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Experimental Studies on Pulmonary Vascular Response to Alveolar Hypoxia during Almitrine Infusion in Anesthetized Dogs

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ABSTRACT

Almitrine bismesylate, a peripheral chemoreceptor stimulant has been shown to increase arterial oxygen tension in patients with chronic airflow obstruction. This effect is thought to be partly attributable to the enhancement of hypoxic pulmonary vasoconstriction (HPV). However, regarding this point the results of various clinical and animal studies on almitrine are inconclusive.

The aim of this study was to investigate the effect of almitrine on HPV in anesthetized, open chested dogs. HPV was expressed in terms of flow diversion associated with hypoxic challenge to the left lower lobe (LLL) where LLL and the rest of the lung were separately ventilated. Results showed that the HPV was enhanced by relatively lower doses of almitrine infusion while attenuated by higher doses. Stimulus-response curves (relationship between end-tidal oxygen pressure and LLL blood flow) showed shift to the right, indicating that almitrine induced the pulmonary vasoconstriction dose-dependently at progressively higher end-tidal oxygen tensions during LLL hypoxic challenges. This suggested that almitrine, also enhanced the response of pulmonary vessels to hypoxia. These changes were not found during almitrine vehicle infusion.

Plasma level of 6-keto-$PGF_{1\alpha}$, the stable metabolite of PGI_2 did not show any significant changes after infusion of almitrine. Besides this, following denervation of peripheral chemoreceptors, some dogs showed the same effects as observed in those without chemoreceptor denervation i,e HPV was enhanced by low doses of almitrine and attenuated by higher doses where stimulus-response curves also shifted towards the right. Doxapram, another chemoreceptor stimulant drug did not enhance or attenuate HPV. The effect of almitrine was not influenced by blocking the Ca^{++} entry through the voltage dependent channel.

It was therefore concluded that vasoconstriction induced by almitrine may be attributed to a direct effect on pulmonary vessels rather than being mediated via the peripheral chemoreceptors.

Of all regional circulations, the pulmonary vascular bed appears to have the most unique and unusual set of control. In 1946 Von Euler and Liljestrand observed that alveolar hypoxia elicited pulmonary vasoconstriction[15]. However the mechanism of this phenomenon is not yet established[17]. It is appreciated that hypoxic pulmonary vasoconstriction (HPV) could be a con-

trol mechanism for diverting blood from regions of alveolar hypoxia to well ventilated areas and thereby reduce the scatter of ventilation perfusion ratio. Chronic airflow obstruction(CAO) causes mismatching of ventilation to perfusion and areas of local alveolar hypoxia resulting in arterial hypoxemia. But the presence of alveolar hypoxia causes pulmonary vasoconstriction which is reversible in its early stage, although it eventually leads to irreversible narrowing of pulmonary arteries and raised pulmonary arterial pressure, right ventricular hypertrophy and finally right ventricular failure. Bronchodilators and oxygen therapy have been used for the treatment of this condition. Drugs which stimulate the respiratory center have been associated with little convincing therapeutic effect and many undesirable side effects. Almitrine bismesylate, a new triazine derivative is a peripheral chemoreceptor stimulant that has been claimed to increase ventilation[25,26] and improve ventilation/perfusion matching in patients with chronic airflow obstruction[34,47,50]. The primary action of almitrine is an increase in ventilation by stimulation of peripheral chemoreceptor rather than via central action[26]. The site of action of almitrine was first demonstrated by Laubie and Diot[24], who showed that the increase of ventilation in dogs was abolished by denervation of the carotid body and vagal section, and was enhanced by carotid artery infusion of almitrine. It has subsequently been shown that even in the absence of stimulation of ventilation, almitrine improves arterial oxygen tension in patients with chronic airflow obstruction, possibly because of redistribution of blood flow away from poorly ventilated areas[10,11]. Furthermore, in patients treated for acute respiratory failure with mechanical ventilation, the arterial oxygen tension increased significantly following intravenous administration of almitrine[46]. Rigaud and co-workers[47], using a radioisotopic method and Castaing et al[11], using a multiple inert gas technique showed a decrease in blood flow to poorly ventilated areas and improve in ventilation and perfusion ratio after almitrine administration. Thus it was speculated that, improvement of ventilation/perfusion ratio after almitrine infusion may be due to enhancement of HPV and diverting blood flow to well ventilated areas.

Romaldini et al[48] in their experiments in anesthetized dogs observed that the increase in pulmonary vascular resistance (PVR) during almitrine infusion was greater when 12% oxygen was breathed and was considerably reduced by 100% oxygen and inferred that almitrine might enhance HPV. However results of some experiments have failed to present any supporting evidence of reinforcement to HPV by almitrine. Wach et al[55] in their experiments with dogs and cats observed that almitrine caused a rise in pulmonary arterial pressure, increased blood flow of the hypoventilated lobe and failed to improve gas exchange in this hypoventilated lobe. These results do not support the view that improved arterial gas tension in patients after almitrine are attributable to diversion of blood flow away from hypoxic lung. Hughes et al[20] also described a dual action of almitrine where the pulmonary vasoconstrictor effect can convert in vasodilation in presence of local hypoxia.

In the anesthetized dog, Laubi[24] observed that there was an increased arterial oxygen tension by small dose of almitrine given intravenously without any increase in the respiratory rate. It was confirmed later that an infusion of almitrine in the dogs increased the arterial oxygen tension in small doses which can not be explained purely by an effect upon ventilation[24].

The mechanism of vasoconstrictor effect of almitrine is not yet well understood. Mazmanian and Lockhart[28,29] who found that almitrine reduced hypoxic vasoconstriction in isolated rat lung in which systemic neural and humoral factors had been eliminated. It was also reported that almitrine can act as a vasodilator in lobes of the ferret lungs[8]. Romaldini et al[48] proposed that, the vasoconstrictor effect of almitrine in the intact dog could be mediated via the stimulation of peripheral chemoreceptors and the sympathetic nervous system. Furthermore Hughes et al reported that almitrine induced pulmonary vasoconstriction could be blunted by Ca^{++} entry blocking drugs during normoxic condition but the effect of this agent during hypoxic condition has not yet been investigated.

Again Gryglewski[18] found that almitrine released prostacyclin(PGI_2) like substance from the lungs of anesthetized cat and this report was supported by Korbut et al[22] and they postulat-

ed that chemoreceptor stimulation by almitrine, induced release of endogenous prostacyclin. But Bult et al[9] showed that although almitrine induced increase in respiratory movement, it did not stimulate prostacyclin synthesis in rabbits.

Thus the present study was designed to investigate the effect of almitrine on HPV by infusing different doses of almitrine intravenously and the effect of almitrine on HPV after peripheral chemoreceptor denervation in open chested dogs where left lower lobes were separately ventilated. The effect of another chemoreceptor stimulant drug (doxapram) on HPV and the effect of Ca^{++} entry blocking agent (nifedipine) on HPV during almitrine administration was also investigated.

METHODS

Animal preparation:

Thirty adult mongrel dogs of either sex, weighing 10-15 kg were anesthetized with sodium pentobarbital (30 mg/kg). The dogs were then intubated with a cuffed endotracheal tube and ventilated using one side of a dual piston respirator (Harvard 608) with a tidal volume of 15 ml/kg with 100% oxygen (Fig.1). These dogs were then paralysed with suxamethonium chloride (2 mg/kg) to prevent spontaneous breathing. Thereafter a polyethylene tube was placed in the right femoral artery for measuring systemic arterial pressure and sampling arterial blood for gas analysis. Following this, a double lumened catheter was inserted in the left femoral vein for infusion of saline and administration of drugs. The tip of a Swan-Ganz thermo-dilution catheter (93A-131H-7F, Gould) was positioned in the pulmonary artery for measuring pulmonary arterial pressure and for sampling of mixed venous blood through the left femoral vein. After thoracotomy through the left 5th or 6th intercostal space, a catheter was placed directly into the left atrium for measuring left atrial pressure. The pulmonary trunk was dissected free from its surrounding fat and an electromagnetic flow probe was placed around it and connected to a flowmeter (MFV 1100, Nihon Koden, Tokyo, Japan.) to measure total pulmonary blood flow ($\dot{Q}_T$). A second flow probe was also placed around the left lower lobe (LLL) pulmonary artery to measure LLL blood flow ($\dot{Q}_{LLL}$). The LLL bronchus was incised distal to a ligature and a plastic cannula was tied tightly into it so that the LLL and the rest of the lung (RL) could be ventilated independently. The tidal volume of the LLL (50-90 ml) and RL (150-200 ml) was adjusted to produce the

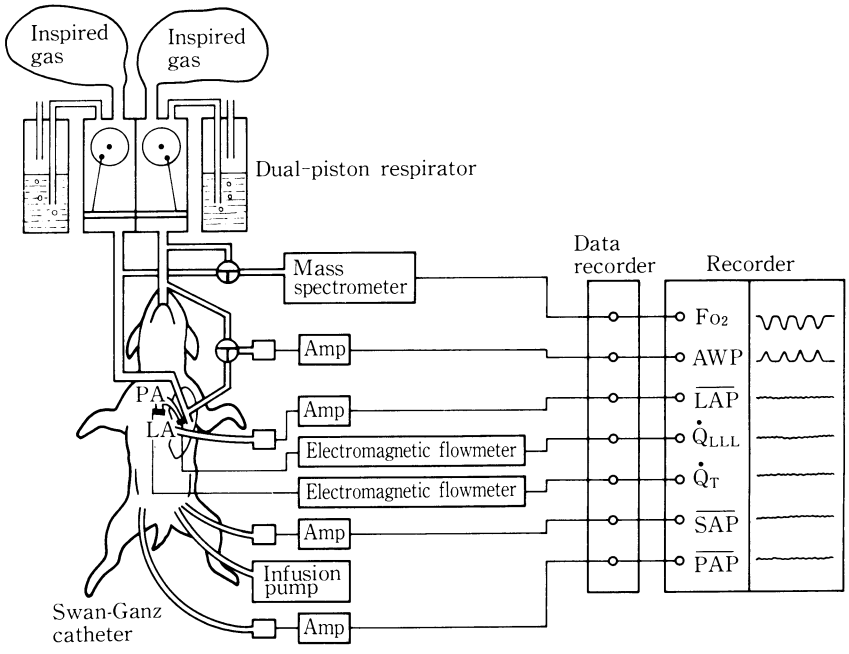

Fig. 1. Schematic representation of experimental preparation

same peak airway pressure (AWP peak). A positive end-expiratory pressure (PEEP, 5 cm H_2O) was applied to both LLL and RL. Occasional hyperinflations were performed to minimize collapse throughout the experiment.

Respiratory rate was adjusted to achieve arterial carbon-dioxide tension of approximately 30-40 mmHg. End-tidal oxygen and carbon dioxide concentrations were measured using a mass spectrometer (Perkin-Elmer MGA 1100). Airway pressure was measured by a pressure transducer (MP45, Validyne). Systemic arterial, left atrial and pulmonary arterial pressures were measured by using pressure transducers (Statham, 23ID). Fractional oxygen concentration (Fo_2), airway pressure AWP, mean left atrial pressure ($\overline{LAP}$), $\dot{Q}_{LLL}$, $\dot{Q}_T$, mean systemic arterial pressure ($\overline{SAP}$) and mean pulmonary arterial pressure ($\overline{PAP}$) were recorded on a data recorder (R-260 LT, TEAC) and a polyrecorder (Nippon Denshi Kagaku U-629). Arterial and mixed venous blood samples were drawn before and at the end of each LLL hypoxic challenge and analyzed for pH, oxygen and carbon-dioxide tensions by electrode method (ABL 1, Radiometer Co, Copenhagen, Denmark) and values were corrected for the body temperature of dogs. Body temperature of the dogs was maintained (38°—39°C) by heating pads and metabolic acidosis was adjusted by infusion of 7% sodium bicarbonate solution when required. Proper level of anesthesia was maintained by pentobarbital injection. Suxamethonium chloride was also administered from time to time. Normal saline was infused throughout the experiment at a rate of 5 ml/kg/hr to compensate the blood loss due to surgical procedure and during the experimental period.

After preparation of each dog, the LLL was separately ventilated with a gas mixture (95% N_2 + 5% CO_2) for 10 min (LLL-N_2). LLL ventilation was then changed back again to 100% O_2 (LLL-O_2) and it was confirmed that hemodynamic variables returned almost to the same values as were obtained prior to the hypoxic challenge. The sequential change of LLL hypoxic ventilation to hyperoxic ventilation was repeated five times allowing approximately 20 min recovery time between cycles. Then dogs were divided according to the following experimental protocols.

1) Infusion of different doses of almitrine and its vehicle

a) Almitrine in low doses (n=5): Almitrine was infused intravenously by an infusion pump (Harvard 940D), at a dose of 0.3 μg/kg/min starting 10 min before and continuing for 10 min during hypoxic challenge to the LLL. This was followed by about 10 min of 100% O_2 ventilation after which almitrine was infused at doses of 1.0,3.0 or 5.0 μg/kg/min 10 min before and during 10 min of LLL hypoxia. To prepare the solution for infusion 15 mg almitrine bismesylate lyophylized preparation was dissolved in 5 ml of 0.6% malic acid in distilled water. This solution was diluted 20 to 80 times with 10% aquous glucose solution before use. Hypoxia was also challenged at 30,60,90 and 120 min after discontinuation of drug infusion.

b) Almitrine in higher doses (n=5): The drug was infused at doses of 1.0,5.0,10.0 or 20.0 μg/kg/min for 10 min before and during 10 min of hypoxic challenge to the LLL. The same challenge was repeated at 30 and 60 min after discontinuation of almitrine infusion.

c) Control with vehicle (n=5): 0.6% malic acid used for dissolving the almitrine was dilulated 20 to 80 times with 10% aquous glucose solution. The resulting solution was continuously infused 10 min before and 10 min during hypoxic challenge at rates of 0.0764 or 0.382 ml/min. These rates of infusion of the vehicle corresponded to 0.3 and 5.0 μg/kg/min of almitrine respectively.

d) Measurement for plasma level of 6-keto-$PGF_{1\alpha}$ during infusion at different doses of almitrine:

Blood samples were taken from the left atrium at the end of each hypoxic challenge before and during infusion of low and high doses of almitrine. Samples were withdrawn in a syringe and stored in a tube containing indomethacin. The blood samples were then centrifuged and plasma was stored at −80°C until the day of assay. The plasma was used for determination of 6-keto-$PGF_{1\alpha}$ by radioimmunoassay.

2) Infusion of almitrine after peripheral chemoreceptor denervation (n=5):

After careful dissection of the neck, peripheral chemoreceptors were denervated by cutting the nerve for the carotid sinuses and the vagi. Then hypoxia was challenged during infusion of almi-

trine at doses of 0.3,1.0,3.0,5.0,10.0 or 20.0 μg/kg/min. The same hypoxic challenge was repeated at 30 and 60 min after discontinuation of almitrine administration.

3) Infusion of doxapram (n=5): Hypoxia was challenged before, during and after infusions of doxapram at doses of 20 and 200 μg/kg/min.

4) Infusion of almitrine along with calcium antagonist (n=5): Nifedipine, a calcium channel blocker was infused at a dose of 3.0 μg/kg/min along with almitrine at the dose of 3.0 μg/kg/min 10 min before and 10 min during LLL hypoxic challenge.

The degree of HPV was expressed as the maximum percentage decrease in the ratio of $\dot{Q}_{LLL}$ to $\dot{Q}_T$ (% decrease $\dot{Q}_{LLL}/\dot{Q}_T$) (Fig.2). This was calculated in the following way.

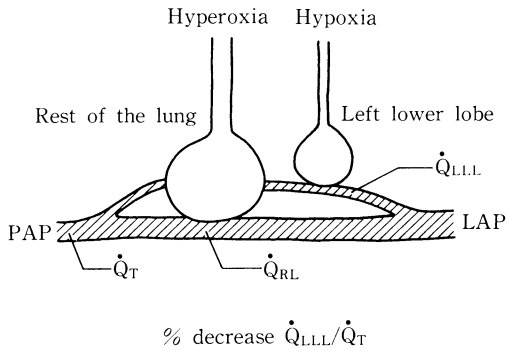

Fig. 2. Index of regional hypoxic pulmonary vasoconstriction

$$\dot{Q}_{LLL}/\dot{Q}_T = \frac{\dot{Q}_{LLL}}{\dot{Q}_T} \times 100\ (\%)$$

$$\%\ \text{decrease}\ \dot{Q}_{LLL}/\dot{Q}_T = \frac{\dot{Q}_{LLL}/\dot{Q}_T\ \text{before LLL hypoxia} - \dot{Q}_{LLL}/\dot{Q}_T\ \text{end of LLL hypoxia}}{\dot{Q}_{LLL}/\dot{Q}_T\ \text{before LLL hypoxia}} \times 100\ (\%)$$

$\dot{Q}_{LLL}$, measured using electromagnetic flowmeter and oxygen partial pressure of inspired and expired gas of LLL using mass spectrometer were continuously monitored and were connected to an X-Y recorder (Hewlett Packard 7046 A). At each end-expiratory phase during the LLL-N_2 challenge, the pen of the X-Y recorder was downed on the paper. The relationship between $\dot{Q}_{LLL}$ and end-tidal oxygen partial pressure of LLL (LLL-$P_{ET_{O_2}}$) was plotted with $\dot{Q}_{LLL}$ as abscissa and LLL-$P_{ET_{O_2}}$ as ordinate to give the stimulus-response curve (Fig.3). The

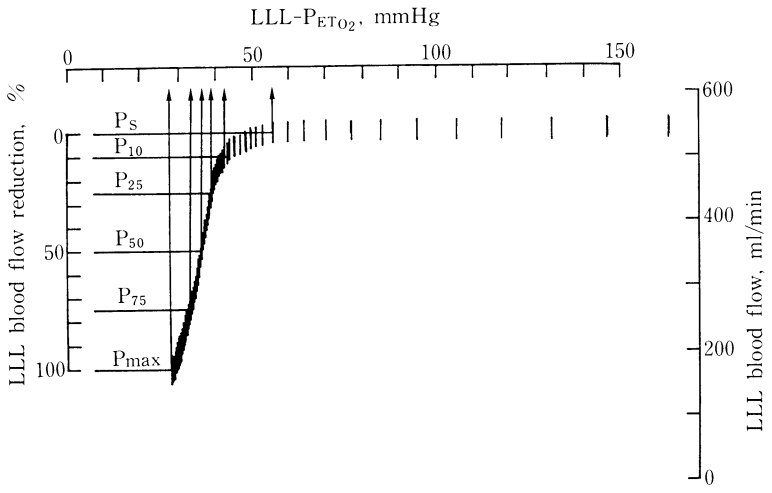

Fig. 3. Example of a typical stimulus-response curve

Relationship between left lower lobe blood (LLL) flow and LLL end-tidal P_{O_2} (LLL-$P_{ET_{O_2}}$).

P_S: value of LLL-$P_{ET_{O_2}}$ at which $\dot{Q}_{LLL}$ starts to decrease.

P_{10}, P_{25}, P_{50}, and P_{75}: values of LLL-$P_{ET_{O_2}}$ at which $\dot{Q}_{LLL}$ decrease from P_S to P_{max} by 10%,25%,50% and 75% respectively.

P_{max}: value of LLL-$P_{ET_{O_2}}$ at which $\dot{Q}_{LLL}$ decrease maximally.

value of LLL-$P_{ET_{O_2}}$ at which $\dot{Q}_{LLL}$ started to decrease and at which this decrease became maximal were defined as P_S and P_{max}, respectively. Furthermore, the value of LLL-$P_{ET_{O_2}}$ at which $\dot{Q}_{LLL}$ decreased by 10%, 25%, 50% and 75% were defined as P_{10}, P_{25}, P_{50} and P_{75}, respectively (Fig.3).

All values shown in the tables are mean ± standard deviation. Data were statistically analyzed by student's paired t test at a significance of $p<0.05$.

Table 1. Glossary of abbreviations

Abbreviations	unit	
AWP	cmH_2O	airway pressure
AWP peak	cmH_2O	peak airway pressure
CAO		chronic airflow obstruction
Fo_2	%	Oxygen concentration
HPV		hypoxic pulmonary vasoconstriction
HR	beats/min	heart rate
$\overline{LAP}$	mmHg	mean left atrial pressure
LLL		left lower lobe lung
LLL-O_2		left lower lobe lung ventilated with 100% Oxygen
LLL-N_2		left lower lobe lung ventilated with 95% N_2 and 5% CO_2
LLL-$P_{ET_{O_2}}$	mmHg	end-tidal partial pressure of O_2 of left lower lobe
$\overline{PAP}$	mmHg	mean pulmonary arterial pressure
Pa_{O_2}	mmHg	partial pressure of O_2 in arterial blood
Pa_{CO_2}	mmHg	partial pressure of CO_2 in arterial blood
pHa		pH in arterial blood
$P\bar{v}_{O_2}$	mmHg	partial pressure of O_2 in mixed venous blood
$P\bar{v}_{CO_2}$	mmHg	partial pressure of CO_2 in mixed venous blood
$pH\bar{v}$		pH in mixed venous blood
$\dot{Q}_{LLL}$	ml/min	left lower lobe lung arterial blood flow
$\dot{Q}_T$	ml/min	total pulmonary arterial blood flow
$\dot{Q}_{LLL}/\dot{Q}_T$	%	ratio of left lower lobe blood flow to total pulmonary blood flow
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$	%	ratio of decrease in left lower lobe blood flow during hypoxic challenge (index of HPV)
RL		rest of the lung
$\overline{SAP}$	mmHg	mean systemic arterial pressure

RESULTS

I) Effect of almitrine at low doses (0.3,1.0,3.0,5.0 μg/kg/min)

Table 2 shows changes in peak airway pressure(AWP peak), hemodynamic values and blood gas findings in dogs which received low doses of almitrine infusion. $\overline{PAP}$ increased dose dependently before hypoxic loading. It was increased from 14.2 ± 3.0 mmHg to 14.4 ± 3.2 mmHg during 0.3 μg/kg/min and up to 19.7 ± 5.6 mmHg during 5.0 μg/kg/min almitrine infusion. AWP peak, Heart rate (HR) and $\overline{LAP}$ did not significantly change before and during almitrine administration or hypoxic loading. $\dot{Q}_T$ and $\overline{SAP}$ showed a tendency to decrease over time during the experimental period. $\dot{Q}_T$ decreased from 2198 ± 516 ml/min to 1826 ± 151 ml/min and $\overline{SAP}$ from 119 ± 11 mmHg to 114 ± 12 mmHg at the end of experiment. $\dot{Q}_{LLL}$ decreased from 492 ± 138 ml/min to 254 ± 86 ml/min during LLL hypoxic ventilation before almitrine but it decreased from 464 ± 147 ml/min to 171 ± 53 ml/min during almitrine infusion at the dose of 0.3 μg/kg/min and from 486 ± 65 ml/min to 207 ± 82 ml/min at the dose of 5 μg/kg/min. % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ which was the index of HPV, increased from 46.2 ± 14.5% to 60.8 ± 12.1%, 65.5 ± 17.6% and 67.9 ± 22.3% ($p<0.05$) during administration of almitrine at doses of 0.3, 1.0 and 3.0 μg/kg/min,

Table 2. Airway pressure, hemodynamics and blood gas analysis during hypoxic challenge before and during administration of almitrine

Challenge / Variables	before almitrine		during almitrine 0.3μg/kg/min		1μg/kg/min		3μg/kg/min		5μg/kg/min	
	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWPpeak (cmH_2O)	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7
$\overline{SAP}$ (mmHg)	119±11	119±11	116±11	116±11	116±11	116±11	112±12	114±12†	114±12†	114±12
HR (beats/min)	186±38	185±38	184±36	182±33	183±32	183±28	185±28	183±23	182±18	179±14
$\overline{LAP}$ (mmHg)	6.9±2.5	6.9±2.5	6.6±2.4	6.6±2.5	6.6±2.4	6.6±2.4	6.4±2.2	6.4±2.2	6.3±2.1	6.3±2.1
$\overline{PAP}$ (mmHg)	14.2±3.0	16.1±3.3**	14.4±3.2	17.0±3.4**	15.1±3.8	17.6±3.9**	16.5±4.5†	19.8±5.1**†	19.7±5.6†	24.7±5.9**††
$\dot{Q}_T$ (ml/min)	2198±516	2160±510	2046±563†	2018±550†	2012±572††	1980±556††	1988±580†	2002±548†	1878±180	1826±151
$\dot{Q}_{LLL}$ (ml/min)	492±138	254±86**	464±147	171±53**†	447±139†	137±42**†	474±95	140±70**	486±65	207±82**
$\dot{Q}_{LLL}/\dot{Q}_T$ (%)	22.2±1.7	11.8±2.8**	22.4±2.3	8.6±1.9**†	22.0±2.4	7.3±3.0**†	24.5±3.7	7.9±6.0**	26.2±4.9	11.5±5.4**
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$ (%)		46.2±14.5		60.8±12.1†		65.5±17.6†		67.9±22.3†		55.7±17.2
pHa	7.43±0.03	7.41±0.02*	7.42±0.03†	7.41±0.02*	7.43±0.02	7.41±0.01**	7.42±0.04	7.40±0.02	7.43±0.03	7.40±0.01*
Pa_{O_2} (mmHg)	480.9±17.8	242.8±48.1***	472.1±7.3	270.2±66.1**	474.1±15.1	283.6±66.1**†	484.4±20.7	293.4±67.7**	484.6±17.1	222.4±28.6***
Pa_{CO_2} (mmHg)	36.7±4.6	39.8±5.2*	36.4±3.7	39.0±3.2*	36.0±2.9	38.4±1.5*	37.4±5.4	40.7±4.2*	37.1±4.2	40.6±5.0*
$pH\bar{v}$	7.39±0.02	7.37±0.01**	7.40±0.01*	7.38±0.01	7.39±0.02†	7.39±0.01	7.39±0.02	7.38±0.02	7.40±0.02	7.37±0.03*
$P\bar{v}_{O_2}$ (mmHg)	76.7±6.3	67.1±6.2	94.4±44.7	67.4±5.5	74.7±8.1	68.0±6.8	74.4±9.2	65.5±8.3	70.3±5.5	66.7±7.3
$P\bar{v}_{CO_2}$ (mmHg)	45.6±5.3	46.9±4.2*	44.6±4.5	47.6±4.9	44.8±4.3	47.5±3.5*	43.4±4.0	46.0±4.0*	45.4±5.8	46.6±5.6

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared with the corresponding LLL-O_2 period
† $p<0.05$, †† $p<0.01$ compared with before almitrine

Table 3. Airway pressure, hemodynamics and blood gas analysis during hypoxic challenge after discontinuation of administration of almitrine

Challenge / Variables	30 min		60 min		90 min		120 min	
	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWPpeak (cmH_2O)	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7	12.7±1.7
$\overline{SAP}$ (mmHg)	113±12	113±12	112±12	112±12	111±10	111±10	113±13	113±13
HR (beats/min)	173±18	171±18	173±19	173±20	168±22	168±21	171±20	172±20
$\overline{LAP}$ (mmHg)	6.2±2.1	6.2±2.1	5.9±1.7	5.9±1.7	5.9±1.7	5.9±1.7	5.9±1.7	5.9±1.7
$\overline{PAP}$ (mmHg)	14.4±2.3†	17.0±2.7**††	13.9±2.0†	16.1±2.4**††	13.3±1.8†	15.6±2.0**††	13.1±1.7†	15.7±1.4**†
$\dot{Q}_T$ (ml/min)	1736±217†	1726±224	1698±244††	1668±259	1578±256††	1614±254†	1636±240†	1652±219
$\dot{Q}_{LLL}$ (ml/min)	384±69	125±75**††	389±78	101±47**††	340±54†	97±53**††	344±39†	121±39**†
$\dot{Q}_{LLL}/\dot{Q}_T$ (%)	22.1±2.9	7.6±5.1**†	22.8±2.4	6.4±3.8**†	21.6±1.7	6.3±4.0**††	21.1±1.1	7.4±2.7***
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$ (%)		64.5±26.2		70.9±19.7†		70.1±20.3†		64.6±13.2
pHa	7.42±0.03	7.39±0.01	7.42±0.04	7.40±0.03*	7.42±0.02	7.39±0.01*	7.41±0.01†	7.39±0.01*
Pa_{O_2} (mmHg)	476.1±8.8	262.1±80.6**	469.8±13.7	225.4±43.3***	475.5±19.3	243.1±69.9**	488.3±12.9	236.2±40.4***
Pa_{CO_2} (mmHg)	37.0±4.6	38.6±4.0	37.2±4.7	39.1±4.0*	37.2±3.6	40.7±5.0	38.4±4.3	42.2±5.3
$pH\bar{v}$	7.39±0.02	7.36±0.02*	7.40±0.02	7.37±0.02*	7.40±0.01	7.38±0.02*	7.40±0.02	7.37±0.02**
$P\bar{v}_{O_2}$ (mmHg)	70.8±5.6	66.1±6.8**	71.2±6.8	65.3±3.7*	70.9±4.6	66.0±7.7	72.8±4.5	66.3±5.7*
$P\bar{v}_{CO_2}$ (mmHg)	45.0±4.7	48.0±6.5	45.1±5.4	47.4±6.6	45.2±5.1	48.1±5.1**	44.7±5.0	49.6±6.2**

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared with the corresponding LLL-O_2 period
† $p<0.05$, †† $p<0.01$ compared with during almitrine (5μg/kg/min)

respectively. However, it decreased to 55.7 ± 17.2% after 5.0 μg/kg/min. Similarly arterial oxygen tension associated with hypoxic loading gradually increased from 242.8 ± 48.1 mmHg to 270.2 ± 66.1 mmHg, 283.6 ± 66.1 mmHg ($p<0.05$) and 293.4 ± 67.7 mmHg during almitrine infusion at the doses of 0.3,1.0 and 3.0 μg/kg/min, respectively, but decreased to 222.4 ± 28.6 mmHg during 5.0 μg/kg/min. Carbon dioxide tension and pH in arterial blood increased during LLL hypoxia but did not show any significant changes during almitrine infusions. Oxy-

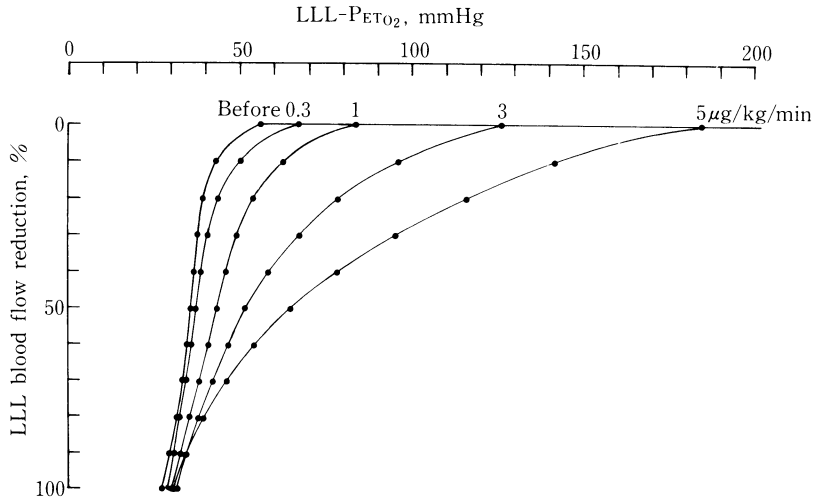

Fig. 4. The change of stimulus-response curve obtained with varying rates of almitrine infusion

Table 4. Changes of LLL end-tidal oxygen pressure before, during and after administration of almitrine

Pressure \ Period		before almitrine	during almitrine				after almitrine			
			0.3μg/kg/min	1μg/kg/min	3μg/kg/min	5μg/kg/min	30 min	60 min	90 min	120 min
P_S	(mmHg)	48.5±8.5	61.0±10.3*	87.0±18.3**	154.4±20.9***	213.3±30.6***	177.4±32.3	148.2±24.4†	112.5±20.2†††	91.0±14.0†††
P_{10}	(mmHg)	39.4±4.0	50.2±9.2*	68.0±19.2*	112.1±27.5**	158.4±24.2***	127.5±37.0†	96.8±21.0†††	85.1±16.4†††	68.3±17.2†††
P_{25}	(mmHg)	35.7±4.3	43.4±6.3	56.9±19.6	81.0±22.5*	116.2±24.3**	90.3±26.7†	65.3±19.1†††	57.8±12.0†††	49.1±11.6†††
P_{50}	(mmHg)	33.4±4.3	36.5±5.0	43.8±9.2	54.6±14.2*	68.2±20.7*	58.5±18.2†	43.4±13.1†	39.5±7.8†	35.5±7.8†
P_{75}	(mmHg)	30.9±4.1	31.4±4.4	34.8±8.0	38.6±8.4*	39.6±8.2*	36.2±8.4	32.5±6.0††	30.1±6.6††	29.7±5.8††
P_{max}	(mmHg)	29.5±4.8	28.4±4.3	27.9±4.0	27.9±3.0	28.7±3.6	27.0±2.5	25.2±2.0	24.4±4.7	26.1±4.5

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared with before almitrine
† $p<0.05$, †† $p<0.01$, ††† $p<0.001$ compared with during almitrine (5μg/kg/min)

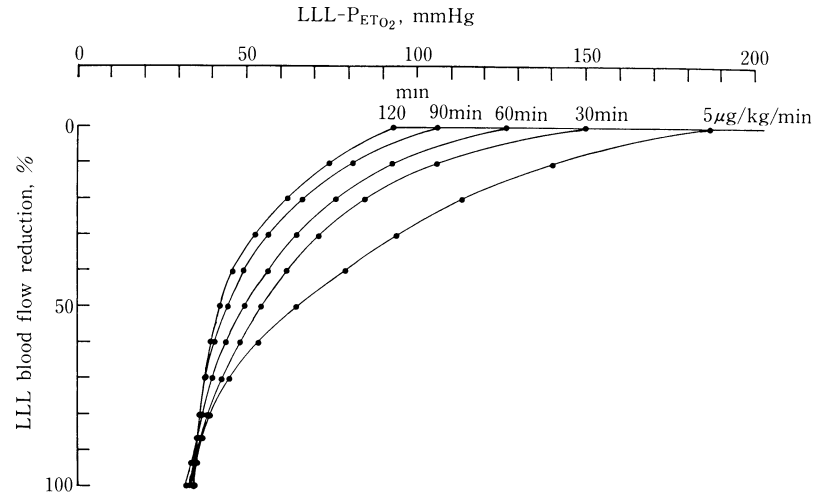

Fig. 5. The change of stimulus-response curve after discontinuation of almitrine infusion

Table 5. Airway pressure, hemodynamics and blood gas analysis during hypoxic challenge before and during administration of almitrine

Variables \ Challenge		before almitrine		during almitrine 1 μg/kg/min		5 μg/kg/min		10 μg/kg/min		20 μg/kg/min	
		LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWP peak	(cmH_2O)	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5
$\overline{SAP}$	(mmHg)	106±4	106±4	107±4	107±4	107±7	107±7	108±10	109±10	107±9	108±9
HR	(beats/min)	156±23	158±24	154±23	158±24	157±22	160±22	160±22	155±22	159±24	153±20
$\overline{LAP}$	(mmHg)	5.3±1.3	5.3±1.3	5.2±1.3	5.2±1.3	5.2±1.2	5.2±1.2	5.2±1.0	5.5±1.1	5.4±1.0	5.6±1.0
$\overline{PAP}$	(mmHg)	14.9±0.7	15.9±0.4*	14.9±0.4	16.3±0.9*	15.6±0.7	17.3±1.0**	19.3±2.0††	21.3±2.2††	20.8±2.0††	21.4±1.1†††
$\dot{Q}_T$	(ml/min)	1656±262	1610±274	1558±330	1544±324	1552±368	1556±437	1634±360	1662±352	1760±510	1738±474
$\dot{Q}_{LLL}$	(ml/min)	351±50	193±39**	324±84	152±31**†	330±101	177±75**	443±145	276±152**	502±242	299±142*
$\dot{Q}_{LLL}/\dot{Q}_T$	(%)	21.3±1.0	12.1±2.3**	20.6±1.1	9.9±1.0***	21.0±1.5	11.2±3.0**	26.9±3.9†	15.9±6.2**	27.5±6.2	16.7±5.1*
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$	(%)		42.9±11.5		52.0±6.1		46.7±15.2		41.1±18.6		37.5±22.0
pHa		7.44±0.05	7.41±0.03	7.43±0.01	7.40±0.03	7.44±0.02	7.42±0.01	7.42±0.02	7.42±0.01	7.43±0.03	7.41±0.03
Pa_{O_2}	(mmHg)	546.8±52.0	213.1±71.6***	484.8±185.9	244.5±56.9**†	556.7±40.0	207.4±75.9***	555.2±40.7	162.2±93.0***	544.1±38.7	124.8±57.4***†
Pa_{CO_2}	(mmHg)	33.1±2.8	36.9±2.6**	34.3±2.6	37.7±3.2**	34.7±2.8†	36.7±3.2**	34.8±2.8†	37.4±3.8*	34.8±2.8	37.3±4.1*
pHv̄		7.39±0.03	7.38±0.03*	7.38±0.02	7.37±0.02	7.39±0.02	7.38±0.02	7.38±0.02	7.37±0.01	7.39±0.02	7.36±0.03†
$P\bar{v}_{O_2}$	(mmHg)	74.7±10.7	64.5±7.3*	71.8±10.2	62.7±9.8	73.7±7.9	62.4±7.8**	70.4±10.7†	59.1±11.7**	71.1±10.0†	53.6±11.9**
$P\bar{v}_{CO_2}$	(mmHg)	38.8±3.2	40.0±2.4	39.4±1.9	40.4±2.8	39.5±3.0	40.9±2.6†	41.5±2.2†	42.7±2.5†	41.9±3.0†	43.6±3.2†

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$: significance LLL-O_2 vs LLL-N_2
$^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$, $^{\dagger\dagger\dagger}p<0.001$: significance before vs during almitrine administration

Table 6. Airway pressure, hemodynamisc and blood gas analysis during hypoxic challenge after discontinuation of administration of almitrine

Variables \ Challenge		30 min		60 min	
		LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWP peak	(cmH_2O)	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5
$\overline{SAP}$	(mmHg)	102±9†	102±9†	100±10†	100±10†
HR	(beats/min)	158±24	157±21	160±23	161±27
$\overline{LAP}$	(mmHg)	5.5±1.2	5.4±1.1	5.4±1.4	5.4±1.4
$\overline{PAP}$	(mmHg)	16.5±2.6	18.0±2.6**	15.4±2.2†	17.0±2.2**†
$\dot{Q}_T$	(ml/min)	1458±337†	1436±316†	1420±240	1436±242
$\dot{Q}_{LLL}$	(ml/min)	314±68	141±72**†	298±67	121±58***†
$\dot{Q}_{LLL}/\dot{Q}_T$	(%)	21.6±1.5	9.5±4.0**††	21.1±3.7	8.3±3.3***†
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$	(%)		56.2±16.5††		61.5±9.7†
pHa		7.43±0.02	7.40±0.02**	7.43±0.02	7.41±0.02
Pa_{O_2}	(mmHg)	551.2±44.9	212.2±96.6***	539.2±40.4	236.7±108.9**
Pa_{CO_2}	(mmHg)	34.6±3.3	36.5±4.1*†	34.8±3.2	35.2±1.8
pHv̄		7.40±0.03	7.38±0.02**	7.39±0.02	7.37±0.03
$P\bar{v}_{O_2}$	(mmHg)	72.4±14.1	57.3±10.5**†	73.2±9.1	59.2±8.1**
$P\bar{v}_{CO_2}$	(mmHg)	40.8±1.9	44.8±1.6**	43.4±3.2	45.5±2.8**

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$: significance LLL-O_2 vs LLL-N_2
$^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$: significance almitrine infusion (20 μg/kg/min) vs after admitrine discontinuation

gen tension in mixed venous blood ($P\bar{v}_{O_2}$) associated with hypoxic loading did not change significantly during administration of almitrine. Table 3 shows the same parameters after discontinuation of the drug infusion. $\overline{PAP}$ decreased and % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ increased significantly at 90 and 120 min after discontinuation of almitrine at the dose of 5.0 μg/kg/min. Corresponding arterial oxygen tensions also increased. Figure 4 shows stimulus-response curves recorded during almitrine infusions in different doses. The curve shifted dosedependently to the right. During administration of almitrine at the dose of 3.0 μg/kg/min, vasocon-

Table 7. Changes of LLL end-tidal oxygen pressure before, during and after administration of almitrine

Pressure \ Period		before almitrine	during almitrine 1 μg/kg/min	during almitrine 5 μg/kg/min	during almitrine 10 μg/kg/min	during almitrine 20 μg/kg/min	after almitrine 30 min	after almitrine 60 min
P_S	(mmHg)	61.0±17.9	81.4±14.4*	183.5±47.9***	295.8±26.6***	381.3±27.3***	320.3±33.9††	248.6±25.6†††
P_{10}	(mmHg)	39.1±7.2	44.9±10.2	123.1±47.0*	192.5±52.8**	302.7±45.6***	194.9±37.6††	134.0±28.3††
P_{25}	(mmHg)	30.2±8.2	34.8±9.2**	84.1±33.4*	126.6±29.8***	176.5±47.9**	143.3±35.3	90.3±32.9†
P_{50}	(mmHg)	27.4±6.5	28.5±6.5	51.9±14.1*	65.6±19.0**	100.2±36.8*	87.8±30.4	71.0±33.5†
P_{75}	(mmHg)	25.8±6.3	26.0±6.0	34.4±4.0**	37.8±5.2*	44.5±12.6*	46.6±26.6	31.1±16.1
P_{max}	(mmHg)	24.4±5.9	23.1±5.5	22.0±5.9	24.2±7.1	22.7±6.2	19.0±5.4*	16.7±2.3

*p<0.05, **p<0.01, ***p<0.001 : significance before vs during almitrine administration
†p<0.05, ††p<0.01, †††p<0.001 : significance almitrine infusion (20 μg/kg/min) vs after almitrine discontinuation

Table 8. Airway pressure, hemodynamics and blood gas analysis during hypoxic challenge before, during and after administration of almitrine vehicle

Variable \ Challenge		before almitrine vehicle LLL-O_2	before almitrine vehicle LLL-N_2	during almitrine vehicle 0.0764 ml/min LLL-O_2	during almitrine vehicle 0.0764 ml/min LLL-N_2	during almitrine vehicle 0.382 ml/min LLL-O_2	during almitrine vehicle 0.382 ml/min LLL-N_2	after almitrine vehicle LLL-O_2	after almitrine vehicle LLL-N_2
AWPpeak	(cmH_2O)	12.8±0.8	12.8±0.8	12.8±0.8	12.8±0.8	12.8±0.8	12.8±0.8	12.8±0.8	12.8±0.8
$\overline{SAP}$	(mmHg)	110±12	110±13	110±13	110±13	109±14	109±14	109±14	109±14
HR	(beats/min)	155±30	155±31	156±28	156±28	156±28	157±28	160±28	160±28
$\overline{LAP}$	(mmHg)	5.1±2.0	5.1±2.0	5.0±1.8	5.0±1.8	5.0±1.8	5.0±1.8	5.0±1.8	5.0±1.8
$\overline{PAP}$	(mmHg)	15.6±2.3	17.1±2.4**	15.4±2.4	16.9±2.6***	15.2±2.4	17.0±2.3***	14.7±1.7	16.7±2.1**
$\dot{Q}_T$	(ml/min)	1988±746	1948±740	1822±708†	1630±410	1696±557	1676±533	1466±515†	1470±517†
$\dot{Q}_{LLL}$	(ml/min)	434±143	198±66**	393±120†	167±42**	377±90	166±67**	323±89†	129±52**††
$\dot{Q}_{LLL}/\dot{Q}_T$	(%)	22.2±2.1	10.5±2.7***	22.3±2.9	10.4±2.0***	22.8±2.3	10.1±3.1**	22.6±2.9	9.0±3.0***
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$ (%)			53.0±9.1		53.1±7.1		55.6±13.8		60.5±11.8
pHa		7.42±0.01	7.41±0.01**	7.42±0.01	7.41±0.01**	7.42±0.01	7.41±0.02	7.44±0.04	7.41±0.04**
Pa_{O_2}	(mmHg)	491.4±16.4	275.3±15.6***	499.2±12.0	280.2±28.9***	484.8±18.8	257.9±40.8***	490.3±18.0	272.8±19.1***
Pa_{CO_2}	(mmHg)	34.7±4.0	38.5±5.4	35.9±4.2	39.0±5.5	36.0±3.5	37.9±3.9	34.8±3.7	38.3±4.5
$pH\bar{v}$		7.39±0.03	7.37±0.02*	7.40±0.02	7.38±0.01*	7.41±0.03	7.37±0.02	7.39±0.02	7.38±0.01
$P\bar{v}_{O_2}$	(mmHg)	64.0±4.5	59.8±3.4*	64.7±6.4	64.0±5.9	64.9±6.4	61.9±5.2*	67.0±6.1	61.3±5.1
$P\bar{v}_{CO_2}$	(mmHg)	42.4±4.6	45.1±3.3	43.9±3.8	45.4±6.0	42.4±4.4	44.9±4.5*	42.6±4.4	45.6±4.1*

* p<0.05, ** p<0.01, p<0.001 compared with the corresponding LLL-O_2 period
† p<0.05, †† p<0.01 compared with before almitrine vehicle

Table 9. Changes of LLL end-tidal oxygen pressure before, during and after administration of almitrine vehcle

Pressure \ Period		before almitrine vehicle	during almitrine vehicle ml/min 0.0764	during almitrine vehicle ml/min 0.382	after almitrine vehicle
P_S	(mmHg)	42.9±7.3	42.9±7.7	43.4±8.4	44.1±8.1
P_{10}	(mmHg)	37.6±6.1	38.1±6.9	37.5±7.6	38.9±7.5
P_{25}	(mmHg)	32.5±6.4	32.9±6.3	32.9±6.9	34.2±7.5
P_{50}	(mmHg)	28.9±5.6	28.8±5.3	28.8±5.1	28.4±5.2
P_{75}	(mmHg)	26.8±5.2	26.1±4.3	26.1±4.3	25.2±4.4
P_{max}	(mmHg)	25.0±5.2	24.0±4.3	24.1±4.4	23.0±4.1

striction occurred at a LLL-$P_{ET_{O_2}}$ greater than 100 mmHg. Table 4 compares P_S, P_{10}, P_{25}, P_{50}, P_{75} and P_{max} before, during and after each level of almitrine infusion. $\dot{Q}_{LLL}$ started to decrease at 48.5 ± 8.5 mmHg of LLL-$P_{ET_{O_2}}$ before almitrine. It started to decrease at 61.0 ± 10.3 mmHg, 87.0 ± 18.3 mmHg, 154.4 ± 20.9 mmHg and 213.3 ± 30.6 mmHg of LLL-$P_{ET_{O_2}}$ during infusions of almitrine at doses of 0.3,1.0,3.0 and 5.0 μg/kg/min, respectively. P_{10}, P_{25}, P_{50}, P_{75} values also increased dose dependently with almitrine administration. Almitrine caused vasoconstriction to occur at higher end-

Table 10. Changes of plasma 6-keto-$PGF_{1\alpha}$ concentration before and during almitrine at the end of each left lower lobe hypoxic challenge

a) before and during infusion of low doses of almitrine.

	before almitrine	during almitrine			
		0.3 μg/kg/min	1 μg/kg/min	3 μg/kg/min	5 μg/kg/min
6-keto-$PGF_{1\alpha}$ pg/ml	251.2 ± 175.1	240.4 ± 125.6	227.2 ± 99.8	198.8 ± 95.7	218.2 ± 126.3

before vs during almitrine: no statistical significance

b) before and during infusion of high doses of almitrine

	before almitrine	during almitrine			
		1 μg/kg/min	5 μg/kg/min	10 μg/kg/min	20 μg/kg/min
6-keto-$PGF_{1\alpha}$ pg/ml	205.5 ± 97.0	265.6 ± 168.8	209.4 ± 102.5	235.8 ± 125.7	235.8 ± 118.2

before vs during almitrine: no statistical significance

tidal oxygen level dose dependently i.e. the curve shifted to the right. This effect was reversed after discontinuation of the drug infusion. The $\dot{Q}_{LLL}$ started to decrease at 91.0 ± 14.0 mmHg of LLL end-tidal oxygen level 120 min after discontinuation of the drug infusion (Table 4, Fig.5).

II) Effect of almitrine at higher doses (1.0,5.0,10.0 and 20.0 μg/kg/min):

When almitrine was infused at relatively higher doses AWP peak,$\overline{SAP}$,HR and $\overline{LAP}$ were almost unchanged during hypoxic loading to the LLL (Table 5). $\overline{PAP}$ increased dose dependently during administration of the drug. It was increased from 14.9 ± 0.7 mmHg to 19.3 ± 2.0 mmHg and 20.8 ± 2.0 mmHg during 10.0 and 20.0 μg/kg/min of almitrine infusion. % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ increased from 42.9 ± 11.5% to 52.0 ± 6.1% and 46.7 ± 15.2% during doses of 1.0 and 5.0 μg/kg/min but decreased to 41.1 ± 18.6% and 37.5 ± 22.0% at doses of 10.0 and 20.0 μg/kg/min, respectively. Similarly arterial oxygen tension was increased from 213.1 ± 71.6 mmHg to 244.5 ± 56.9 mmHg during 1.0 μg/kg/min but decreased to 207.4 ± 75.9 mmHg, 162.2 ± 93.0 mmHg and 124.8 ± 57.4 mmHg during infusion of almitrine at doses of 5.0,10.0,20.0 μg/kg/min, respectively. Again after discontinuation of almitrine infusion, $\overline{PAP}$ decreased significantly from 20.8 ± 2.0 mmHg to 15.4 ± 2.2 mmHg after 60 min (Table 6). % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ increased to 56.2 ± 16.5% and 61.5 ± 9.7% after 30 and 60 min, respectively. Arterial oxygen tensions also increased corresponding to increased HPV. The LLL blood flow started to decrease at 61.0 ± 17.9 mmHg of LLL-$P_{ET_{O_2}}$ before almitrine. During infusion of almitrine at doses of 1.0, 5.0, 10.0 and 20.0 μg/kg/min the LLL blood flow started to decrease at 81.4 ± 14.4 mmHg, 183.5 ± 47.9 mmHg, 295.8 ± 26.6 mmHg and 381.3 ± 27.3 mmHg of LLL-$P_{ET_{O_2}}$, respectively, indicating right shift of the stimulus-response curve (Table 7).

III) Effect of almitrine vehicle infusion:

Table 8 shows changes in AWP peak, hemodynamics and blood gas analysis during hypoxic challenges before and during administration of almitrine vehicle. There were no significant changes in AWP peak,$\overline{SAP}$,HR and $\overline{LAP}$ during infusion of the vehicle. $\overline{PAP}$ was not increased by vehicle infusion but it did increase during LLL hypoxia. $\dot{Q}_T$ decreased from 1988 ± 746 ml/min to 1676 ± 533 ml/min at the end of the experiment. % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ did not change significantly during administration of low or high volumes of the vehicle. Arterial oxygen tensions associated with hypoxic loading was not changed either by low or high volumes of vehicle infusions. Administration of vehicle did not show any significant changes of LLL end-tidal oxygen pressures, (P_S, P_{10}, P_{25},

Table 11. Airway pressure, hemodynamics and blood gas analysis during hypoxic challenge before and during administration of almitrine in peripheral chemoreceptor denervated dogs

Challenge / Variables		control		after vagotomy		after carotid body denervation		during almitrine 0.3 μg/kg/min		1 μg/kg/min		3 μg/kg/min		5 μg/kg/min		10 μg/kg/min		20 μg/kg/min	
		LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWP peak	(cmH_2O)	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7
$\overline{SAP}$	(mmHg)	112±17	112±17	125±20	125±20	131±20†	130±22†	122±21†	120±17	120±22	120±22	116±21	116±21	115±22	115±22	109±20	109±19	112±23	113±24
HR	(beats/min)	155±16	158±17	163±12	164±13	171±17	170±17	175±27	177±22	176±23	179±23	181±24	181±24	178±22	182±24	180±22	182±22	183±21	181±19†
$\overline{LAP}$	(mmHg)	5.2±0.8	5.2±0.8	5.4±1.0	5.4±1.0	5.5±1.1	5.5±1.1	5.5±0.9	5.5±0.9	5.4±0.8	5.4±0.8	5.4±0.8	5.4±0.8	5.2±0.8	5.2±0.8	5.2±0.8	5.2±0.8	5.2±0.8	5.2±0.8
$\overline{PAP}$	(mmHg)	15.7±2.7	16.6±2.8**	17.5±3.2**	16.4±3.0†	17.2±2.5	18.1±3.0†	17.1±3.0	18.4±3.4**	17.9±3.2	19.4±3.7**	19.2±4.2	21.0±4.8**†	22.7±4.5†	25.2±5.7**†	25.8±3.2**†	26.6±3.4**	27.3±3.9**†	28.7±3.5**†
$\dot{Q}_T$	(ml/min)	1454±295	1458±320	1452±295	1430±310	1442±299	1420±324	1378±254	1378±246	1360±216	1384±226	1416±224	1434±251	1534±309	1500±310	1536±274	1546±286	1536±255	1534±306
$\dot{Q}_{LLL}$	(ml/min)	308±61	170±75**	314±76	161±72**	304±70	160±74***	306±99	134±76***	318±96	125±70***	349±99	141±77***†	435±161	208±109**	477±90†	253±81**	408±137	314±80††
$\dot{Q}_{LLL}/\dot{Q}_T$	(%)	21.2±1.0	11.4±3.9**	25.5±1.4	10.9±3.2**	21.0±1.9	10.9±3.9**	22.0±4.8	9.4±4.6***	23.1±4.5	8.8±4.5***†	24.4±4.2	9.5±4.7***†	27.6±5.3†	13.3±6.0***	31.3±5.1†	16.5±5.5**	26.1±5.4	20.3±3.0††
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$	(%)		46.6±16.9		48.8±16.1		48.5±17.4		58.9±13.1†		63.5±12.1††		62.6±13.3††		53.5±15.9		46.7±19.1		18.3±25.3
pHa		7.43±0.01	7.41±0.02	7.43±0.01	7.40±0.01**	7.43±0.02	7.41±0.02	7.43±0.01	7.40±0.02**	7.41±0.02	7.40±0.03**	7.42±0.01	7.40±0.02**	7.42±0.02	7.40±0.02*	7.41±0.02	7.40±0.03	7.41±0.01	7.40±0.02
Pa_{O_2}	(mmHg)	529.0±61.3	275.3±127.4**	526.0±54.3	254.2±124.7**	521.1±59.5	251.4±123.6**	521.4±54.9	271.0±108.1***	534.6±60.9	336.5±95.7***	539.5±59.1	342.0±101.9**	542.4±47.6	290.1±75.7***	524.7±59.0	186.4±57.9***	503.4±42.6†	152.3±37.6***†
Pa_{CO_2}	(mmHg)	35.1±0.7	37.7±1.4*	35.5±0.6	37.9±1.6*	35.3±0.9	36.9±1.3	35.3±1.0	37.7±0.7**	36.9±1.9	39.1±1.9*	37.1±1.2	39.3±5.5**	36.4±0.9	38.8±1.5**	37.2±1.1†	37.4±3.8	37.4±2.8	40.2±2.6***
pHv		7.39±0.02	7.37±0.03*	7.38±0.01	7.36±0.02**	7.39±0.02	7.37±0.02*	7.38±0.02	7.36±0.02*	7.38±0.01	7.36±0.02*	7.38±0.02†	7.36±0.01*	7.38±0.02	7.36±0.02**	7.38±0.03	7.35±0.03*	7.37±0.02†	7.35±0.02*
Pv_{O_2}	(mmHg)	65.9±7.9	61.9±5.7	65.4±8.0	61.0±5.6	64.2±6.9	60.2±6.1*	64.1±6.3	58.3±5.3*	64.8±5.3	58.9±5.1*	66.3±8.2	61.1±6.4**	63.2±6.7	57.3±6.2**	63.3±5.6	58.1±8.4*	63.8±8.1	55.2±10.1*
Pv_{CO_2}	(mmHg)	41.0±0.4	43.0±0.6**	40.6±1.2	42.4±1.2	40.6±1.5	41.9±1.7	40.5±1.5	42.7±1.3*	41.4±1.2	44.1±0.8**	41.1±1.5	43.4±3.1	42.6±2.1†	43.8±2.8†	42.2±0.8†	44.4±2.0†	42.4±1.8	44.0±1.8*

*p<0.05, **p<0.01, ***p<0.001 : significance LLL-O_2 vs LLL-N_2

†p<0.05, ††p<0.01, †††p<0.001 : significance control vs vagotomy, carotid body denervation and almitrine infusion

P_{50}, P_{75} and P_{max}) so there was no change in the stimulus-response curve (Table 9).

IV) Changes in plasma concentration of 6-keto-$PGF_{1\alpha}$ after infusion of almitrine and vehicle:

There were no significant changes in plasma 6-keto-$PGF_{1\alpha}$ concentrations at the end of each hypoxic loading before and after infusion of different doses of almitrine and vehicle (Table 10). The values changed from 251.2 ± 175.1 pg/ml to 240.4 ± 125.6 pg/ml, 227.2 ± 99.8 pg/ml, 198.8 ± 95.7 pg/ml and 218.2 ± 126.3 pg/ml during administration of the drug at doses of 0.3,1.0,3.0 and 5.0 μg/kg/min, respectively. Similarly during infusion of higher doses of almitrine, the level of 6-keto-$PGF_{1\alpha}$ did not change significantly. It changed from 205.5 ± 97.0 pg/ml to 265.6 ± 168.8 pg/ml, 209.4 ± 102.5 pg/ml, 235.8 ± 125.7 pg/ml and 235.8 ± 118.2 pg/ml during almitrine infusions at doses of 1.0,5.0,10.0 and 20.0 μg/kg/min respectively.

V) Effect of almitrine infusion after denervation of peripheral chemoreceptors:

Table 11 shows the changes in AWP(peak), hemodynamics and blood gas analysis during hypoxic challenges before and during infusion of almitrine in peripheral chemoreceptor denervated dogs. AWP peak did not change after denervation of carotid bodies or vagotomy or after administration of almitrine at different doses. $\overline{SAP}$ increased from 112 ± 17 mmHg to 131 ± 20 mmHg due to carotid sinus nerve section and vagotomy but gradually decreased during infusions at different doses of almitrine. HR and $\overline{LAP}$ did not change significantly. $\overline{PAP}$ increased from 15.7 ± 2.7 mmHg to 16.4 ± 3.0 mmHg after vagotomy and increased dose dependently during almitrine infusion. There were insignificant changes in % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ after vagotomy and carotid body denervation. But it increased from 48.5 ± 17.4% to 58.9 ± 13.1% ($p<0.05$), 63.5 ± 12.1% ($p<0.01$) and 62.6 ± 13.3% ($p<0.01$) during almitrine at doses of 0.3,1.0,3.0 μg/kg/min but gradually decreased to 53.5 ± 15.9%, 46.7 ± 19.1% and 18.3 ± 25.3% during almitrine administration at doses of 5.0,10.0,20.0 μg/kg/min, respectively. Arterial oxygen tension increased from 251.4 ± 123.6 mmHg to 271.0 ± 108.1 mmHg, 336.5 ± 95.7 mmHg and 342.0 ± 101.9 mmHg at doses of 0.3,1.0 and 3.0 μg/kg/min, respectively, and gradually decreased to 290.1 ± 75.7

Table 12. Airway pressure, hemodynamics and blood gas analysis during hypoxic challenge after discontinuation of administration of almitrine in peripheral chemoreceptor denervated dogs

Variables \ Challenge		30 min		60 min	
		LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWP peak	(cmH_2O)	13.0±0.7	13.0±0.7	13.0±0.7	13.0±0.7
$\overline{SAP}$	(mmHg)	107±18	107±18	106±17	106±17
HR	(beats/min)	187±24	187±24	189±26	189±26
$\overline{LAP}$	(mmHg)	5.1±0.7	5.1±0.7	5.1±0.7	5.1±0.7
$\overline{PAP}$	(mmHg)	21.3±1.4†	23.2±2.1†	21.1±5.6†	23.0±5.5
$\dot{Q}_T$	(ml/min)	1444±290†	1472±315†	1444±266†	1452±287†
$\dot{Q}_{LLL}$	(ml/min)	323±79	182±62**††	349±98	171±61**†
$\dot{Q}_{LLL}/\dot{Q}_T$	(%)	22.3±2.5	12.2±2.2**††	23.9±2.9	11.7±2.9**†
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$	(%)		44.3±13.9		50.2±16.0
pHa		7.41±0.02	7.38±0.03†	7.41±0.02	7.39±0.02*
Pa_{O_2}	(mmHg)	521.3±57.3	189.1±71.8***	526.1±56.3	210.7±81.8***
Pa_{CO_2}	(mmHg)	37.8±2.2	38.8±2.2	38.3±2.8	40.4±2.4**
pH$\bar{v}$		7.37±0.03	7.35±0.01*	7.37±0.02	7.36±0.01*
$P\bar{v}_{O_2}$	(mmHg)	65.8±6.7	58.3±7.3**	64.3±6.4	56.3±5.3*
$P\bar{v}_{CO_2}$	(mmHg)	43.4±0.9	45.6±2.1*	43.0±1.1	45.3±2.1*

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$: significance LLL-O_2 vs LLL-N_2
$^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$: significance almitrine infusion (20 μg/kg/min) vs after almitrine discontinuation

Table 13. Changes of LLL end-tidal oxygen pressure before, during and after administration of almitrine in peripheral chemoreceptor denervated dogs

Pressure \ Period		control	vagotomy	carofid body denervation	during almitrine						after almitrine	
					0.3 μg/kg/min	1 μg/kg/min	3 μg/kg/min	5 μg/kg/mln	10 μg/kg/min	20 μg/kg/min	30 min	60 min
P_S	(mmHg)	55.2±21.6	60.7±22.0	61.0±21.8	75.9±30.9*	102.2±24.2***	202.6±61.6**	283.9±85.2**	389.9±23.6***	451.0±24.2***	373.5±64.6†	300.7±49.6††
P_{10}	(mmHg)	36.5±11.3	40.2±13.2	40.2±13.7	45.5±12.9*	55.9±14.7**	128.4±44.1**	200.6±73.8**	274.6±40.8***	344.8±28.6***	270.7±83.0	179.4±91.0††
P_{25}	(mmHg)	30.2±7.6	31.9±8.4	33.1±9.5	34.9±9.1*	39.2±8.0*	81.9±23.1**	133.1±55.0*	186.9±41.2***	242.6±38.0***	177.3±77.0†	115.1±61.7††
P_{50}	(mmHg)	28.1±7.0	27.9±7.2	28.8±7.9	29.4±7.6	30.9±7.7	52.2±12.7*	76.3±33.8*	107.4±51.8*	158.9±33.5***	117.9±60.4†	68.7±34.1†††
P_{75}	(mmHg)	25.5±6.8	25.7±6.7	25.8±7.2	26.1±8.4	26.5±7.7	34.9±8.1	43.9±15.3	49.9±15.3	86.7±24.6**	66.5±31.6	39.2±18.4†
P_{max}	(mmHg)	23.5±7.4	22.8±6.5	22.2±7.7	22.5±9.5	21.8±8.6	21.2±8.3	22.1±8.9	22.8±8.3	24.5±8.4	21.7±9.0	20.8±9.3

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$: significance control vs almitrine administration
$^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$, $^{\dagger\dagger\dagger}p<0.001$: significance almitrine infusion (20 μg/kg/min) vs after almitrine discontinuation

mmHg, 186.4 ± 57.9 mmHg and 152.3 ± 37.6 mmHg in the same fashion as of % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ during ifusion of almitrine at doses of 5.0,10.0,20.0 μg/kg/min. $P\bar{v}_{O_2}$ values did not change significantly. After discontinuation of infusion, $\overline{PAP}$ decreased and % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ increased gradually with the increase of arterial oxygen tensions (Table 12). Table 13 shows LLL end-tidal oxygen pressure before, during and after administration of almitrine in chemoreceptor denervated dogs. The LLL blood flow started to decrease at a higher LLL-$P_{ET_{O_2}}$ dose-dependently during infusion of almitrine. LLL blood flow started to decrease at 75.9 ± 30.9 mmHg, 102.2 ± 24.2 mmHg, 202 ± 61.6 mmHg and 283.9 ± 85.2 mmHg of LLL-$P_{ET_{O_2}}$ during infusion of 0.3,1.0,3.0 and 5.0 μg/kg/min of almitrine, respectively, in comparison to 61.0 ± 21.8 mmHg before almitrine. P_{10}, P_{25}, P_{50} and P_{75} also increased dose-dependently.

VI) Effect of doxapram infusion:

Administration of doxapram at the dose of 20 μg/kg/min increased HR from 162 ± 30 to 173 ± 32 beats/min and $\overline{SAP}$ from 103 ± 3 mmHg to 107 ± 4 mmHg with slight change in $\overline{PAP}$ (Table 14). % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ did not change significantly during hypoxic loading to LLL. During infusion of 200 μg/kg/min of doxapram, HR increased to 184 ± 27 beats/min. $\overline{SAP}$ and $\overline{PAP}$ increased significantly to 114 ± 12.4

Table 14. Airway pressure, hemodynamisc and blood gas analysis during hypoxic challenge before, during and after administration of doxapram hydrochloride

Variables \ Challenge		before doxapram		during doxapram 20 μg/kg/mim		during doxapram 200 μg/kg/min		after doxapram	
		LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWPpeak	(cmH_2O)	11.4±0.5	11.4±0.5	11.4±0.5	11.4±0.5	11.4±0.5	11.4±0.5	11.4±0.5	11.4±0.5
$\overline{SAP}$	(mmHg)	103±3	104±4	107±4 †	107±4	114±4 ††	114±4 ††	107±7	107±7
HR	(beats/min)	162±30	164±32	173±32 ††	176±29 ††	184±27 ††	187±26 †	193±29 ††	191±28 †
$\overline{LAP}$	(mmHg)	3.4±0.8	3.4±0.8	3.3±0.7	3.3±0.7	3.3±0.7	3.3±0.7	3.3±0.7	3.3±0.7
$\overline{PAP}$	(mmHg)	13.5±1.5	15.0±2.1 *	14.8±1.9	16.4±2.5 *	15.9±2.0	17.5±2.1 *†	15.5±2.5	17.5±2.8 **†
$\dot{Q}_T$	(ml/min)	1416±174	1392±174	1450±187 †	1454±189	1474±242	1460±215	1334±241	1304±231
$\dot{Q}_{LLL}$	(ml/min)	312±27	115±30 **	324±34 †	125±26 **	321±40	148±24 ***	307±17	111±26 ***
$\dot{Q}_{LLL}/\dot{Q}_T$	(%)	22.1±1.6	8.4±2.8 ***	22.4±1.7	8.8±2.3 ***	22.0±1.3	10.2±1.3 ***	23.7±5.3	8.7±2.9 ***
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$	(%)		61.8±12.4		60.7±10.6 *		53.4±5.2 *		63.7±7.7 *
pHa		7.44±0.06	7.42±0.03	7.46±0.03	7.42±0.04 ***	7.48±0.03	7.42±0.04 ***	7.46±0.02	7.41±0.02 **
Pa_{O_2}	(mmHg)	567.8±24.3	343.5±80.0 *	578.1±21.1	322.0±70.9 *	581.3±31.9	285.3±82.2 *	566.9±35.5	342.0±36.4 *
Pa_{CO_2}	(mmHg)	33.2±2.4	36.0±1.8 *	33.8±2.5	36.5±2.2 *	34.1±3.0	36.0±2.8 *	32.9±2.7	36.3±1.7 *
pHv̄		7.42±0.01	7.39±0.02 *	7.42±0.01	7.39±0.02 *	7.42±0.02	7.39±0.03 *	7.41±0.02	7.39±0.03
$P\bar{v}_{O_2}$	(mmHg)	52.8±7.4	47.1±5.2 *	53.1±7.1	45.8±4.7 *	52.6±8.9	47.2±8.1 *	50.6±6.0	45.6±6.5
$P\bar{v}_{CO_2}$	(mmHg)	37.8±2.1	40.0±2.5 *	37.9±2.1	41.0±3.1 *	37.8±2.3	41.0±3.0 *	39.0±1.9	42.8±3.5 *†

*p<0.05. **p<0.01. ***p<0.001 : significance LLL-O_2 vs LLL-N_2
†p<0.05. ††p<0.01 : significance before vs during or after doxapram administration

Table 15. Changes of LLL end-tidal oxygen pressure before, during and after administration of doxapram hydrochloride

Pressure \ Period	before doxapram	during doxapram 20 μg/kg/min	during doxapram 200 μg/kg/min	after doxapram
P_S (mmHg)	67.4 ± 10.6	64.7 ± 7.7	64.3 ± 7.4	86.3 ± 8.88
P_{10} (mmHg)	48.1 ± 8.7	44.9 ± 6.9	46.6 ± 6.8	48.6 ± 13.9
P_{25} (mmHg)	38.1 ± 8.7	33.9 ± 7.2	34.7 ± 7.4	39.4 ± 5.0
P_{50} (mmHg)	31.8 ± 7.5	28.4 ± 5.8	27.5 ± 7.0	32.1 ± 4.5
P_{75} (mmHg)	25.7 ± 4.5	23.4 ± 3.7	23.4 ± 5.3	25.2 ± 4.5
P_{max} (mmHg)	17.5 ± 2.5	17.3 ± 3.2	18.5 ± 3.6	17.3 ± 1.6

before vs during vs after doxapram infusion : no statistical significance

mmHg and to 17.5 ± 2.1 mmHg with little changes in % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ from 61.8 ± 12.4% to 53.4 ± 5.2%. Results of blood gas analysis also did not show any significant changes. The LLL blood flow started to decrease at 67.4 ± 10.6 mmHg of LLL-$P_{ET_{O_2}}$ before doxapram. It started to decrease at 64.7 ± 7.7 mmHg and 64.3 ± 7.4 mmHg during doxapram infusion at doses of 20 and 200 μg/kg/min, respectively (Table 15) indicating the stimulus-response curve shifted slightly to the left and not to the right as seen in case of administration of almitrine at different doses.

VII) Effect of calcium antagonist (Nifedipine) during almitrine infusion:

Table 16 shows the changes in the AWP peak, hemodynamics and blood gas analysis before and during administration of nifedipine (3.0 μg/kg/min). $\overline{SAP}$ decreased from 116 ± 12 mmHg to 74 ± 7 mmHg and HR was increased from 187 ± 16 to 205 ± 7 beats/min when nifedipine was infused along with almitrine but no changes were observed in $\overline{SAP}$ and HR during almitrine infusion. $\overline{PAP}$ also increased from 15.2 ± 3.6 mmHg to 17.1 ± 3.3 mmHg and 20.3 ± 5.4 mmHg, during almitrine and almitrine along with nifedipine infusion, respectively. $\dot{Q}_T$ and $\dot{Q}_{LLL}$ increased from 1322 ± 217 ml/min to 2060 ± 330 ml/min and 305 ± 82 ml/min to 516 ± 124 ml/min during nifedipine infusion. % decrease $\dot{Q}_{LLL}/\dot{Q}_T$ increased from 45.7 ± 16.4% to 51.8 ± 18.1% during infusion of almitrine (3.0 μg/kg/min) but decreased to 32.3 ± 11.9% when nifedipine (3.0 μg/kg/min)

Table 16. Airway pressure, hemodynamics and blood gas analysis during hypoxic challenge before and during administration of almitrine and nifedipine

Variables \ Challenge		before almitrine		during almitrine 3 μg/kg/min		during almitrine (3 μg/kg/min) and nifedipine (3 μg/kg/min)	
		LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2	LLL-O_2	LLL-N_2
AWPpeak	(cmH_2O)	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5	12.6±0.5
$\overline{SAP}$	(mmHg)	116±12	116±12	116±12	116±12	75±9 †††	74±7 †††
HR	(beats/min)	184±17	188±16	187±16	188±14	205±7	201±7
$\overline{LAP}$	(mmHg)	6.1±1.4	6.1±1.4	6.1±1.4	6.1±1.4	5.6±1.3	5.6±1.3
$\overline{PAP}$	(mmHg)	14.2±3.1	15.2±3.6 *	15.2±3.1 †	17.1±3.3 **†	17.8±4.6 †	20.3±5.4 **†
$\dot{Q}_T$	(ml/min)	1136±151	1112±139	1322±217	1326±235	2060±330 ††	2076±246 †††
$\dot{Q}_{LLL}$	(ml/min)	263±58	134±24 *	305±82	137±23 *	516±124 †	345±52 *††
$\dot{Q}_{LLL}/\dot{Q}_T$	(%)	23.0±2.5	12.2±2.7 **	22.8±2.7	10.8±3.3 **†	24.8±2.6	16.6±1.7 **†
% decrease $\dot{Q}_{LLL}/\dot{Q}_T$	(%)		45.7±16.4 **		51.8±18.1 ††		32.3±11.9 † **
pHa		7.47±0.02	7.43±0.02 **	7.48±0.02	7.43±0.02 **†	7.46±0.03	7.42±0.03 ***
Pa_{O_2}	(mmHg)	589.2±21.8	288.9±80.8 *	582.8±39.5	325.0±67.0 *	589.4±36.4	215.4±10.0 *
Pa_{CO_2}	(mmHg)	33.7±1.3	36.8±1.7 **	33.6±0.6	36.4±1.6 **	32.7±0.9	35.5±1.0 **
pHv		7.43±0.06	7.39±0.04 **	7.42±0.03	7.38±0.04 *	7.42±0.04	7.38±0.05
$P\bar{v}_{O_2}$	(mmHg)	52.4±9.3	45.7±9.4 *	51.5±8.5	46.7±8.9 *	59.7±9.1	55.0±11.2
$P\bar{v}_{CO_2}$	(mmHg)	39.0±1.2	41.4±2.4	39.1±1.9	42.8±2.0	38.7±2.9	40.5±2.4

*p<0.05, **p<0.01, ***p<0.001 : significance LLL-O_2 vs LLL-N_2
†p<0.05, ††p<0.01, †††p<0.001 : significance before vs during almitrine administration

Table 17. Changes of LLL end-tidal oxygen pressure before and during administration of almitrine and nifedipine

Pressure \ Period	before almitrine	during almitrine (3 μg/kg/min)	during almitrine (3 μg/kg/min) and nifedipine (3 μg/min/kg)
P_S (mmHg)	65.5 ± 9.7	129.2 ± 11.0***	139.5 ± 11.5***†
P_{10} (mmHg)	46.1 ± 6.3	93.0 ± 9.1***	109.2 ± 13.7***††
P_{25} (mmHg)	35.2 ± 3.5	65.5 ± 5.2***	82.1 ± 8.2***††
P_{50} (mmHg)	25.5 ± 6.9	38.2 ± 6.0**	60.2 ± 3.3***††
P_{75} (mmHg)	20.1 ± 6.4	24.0 ± 6.8*	40.1 ± 6.7***††
P_{max} (mmHg)	15.8 ± 5.7	15.8 ± 5.9	27.8 ± 6.7**†††

* p<0.05, ** p<0.01, *** p<0.001: significance before vs during almitrine infusion.
† p<0.05, †† p<0.01, ††† p<0.001: significance during almitrine vs during nifedipine infusion.

was infused along with almitrine. Arterial oxygen tension also increased from 288.9 ± 80.8 mmHg to 325.0 ± 67.0 mmHg after almitrine but decreased to 215.4 ± 10.0 mmHg when infused simultaneously with nifedipine. Results of the stimulus-response curve showed that LLL blood flow started to decrease at LLL-$P_{ET_{O_2}}$ of 65.5 ± 9.7 mmHg before almitrine but it started to decrease at 129.2 ± 11.0 mmHg during almitrine infusion i.e. the curve shifted to the right. When nifedipine was infused with almitrine the LLL blood flow started to decrease at LLL-$P_{ET_{O_2}}$ of 139.5 ± 11.5 mmHg (Table 17).

DISCUSSION

Almitrine has recently been recognized as a drug which increases arterial oxygen tension in patients with chronic airflow obstruction or respiratory insufficiency. The possible mechanisms for this effect include increase in ventilation due to stimulation of peripheral chemoreceptors[3,26] and improvement of ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch through enhancement of HPV. The effect of almitrine on $\dot{V}_A/\dot{Q}$ was evaluated in patients with chronic airflow obstruction using multiple inert gas method or by ventilation-perfusion scintigram[47]. With respect to effect of almitrine on HPV, however, previous animal studies have been

quite inconsistent. Some reported that almitrine enhanced HPV[48], while others that, the drug either exerted no effect[12] or attenuated it[5,50]. Some investigators performed separate ventilation studies similar to the present study, but they failed to show that almitrine enhanced HPV[20]. In this study, the effects of various doses of almitrine on pulmonary hemodynamics during lobar alveolar hypoxia and role of peripheral chemoreceptors were evaluated.

In this study with open chested dogs, only the left lower lobe was ventilated with anoxic gas mixture. The degree of HPV was expressed as the maximum percentage decrease in ratios of $\dot{Q}_{LLL}$ to $\dot{Q}_T$. Hypoxia was challenged repeatedly five times before administration of almitrine or other drugs because it was found by Benumof et al[6] and in this laboratory by Nakanishi et al[37], that HPV increased by intermittent hypoxic challenges up to the 3rd challenge and became steady thereafter. In this experimental setup, dogs were ventilated with 100% oxygen and hypoxia was challenged by 95% N_2 and 5% CO_2 gas mixture to the LLL. It was also shown that flow diversion was more pronounced when ventilating gas of LLL was changed from 100% O_2 to anoxic gas mixture (95% N_2 ± 5% CO_2). There were apparently no changes in AWP peak, $\overline{SAP}$, HR and $\dot{Q}_T$ during the LLL hypoxic load. $\overline{PAP}$ increased slightly.

Effects of different doses of almitrine infusion on pulmonary hemodynamics

Infusions of different doses of almitrine did not show any variations in airway pressure and heart rate. $\overline{SAP}$ had a tendency to decrease but this effect seems to be not due to almitrine infusion. The same effect was seen in case of almitrine vehicle infusion. $\overline{PAP}$ increased after almitrine before LLL hypoxic challenges dose-dependently. Bee et al[8] also showed in an isolated lung preparation that the increase in pulmonary arterial pressure by almitrine was dose related. Laubi et al[25] showed that intravenous injection of small doses of almitrine was associated with a transient increase in pulmonary arterial pressure in case of normoxia in dogs and ferrets. Romaldini et al[48] have also observed that the rise of pulmonary arterial pressure was associated with an increase of pulmonary vascular resistance. In healthy subjects, Gluskowski et al[19] observed that infusion of almitrine produced a transitory rise in pulmonary arterial pressure. They stated that the increase in $\overline{PAP}$ was due to vasoconstricting effect on pulmonary arterial masculature, as there was no simultaneous change in either cardiac output or pulmonary wedge pressure. Lockhart and Mazmanian[28,29] stated that the pulmonary vasoconstriction induced by almitrine caused a redistribution of blood flow from poorly ventilated zones to better ventilated zones and thereby increased the arterial oxygen tension. The increase in pulmonary vascular resistance during almitrine has been observed in patients with CAO and pulmonary arterial hypertension. In such patients, the effects of almitrine on the pulmonary circulation may be influenced by alveolar hypoxia and structural changes of pulmonary vessels. Paramelle et al[40] reported that a long term follow up of patients taking almitrine for one year showed no change in mean pulmonary artery pressure.

When almitrine was infused, the LLL blood flow diversion increased up to the dose of 3 μg/kg/min. However, during infusion at dose of 5 μg/kg/min or more the LLL blood flow showed a biphasic reaction; first a decrease of flow, then followed by an increase (Fig.6,7). Barer et al[4] demonstrated that almitrine at the dose of 0.5 mg/kg caused vasoconstriction in normoxia and had a dual effect during hypoxic vasoconstriction; there was further constriction followed by dilatation. Hughes et al[20] also found a dual effect of almitrine, they stated that almitrine, generally a pulmonary vasoconstrictor, can dilate vessels when they are constricted by local hypoxia. However in their open chested lobar preparation, almitrine at the dose of 10 μg/kg bolus increased lobar blood flow during lobar hypoxia. In this experiment infusion of almitrine did not increase the LLL blood flow during hypoxic challenges, although a biphasic effect was seen only during infusion of relatively higher doses and not during smaller doses.

In the present study HPV was measured by the change of ratio of LLL blood flow to the total pulmonary blood flow. When almitrine was infused at different doses and hypoxia was challenged to the LLL, as shown in Table 2, 3 μg/kg/min or lower doses of almitrine enhanced HPV but also showed a tendency to be attenuated at 5 μg/kg/min compared to 3 μg/kg/min.

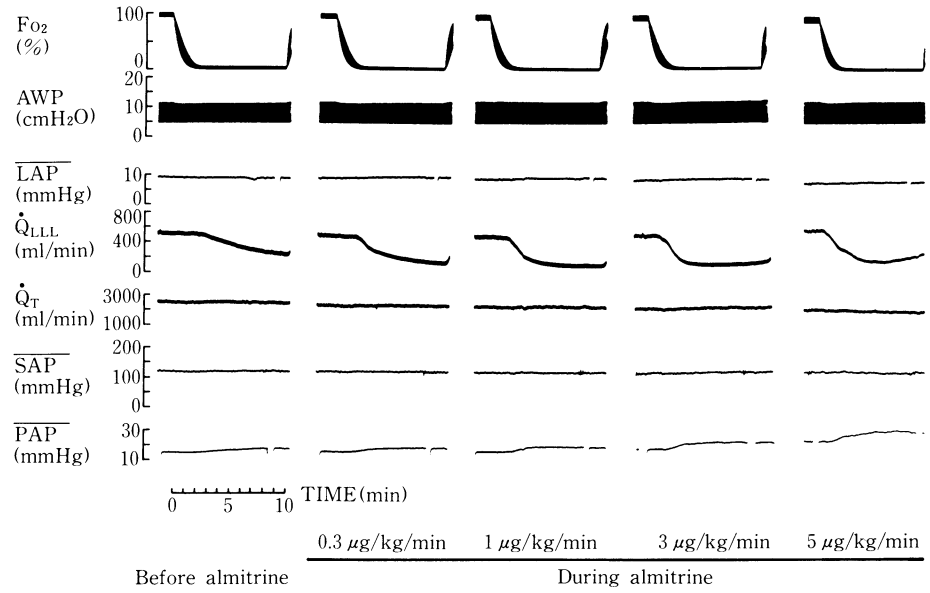

Fig. 6. Sample tracing for responses to hypoxic challenges before and after almitrine administration

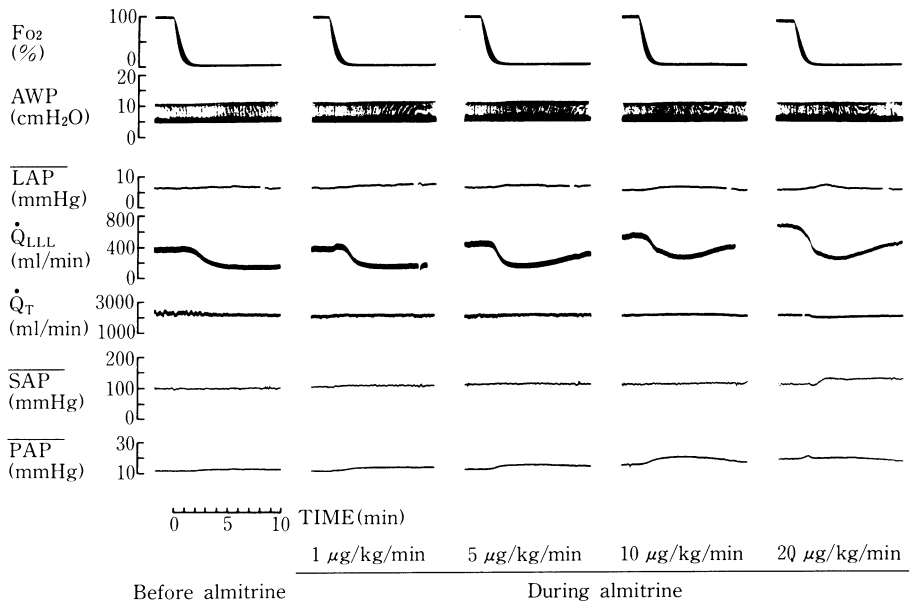

Fig. 7. Example of a typical tracing for responses to hypoxic challenges before and during almitrine infusion

Similar findings were obtained with respect to arterial oxygen tension. Arterial oxygen tensions increased significantly. This indicated the improvement of $\dot{V}_A/\dot{Q}$ mismatch. At doses of 10 or 20 μg/kg/min there were further decrease of HPV with the decrease of arterial oxygen tension. In addition, the stimulus-response curve shifted to the right in a dose dependent fashion (Fig.4, Table 4), suggesting that almitrine also enhanced the reactivity of pulmonary vessels to hypoxia. However, when doses were increased above 3 μg/kg/min, vasoconstriction occurred at an end-tidal oxygen tension more than 100 mmHg, suggesting that vasoconstriction may oc-

cur in non-hypoxic regions. Changes observed in the almitrine group were absent in the vehicle group. These findings seem to indicate that low doses of almitrine enhances vasoconstriction predominantly in hypoxic regions. With higher doses of almitrine also causes vasoconstriction in non-hypoxic regions and impaires HPV, thus the effective HPV would be reduced with the reduction of arterial oxygen tension.

The dual effect of almitrine on HPV as described by Hughes et al and Barer et al[4] might be due to high doses of almitrine administered. Previously 3.3 the lowest dose of almitrine infused for experimental purpose by Romaldini et al[48] and the dose used by Hughes and co-workers was 10 μg/kg as a bolus. The dose used by Wach et al[55] was 0.5 mg/kg and 10 μg/kg/min. So differences in opinions were, may be, due to doses of the drug administered. A dual effect of the drug was also described by Labrid and Laubie[26]. They explained that relatively higher doses of almitrine can increase ventilation but lower dose might enhance pulmonary vasoconstriction. Thus, almitrine appears to have different effects on regional HPV depending on its dosage levels, and seems that this drug must be administered at low doses in order to enhance HPV. Radermecker et al[45] have recently reported a dose-effect study in patients with CAO given a single oral dose of almitrine. At high doses almitrine did not further improve arterial oxygen tension but increased the ventilation.

In considering the effect of varing almitrine doses on the degree of HPV, three factors excluding vasoconstriction induced by almitrine should be considered. First is the influence of $\dot{Q}_T$ on HPV. Smith et al[51] reported that a reduction in cardiac output ($\dot{Q}_T$) was associated with a reduction in intrapulmonary shunt. In the present study $\dot{Q}_T$ was progressively reduced both in the almitrine group and in the vehicle group. It is difficult to believe that enhancement of HPV by almitrine infusion was influenced by the reduction in $\dot{Q}_T$. Secondly, the influence of $\overline{PAP}$ on HPV is to be considered. Benumof et al[6] reported that increased pulmonary vascular pressure blunted HPV. It was confirmed in this experiment that $\overline{PAP}$ was dose-dependently increased by almitrine administration, suggesting that eventually pulmonary vessels in non-hypoxic regions were constricted. It is also possible that the increase in $\overline{PAP}$ with high dose of almitrine administration indirectly attenuates HPV. A third mechanism to be considered is that almitrine has a biphasic action, vasoconstriction followed by vasodilatation. The results of this experiment are not able to explain the mechanism of this biphasic effect of almitrine at higher doses. It could be either due to diverting blood back to the hypoxic region by the vasoconstricting effect on vessels of non-hypoxic region or vasoconstriction followed by vasodilatation in hypoxic region. Chen et al[12] showed in their experiment that although the hypoxic lung showed no further constriction when almitrine was infused, almitrine caused vasoconstriction in the normoxic area and thereby diverting blood back to the hypoxic area and the effectiveness of HPV was diminished by infusion of high dose of almitrine (14.3 μg/kg/min). But in a recent report the same authors in their canine one lung hypoxia model showed that low dose of almitrine enhanced hypoxic pulmonary vasoconstriction. Their results support the findings of this experiment. Here almitrine at a dose of 3 μg/kg/min or less did not show the biphasic effect and at these lower doses it would seem to exert a vascular effect mainly in the hypoxic region.

Mechanism of action of almitrine during alveolar hypoxia: role of peripheral chemoreceptors

The mechanisms of action of almitrine during alveolar hypoxia are not well established as the mechanism involved in the phenomenon of HPV itself. Lockhart and Mazmanian[28,29] observed that the pulmonary pressor effect of almitrine is greater in lungs of dogs in situ during alveolar hypoxia than normoxia, but not in isolated lungs of ferrets and rats in vitro. However they proposed that the mechanism whereby this substance acts upon the pulmonary circulation is not a direct effect on the pulmonary vasculature. On the basis of these reports Romaldini et al[48] and M'elot et al[34] suggested that the vasoconstrictor effect of almitrine in intact dog could be mediated via the peripheral chemoreceptors and stimulation of sympathetic nervous system. In fact, stimulation of peripheral chemoreceptors induces pulmonary vasoconstriction via the sympathetic nervous system. However, constriction caused by this mechanism is limited to large pul-

monary arteries, while HPV is generally thought to occur in small mascular pulmonary arteries[17]. Furthermore, Levitzky et al[27] reported that the peripheral chemoreceptor stimulation by systemic hypoxemia attenuated HPV. It is, therefore, to be considered less likely that stimulation of peripheral chemoreceptors would result in the enhancement of HPV. In the present study the vagi were sectioned at the midcervical level and carotid bodies were denervated before administration of almitrine. The results were the same as dogs without vagotomy and carotid body denervation: that is HPV was enhanced by lower doses of almitrine and attenuated by higher doses. The stimulus-response curve also shifted toward the right, dose dependently before and after peripheral chemoreceptors denervation. Therefore, it could be said that, increased reactivity of pulmonary vessels to alveolar hypoxia induced by almitrine may be attributable to the direct effect of the drug on pulmonary vessels rather than being mediated by stimulation of peripheral chemoreceptors.

Effect of chemoreceptor stimulation by doxapram:

Furthermore, doxapram, a chemoreceptor stimulant drug failed to enhance or attenuate HPV. This drug also failed to shift the stimulus-response curve. Doxapram stimulates central and peripheral chemoreceptors and increase ventilation[35,38], probably it does not affect the pulmonary vascular reactivity to alveolar hypoxia. Although both doxapram and almitrine stimulate the peripheral chemoreceptors, doxapram did not change the reactivity of pulmonary vessels to alveolar hypoxia whereas almitrine enhanced the HPV and changed the reactivity of pulmonary vessels to alveolar hypoxia probably by acting directly on pulmonary blood vessels.

Role of almitrine on prostacyclin synthesis:

Grygleswski[18] described almitrine as a potent releaser of prostacyclin. Later on Korbut et al[22] concluded that almitrine stimulates peripheral chemoreceptors to release PGI_2. However, there are evidences that prostacyclin is a pulmonary vasodilator and decreases the hypoxic pressor response. In this study during infusion of larger doses of almitrine, HPV was attenuated. Therefore, the release of this vasodilator PGI_2 was not unlikely. But measurement of 6-keto-$PGF_{1\alpha}$ which is the stable metabolite of PGI_2 showed no significant changes after infusion of different doses of almitrine. This result supports the findings of Bult et al[9]. They observed that although almitrine increased the respiratory movement, it did not stimulate prostacyclin biosynthesis in rabbits in vivo or did not interfere with it. Differences in observations may be due to different species studied but at least for dogs in this experiment, infusion of almitrine failed to increase the PGI_2 synthesis. Attenuation of HPV after larger doses of almitrine might not be due to vasodilator effect of increased circulating PGI_2 level.

Effect of Ca^{++} blocking agent during almitrine infusion

McMurty et al concluded that alveolar hypoxia act directly on smooth muscle of small arteries and it lead to membrane depolarization and calcium influx and contraction[32,33]. However, it seems that the hypoxic pressor response is Ca^{++} dependent. In various studies it has been shown that inhibition of Ca^{++} influx inhibits hypoxic vasoconstriction and facilitation of Ca^{++} influx augment hypoxic vasoconstriction[54]. In this study it was thought that Ca^{++} influx may ply a role of the pulmonary vascular reactivity to alveolar hypoxia during almitrine administration. Nifedipine was infused to block the Ca^{++} influx during almitrine infusion. Nifedipine decreased index of HPV but failed to prevent the shift of the stimulus-response curve to right. Bee et al[8] reported that the initial vasoconstrictor effect of almitrine could be blocked by pretreatment with a calcium channel blocker, verapamil in isolated rat lungs. Similar results were obtained by Hughes et al[20]. They stated that under normoxic conditions, it proved impossible to abolish almitrine induced vasoconstriction, though the effect could be blunted by verapamil. In the present study nifedipine reduced the HPV during almitrine infusion but the shift of the stimulus-response curve which indicates the increased reactivity of pulmonary vessels to hypoxia was not influenced by blocking the voltage dependent Ca^{++} influx.

In patients with chronic airflow obstruction, it is suggested that almitrine increases arterial oxygen tension by diverting the blood flow from hypoxic area of low $\dot{V}_A/\dot{Q}$ to normoxic areas of normal or high $\dot{V}_A/\dot{Q}$ and thought to be due to

enhancement of hypoxic pulmonary vasoconstriction. Labrid[23] hypothetized that almitrine exerts a global vasoconstrictive effect but this effect becomes "operational" only in hypoventilated zones which have already undergone a weak hypoxic vasoconstriction. But evidence from some animal studies could not agree with this view. Hughes et al[20] suggested that in areas of the lung where vascular tone is near maximal because of alveolar hypoxia, almitrine may cause vasodilatation and a worsenig of atrerial oxygen tension. The differences in opinion may be due to doses of almitrine used during experiments. The results of this study could be explained as follows: only low doses of almitrine constrict the vessels of hypoventilated zones of lungs and enhance the effective HPV causing redistribution of blood flow. Relatively larger doses of almitrine constricts both hypoxic and normoxic areas and effective HPV may be impaired. Vasoconstriction was greater in hypoxic lobe during infusion of relatively low dose of almitrine with increase in arterial oxygen tension indicating improvement of ventilation to perfusion ratio, furthermore this study also revealed the level of alveolar oxygen tension at which almitrine constricts the pulmonary vessels. It was interesting that the reactivity of pulmonary blood vessels to hypoxia was dose related. Although the mechanism is not yet established it could be said that at least peripheral chemoreceptors and vasodilating PGI_2 are not involved to mediate or modulate it, but the role of other prostaglandins could not be ruled out. As regards Ca^{++} kinetics, only one type of blocker was used which blocks the voltage dependent calcium channel in vascular smooth muscles, and it could not prevent the almitrine induced changes in reactivity of pulmonary vessels to hypoxia. Therefore, other pathways of calcium kinetics should be investigated.

Thus from the findings of this study it could be concluded that, almitrine increases the reactivity of the pulmonary vessels to hypoxia dose-dependently and low doses of almitrine enhances hypoxic pulmonary vasoconstriction, however, higher doses attenuate it. Peripheral chemoreceptor denervation could not affect the action of almitrine. Another peripheral chemoreceptor stimulant (doxapram) did not enhance or attenuate HPV. Therefore vasoconstriction induced by almitrine may be attributed to the direct effect on pulmonary vessels rather than to a nervous mechanism mediated via peripheral chemoreceptors.

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