, *i.e.* after the two initial 3% O₂ challenges were completed, 0.25 µg·ml⁻¹ of almitrine was added to the perfusate. In the control group an adequate amount of solvent was added. Following 5 min of normoxic ventilation the dose-response to acute hypoxic stimuli and, after 10 min recovery period, to angiotensin II were measured. The dose-response to hypoxia was assessed by step-wise decreasing oxygen content in the ventilating mixture. Each degree of hypoxia (10, 5 and 3% O₂) lasted 10 min. The challenges were not separated by periods of normoxia. Responses to angiotensin II were measured during normoxic ventilation. Doses of 0.1, 0.2, 0.3, 0.4 and 0.5 µg of angiotensin II in saline were injected into the inflow cannula in 5 min intervals.

Statistics

Results are presented as mean±SEM. The groups in experiment A were compared using one-way analysis

of variance (ANOVA) and Scheffe test [10]. In experiment B the differences in baseline perfusion pressure were evaluated with the unpaired t-test. Increases in perfusion pressure due to different degrees of hypoxia or doses of angiotensin II were compared between the groups using two-way ANOVA and Student-Newman-Keul's test for simultaneous multiple comparisons [10]. The differences where *p*<0.05 were considered significant.

Results

Experiment A

The amount of solvent used did not significantly influence baseline perfusion pressure or the magnitude of perfusion pressure increase in response to acute hypoxia. Baseline perfusion pressure before and after addition of the amount of solvent corresponding to 0.5 and 2.0 µg·ml⁻¹ almitrine was, respectively, 15.0±2.0, 17.3±2.0 and 18.0±1.1 torr (1 torr = 0.133 kPa). Before and after the two doses of solvent, the perfusion pressure increased with hypoxia by 4.2±1.1 torr, 6.2±1.8 and 8.0±0.8 torr, respectively. The effects of various doses of almitrine are presented in figure 1. After higher doses of almitrine (0.5 and 2.0 µg·ml⁻¹) the baseline perfusion pressure was significantly elevated and did not significantly increase during acute hypoxic challenge. The lowest dose of almitrine (0.25 µg·ml⁻¹), in turn, did not elevate baseline perfusion pressure. It did, however, potentiate the response to acute hypoxic stimulus (fig. 1). An additional experiment demonstrated that hypoxic pulmonary vasoconstriction was still potentiated about one hour after administration of a single low dose of almitrine (fig. 2).

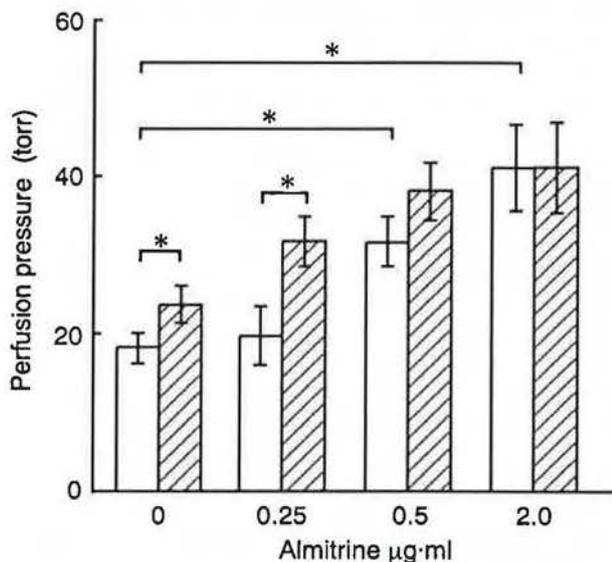


Fig. 1. - Effect of various doses of almitrine on perfusion pressure in isolated rat lungs perfused with constant flow of blood during normoxia (□) and hypoxia (▨) *: *p*<0.05. Mean values±SEM are given, *n*=7.

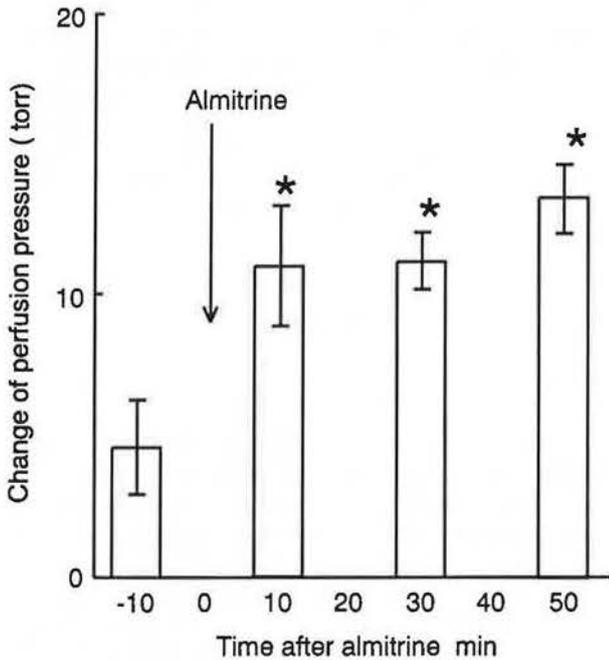


Fig. 2. - The effect of a single dose of almitrine ($0.25 \mu\text{g}\cdot\text{ml}^{-1}$) on the changes of perfusion pressure induced by hypoxic challenges ($\text{FIO}_2=0.05$). Mean values \pm SEM are given, $n=5$. *: significantly different from the effect of hypoxia before the almitrine administration. FIO_2 : fraction of inspired oxygen.

Experiment B

Baseline perfusion pressure before the administration of almitrine (15.0 ± 1.1 torr) was not significantly different from the corresponding value in the control group before the administration of solvent (16.1 ± 1.3 torr). Addition of $0.25 \mu\text{g}\cdot\text{ml}^{-1}$ of almitrine to the perfusate caused an insignificant rise in perfusion pressure (from 15.0 ± 1.1 to 19.7 ± 2.6 torr, $p>0.05$, 5 min after the almitrine injection), as did the addition of solvent (from 16.1 ± 1.3 to 17.4 ± 1.8 torr, $p>0.05$). Perfusion pressure before the measurement of the dose-response to hypoxia in the almitrine group was not significantly different from the value in the control group ($p>0.05$).

The shape of dose-response to acute hypoxia was significantly altered by the injection of $0.25 \mu\text{g}\cdot\text{ml}^{-1}$ of almitrine into the perfusate (fig. 3). The increase in perfusion pressure induced by a mild hypoxia (10% O_2) was significantly higher in almitrine-treated lungs (8.7 ± 1.8 torr) than in solvent-treated ones (2.1 ± 0.6 torr, $p<0.01$, unpaired t-test). Responses to severe hypoxia (3% O_2), however, did not differ between almitrine (14.3 ± 2.7 torr) and solvent (18.1 ± 2.2 torr, $p>0.05$, unpaired t-test) treated lungs. Two-way ANOVA indicated a significant difference between the two dose response curves (fig. 3).

Baseline perfusion pressure after the hypoxic challenges and before the measurement of dose-response to angiotensin II did not differ between the almitrine-treated and control lungs. It was 20.7 ± 2.9 torr in the lungs

given solvent and 21.5 ± 2.4 torr in the lungs given almitrine. Reactivity to angiotensin II in lungs perfused with blood containing $0.25 \mu\text{g}\cdot\text{ml}^{-1}$ almitrine was significantly lower than in lungs perfused with blood to which only solvent was added (fig. 4).

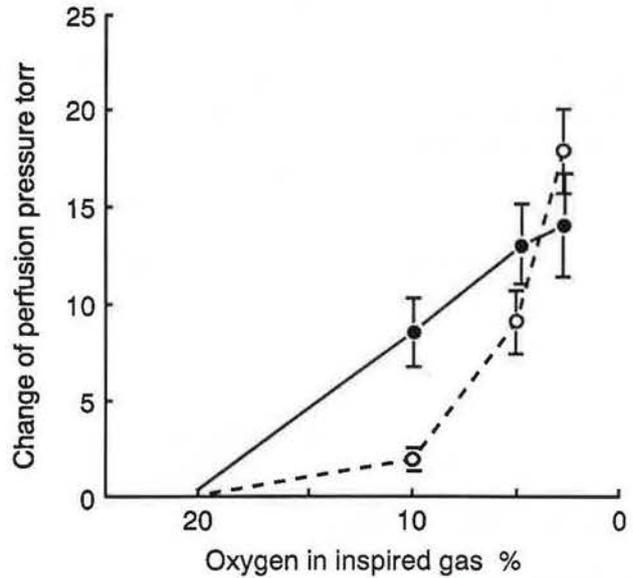


Fig. 3. - Dose-response to acute hypoxia in isolated, constant flow-perfused lungs. Two way analysis of variance (ANOVA) indicates a significant relationship between the amount of oxygen in inspired gas and a change of perfusion pressure (significant factor of hypoxia). It also shows a significantly different shape (significant interaction of factors but insignificant factor of group) of curve obtained from lungs perfused with blood containing $0.25 \mu\text{g}\cdot\text{ml}^{-1}$ of almitrine (●; $n=7$) compared to solvent-treated lungs (-○-; $n=7$).

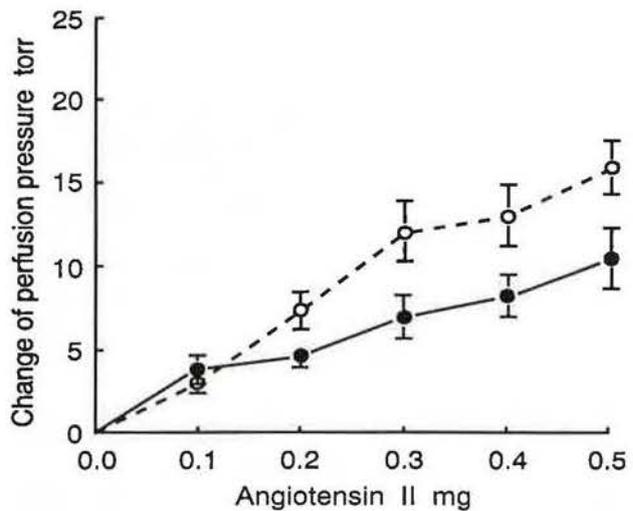


Fig. 4. - Dose-response to angiotensin II in isolated ventilated lungs under constant flow perfusion. Two-way analysis of variance (ANOVA) demonstrates a significant dependence of change of perfusion pressure on the dose of angiotensin II and a significantly lower reactivity to angiotensin II of almitrine-treated (●) than solvent-treated (-○-) lungs. In both groups, $n=7$.

Discussion

The modest level of hypoxia that usually elicits vasoconstriction in isolated lungs is close to fraction of inspired oxygen (F_{iO_2})=0.1 [11, 12]. The present result showed that low dose of almitrine, which did not significantly affect the baseline perfusion pressure, increased the pulmonary vasoconstrictor response to this low degree of hypoxia. By contrast, the vascular response to severe hypoxia was not potentiated by any dose of almitrine. With higher doses of almitrine the baseline perfusion pressure rose and hypoxic pulmonary vasoconstriction was blunted.

The possibility that almitrine might potentiate hypoxic pulmonary vasoconstriction has been discussed over the last few years. It was shown in patients with chronic obstructive lung disease that after administration of almitrine the rise in arterial oxygen tension (P_{aO_2}) did not correlate with an increase in ventilation [13]. To achieve similar improvement of P_{aO_2} with voluntary hyperventilation, the patients would have to increase ventilation about three times, whereas almitrine enhances ventilation only by 20–30% [13, 14]. The rise in P_{aO_2} due to almitrine is often bigger than the drop in arterial carbon dioxide tension P_{aCO_2} [15]. Arterial oxygen tension may be enhanced even by low doses of almitrine (plasma concentration about 70–80 ng·ml⁻¹) that do not significantly stimulate ventilation [6, 16]. Almitrine improves blood gases values even in patients with controlled ventilation [1]. In addition, measurements using the multiple inert gas elimination technique have shown improvement in ventilation/perfusion ratio by almitrine [1, 6, 16] which was not caused by the change in the distribution of ventilation [17]. The possible explanation of these results is that the almitrine increased the hypoxic pulmonary vasoconstriction in hypoventilated lung areas.

In contrast to these indirect suggestions, the direct measurements in animal models have frequently found hypoxic pulmonary vasoconstriction unchanged or even blunted by almitrine [5, 18–22]. More recent studies, however, demonstrated potentiation of hypoxic pulmonary vasoconstriction by almitrine [6, 23–26]. Our results together with those of NAKANISHI *et al.* [25] suggest that the discrepancies might be caused, in part, by use of different doses of almitrine and different degrees of hypoxic stimuli. Doses of almitrine are difficult to compare between the studies as different kinds of administration were used (*i.v.* infusion or bolus injection) and plasma levels were usually not measured. In studies using infusions there appears a clear borderline at the dose of almitrine of about 4 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; at this and lower infusion rates hypoxic pulmonary vasoconstriction is usually potentiated in dogs [23–26] and humans [6], whereas at higher doses hypoxic responses are blunted in dogs [19, 22, 25]. Results obtained after the bolus injections of almitrine are less consistent. HUGHES *et al.* [20] have shown that 5–10 $\mu\text{g}\cdot\text{kg}^{-1}$ slightly enhanced pulmonary vasoconstrictor responses to 12.5–14% O_2 in closed-chest dogs but attenuated them in open-chest dogs [19, 20]. BEE *et al.* [5] have found that

in ferret left lower lobe and isolated lungs a wide range of almitrine doses (0.7–300 $\mu\text{g}\cdot\text{kg}^{-1}$) diminished the increase in pulmonary vascular resistance induced by severe hypoxia (3% O_2). They also reported that vasoconstriction induced in isolated rat lungs by ventilation with gas mixture containing 2% O_2 was weakened by 10 and 100 μg (*i.e.* about 30 and 300 $\mu\text{g}\cdot\text{kg}^{-1}$) of almitrine [5]. In accordance with this study, in our present experiments vasoconstrictor responses of isolated rat lung to 5% O_2 were blunted by two higher doses of almitrine (corresponding approximately to 25 and 100 $\mu\text{g}\cdot\text{kg}^{-1}$). The lowest dose, however (equivalent to about 12.5 $\mu\text{g}\cdot\text{kg}^{-1}$) potentiated responses to 5 and 10 but not to 3% O_2 .

Investigations of the effect of almitrine on hypoxic pulmonary vasoconstriction where almitrine plasma levels were measured are rare. MELOT *et al.* [6] found potentiated hypoxic pulmonary vasoconstriction in humans with almitrine plasma level of 70 ng·ml⁻¹. By contrast, almitrine plasma level of 220 ng·ml⁻¹ caused blunting of hypoxic pulmonary vasoconstriction in closed-chest dogs [22]. The latter value is still lower than the lowest one used in our study (250 ng·ml⁻¹ of perfusate), that potentiated hypoxic pulmonary vasoconstriction. The discrepancy may be related to species differences or to the experimental preparation. The same dose of almitrine could have different effects in the closed-chest animals and in preparations where the influence of pleural pressure was excluded [20, 21, 24].

The studies discussed above demonstrating the potentiating influence of low dose of almitrine on hypoxic pulmonary vasoconstriction were performed on intact dogs [20, 23, 24] and humans [6]. NAKANISHI *et al.* [25] were able to show the same effect after peripheral chemoreceptor denervation. Our study is the first to document a similar result on the isolated lungs. We suppose, therefore, that at least part of the enhancement of hypoxic pulmonary vasoconstriction by almitrine is not mediated *via* the known stimulation of peripheral chemoreceptors as suggested by ROMALDINI *et al.* [23]. It is the direct effect of almitrine on the lung tissue.

The mechanism whereby almitrine in low dose potentiates hypoxic pulmonary vasoconstriction is not clear. An elevation of basal tone of lung vessels has been shown to augment hypoxic pulmonary vasoconstriction [27]. Therefore, we were interested in whether higher responses to hypoxia are not a consequence of nonspecific increase of basal tone by almitrine. The low dose of almitrine, effective in our study, did not increase the perfusion pressure. The pulmonary vasoconstriction, however, need not necessarily follow the increase of basal tone of pulmonary blood vessels [27, 28]. Two arguments, nevertheless, do not favour the possibility that the described effect of almitrine is a simple consequence of the increase of vascular basal tone. Firstly, the vasoconstriction induced by the other agonist, angiotensin II, was depressed after the dose of almitrine which increased the hypoxic pressor response. Secondly, the effects are dose dependent. Only the low doses of almitrine enhanced the vascular response to moderate, but not severe hypoxia.

The latter fact, the change of the dose-response to hypoxic challenges, is in concordance with the results of NAKANISHI *et al* [25], who used different experimental preparation and species in their study. Hence, almitrine appears to increase the sensitivity of lung vessels to hypoxia. It is of interest that in two tissues, which are stimulated by hypoxia, carotid body and pulmonary blood vessels, the effect of hypoxia is enhanced by almitrine. Therefore, further studies on the mode of action of almitrine may be helpful in understanding the nature of oxygen sensing in the tissues excited by hypoxia.

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De petites doses d'Almitrine potentialisent les réponses vasoconstrictives des poumons de rats isolés à l'égard d'une hypoxie modérée. F. Falus, J. Herget, V. Hampl.

RÉSUMÉ: Pour tester si l'effet de l'almitrine sur la vasoconstriction pulmonaire hypoxique était dose-dépendant, nous avons fait deux séries d'expériences sur des poumons isolés de rats perfusés au moyen d'un débit constant de sang. Dans la première série, les effets des différentes doses d'almitrine sur les pressions de perfusion ont été mesurés. La pression basale de perfusion n'est pas modifiée par le solvant, ni par des doses d'almitrine de 0.25 µg·ml⁻¹, mais elle

augmente après 0.5 et 2.0 $\mu\text{g}\cdot\text{ml}^{-1}$ d'almitrine. L'augmentation de la pression de perfusion en réponse à une ventilation pendant 10 minutes au moyen d'un mélange hypoxique de gaz (5% de O_2) est significativement plus élevée après 0.25 $\mu\text{g}\cdot\text{ml}^{-1}$ d'almitrine ($p < 0.05$) (12.0 ± 0.8 torr) qu'avant l'addition du médicament (5.43 ± 1.8 torr). Les réponses à l'hypoxie furent insignifiantes après les doses plus élevées (0.5 et 2.0 $\mu\text{g}\cdot\text{ml}^{-1}$) d'almitrine.

Dans la deuxième série d'expériences, les réponses à divers degrés d'hypoxie ont été mesurées après administration d'une dose d'almitrine (0.25 $\mu\text{g}\cdot\text{ml}^{-1}$). L'almitrine, par comparaison au solvant isolé, modifie de façon significative la forme de la

courbe dose-réponse à l'hypoxie. Les augmentations de la pression de perfusion, en réponse à des degrés modérés d'hypoxie, sont potentialisées (avec 10% de O_2 : 8.7 ± 1.8 torr après almitrine, 2.1 ± 0.6 torr après solvant, $p < 0.05$). Les réponses aux hypoxies sévères (3% de O_2) ne sont pas modifiées par l'almitrine. La réactivité à l'égard de l'angiotensine II diminue sous l'effet de 0.25 $\mu\text{g}\cdot\text{ml}^{-1}$ d'almitrine. Nous concluons que l'almitrine à des doses faibles, mais non à des doses élevées, augmente la vasoconstriction pulmonaire induite par de légers degrés d'hypoxie.

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