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Increased Pulmonary Vascular Pressor Response to Hypoxia in Highland Dogs (39615)

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Several low altitude laboratories have reported much smaller increases in pulmonary vascular resistance induced by acute hypoxia in dogs (1-3) than those which we have observed at 1600-m altitude (4). We wished to determine if this poor hypoxic response in lowland dogs was due to differences in technique, or due to a real physiologic difference. The mechanism by which alveolar hypoxia causes pulmonary arterial vasoconstriction remains unknown. If lowland and highland dogs differ in their response to hypoxia, further studies of these two groups might shed light on this mechanism. Therefore, we studied the pulmonary pressor response to hypoxia in lowland and highland dogs under identical climatic and laboratory conditions.

Methods and materials. Fourteen mongrel dogs of either sex (mean weight 19 ± 1 kg) were flown to Denver, Colorado (1600 m), from sea level laboratories in New Orleans, Louisiana (n = 8), and Madison, Wisconsin (n = 6) (lowland dogs). Ten dogs were studied the day after arrival, while the remaining four dogs were studied 4 (n = 2) or 7 (n = 2) days later. At autopsy, three of the dogs from New Orleans were found to have numerous heart worms (*Dirofilaria immitus*) in the right ventricle and main pulmonary artery. Consequently, these dogs were excluded from the comparison made with 11 "highland" mongrel dogs (mean weight 21 ± 1 kg) obtained in Denver. We assumed that the dogs were residents of the altitude from which they were obtained.

All of the dogs were studied using the same procedures. They were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and intubated with a cuffed endotracheal tube. Additional small doses of anesthetic were administered when needed. Polyethylene catheters (PE-160) were placed in the main pulmonary artery via the jugular vein, and in the abdominal aorta via the femoral artery. A Swan-Ganz balloon-tipped catheter was passed into a peripheral pulmonary artery in order to determine pulmonary wedge pressure.

Pulmonary arterial, pulmonary wedge, and aortic pressures were transduced with strain gauges (Statham P23 Db) calibrated with a mercury manometer and zeroed at right atrial level. Cardiac output was determined by injection of known amounts of indocyanine green dye (Cardio-Green) into the superior vena cava and sampling of arterial blood with a cuvette densitometer (XP-302, Waters Co.). The electrical outputs of the pressure transducers, densitometer, and an electrocardiograph were processed through amplifiers and a NOVA 1200 digital computer (Data General Corp.) and displayed on an oscilloscope. Cardiac output was calculated by the computer using a semilogarithmic replot of the displayed dye curve. Mean blood pressures, heart rate, cardiac output, stroke volume, and pulmonary vascular resistance (mean pulmonary arterial − wedge pressure/cardiac output) were computed on-line and recorded.

Each animal breathed 30% O_2 in N_2 spontaneously during the control period, in which pressures, cardiac output, and arterial blood gas tensions were measured. During hypoxia (10% O_2 in N_2) esophageal temperature (Yellow Springs thermistor probe) was maintained above 38° by warming and humidifying the inspired gas mixtures. End-tidal CO_2 was monitored with a Beckman infra red gas analyzer (Model LB-1) and maintained at the normoxic level by manual addition of 100% CO_2 to the inspired gas. Inspiratory and end-tidal O_2 levels were measured with an oxygen fuel cell. Arterial

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blood gas tensions and pH were measured with a Radiometer blood gas analyzer (Model 27) at 38° and corrected to the animals' deep body temperature.

The hypoxic challenge was maintained for 20 min. Vascular pressures were measured every min, cardiac output at 5, 10, 15, and 20 min, and arterial blood gases at 10 and 20 min of hypoxia. Twenty minutes after the end of the hypoxic exposure, the pulmonary arterial pressor response to an intravenous bolus of prostaglandin $F_{2\alpha}$ was recorded. This response was observed in order to determine if any difference between the groups was purely associated with hypoxic vasoconstriction, or whether it also involved other constrictor stimuli. A dose of 5 μg/kg was chosen because we have found, in other experiments, that this is the lowest dose which will provoke a maximum increase in pulmonary arterial pressure.

Seven of the lowland dogs were allowed to recover from anesthesia and were restudied, in exactly the same manner, between 3 and 4 weeks after the initial experiment. These experiments were conducted to identify any changes in response induced by residence at 1600 m. In addition to the dogs from Denver and sea level, three dogs from Breckenridge, Colorado (approximate altitude 2700 m), were also studied.

The data are given in the text and tables as the mean and 1 SE. The differences between lowland and highland dogs, in terms of their control values and responses to hypoxia, were analyzed with the two population t test. Changes occurring in the lowland dogs that were restudied were examined using the paired Student's t test. Significant differences were considered to exist when $P < 0.05$.

Results. There were no significant differences between the lowland and highland dogs in the hemodynamic variables measured during normoxic conditions. However, the increases in pulmonary arterial pressure and pulmonary vascular resistance induced by hypoxia were greater in the highland dogs (Table I, Fig. 1). The percentage increase in pulmonary vascular resistance was also greater in the highland dogs (+135% ± 17) than in the lowland dogs (+65% ± 7). The severity of the hypoxic challenges was the same as evidenced by the similar blood gas tensions during hypoxia (Table II). Cardiac output and systemic arterial pressure increased during hypoxia in both groups. In the lowland dogs there was a significant fall in systemic arterial resist-

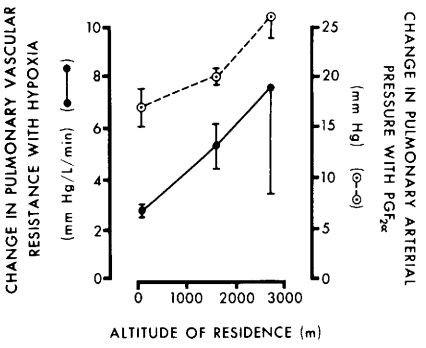

FIG. 1. Change in pulmonary vascular resistance during hypoxia (closed circles and unbroken line) and in pulmonary arterial pressure with prostaglandin $F_{2\alpha}$ (a bolus of 5 μg/kg, open circles and broken line) in dogs native to sea level (n = 11), Denver (1600 m) altitude (n = 11), and 2700 m (n = 3).

TABLE I. NORMOXIC HEMODYNAMICS IN LOWLAND AND HIGHLAND DOGS AND CHANGES WITH ACUTE HYPOXIA.[a]

	Normoxic control		Change with hypoxia	
	Low	High	Low	High
Pulmonary arterial pressure (mm Hg)	16 ± 1	17 ± 1	+12 ± 1	+17 ± 1*
Pulmonary vascular resistance (mm Hg/liter/min)	4.5 ± 0.3	4.0 ± 0.4	+2.8 ± 0.2	+5.3 ± 0.9*
Cardiac output (liter/min)	2.7 ± 0.2	3.3 ± 0.3	+0.7 ± 0.1	+0.2 ± 0.2
Systemic arterial pressure (mm Hg)	134 ± 3	136 ± 6	+13 ± 2	+9 ± 3
Total systemic resistance (mm Hg/liter/min)	51 ± 3	44 ± 4	−6 ± 2	0 ± 2*

[a] Low, lowland dogs (n = 11); high, highland dogs (n = 11). * Difference in hypoxic response between lowland and highland dogs is significant at $P < 0.05$ level.

TABLE II. ARTERIAL BLOOD GAS TENSIONS DURING NORMOXIA AND HYPOXIA IN LOWLAND AND HIGHLAND DOGS.

	Normoxia		Hypoxia	
	Low	High	Low	High
Systemic arterial pH	7.32 ± 0.01	7.32 ± 0.01	7.36 ± 0.01	7.36 ± 0.01
Systemic arterial oxygen tension (mm Hg)	97 ± 2	99 ± 2	38 ± 1	39 ± 1
Systemic arterial carbon dioxide tension (mm Hg)	41 ± 1	41 ± 1	39 ± 1	39 ± 1

TABLE III. NORMIC HEMODYNAMICS IN LOWLAND DOGS AND CHANGES WITH ACUTE HYPOXIA AFTER RESIDENCE AT 1,600 m.

	Normoxic control		Change during hypoxia	
	First study[a]	Second study[b]	First study	Second study
Pulmonary arterial pressure (mm Hg)	16 ± 1	16 ± 1	+12 ± 1	+12 ± 1
Pulmonary vascular resistance (mm Hg/liter/min)	4.7 ± 0.4	4.2 ± 0.8	+2.7 ± 0.3	+2.9 ± 0.6
Cardiac output (liter/min)	2.7 ± 0.2	3.2 ± 0.4	+0.8 ± 0.2	+0.5 ± 0.1

[a] Study on arrival at 1600 m from sea level; $n = 7$.
[b] Study 3-4 weeks later; $n = 7$.

ance in comparison to the highland dogs.

The increase in pulmonary arterial pressure induced by prostaglandin $F_{2\alpha}$ was not significantly different in the two groups. The increase was +17 ± 2 mm Hg in the lowland dogs, and +20 ± 1 mm Hg in the highland dogs (Fig. 1). The pulmonary arterial pressures prior to prostaglandin $F_{2\alpha}$ administration were 15 ± 1 and 16 ± 1 mm Hg, respectively.

Seven lowland dogs were restudied 3 to 4 weeks after the initial experiment. Their pulmonary arterial pressures and resistances during normoxia, and the changes with hypoxia were not different from the values obtained during the first study (Table III). Similarly, the change in pulmonary arterial pressure induced by prostaglandin $F_{2\alpha}$ was unaltered (15 ± 1 to 33 ± 2 mm Hg during the first study, and 15 ± 2 to 33 ± 3 mm Hg during the second study).

The three dogs from 2700 m also exhibited greater pulmonary vascular reactivity (Fig. 1). During hypoxia the mean increase in pulmonary vascular resistance was +7.6 ± 4.2 mm Hg/liter/min (+139% ± 39). While this increase is somewhat greater than the increase observed in the Denver dogs, the percentage change in resistance was not different. The increase in pulmonary arterial pressure stimulated by prostaglandin $F_{2\alpha}$ was +26 ± 2 mm Hg (from 15 ± 1 to 41 ± 3 mm Hg), which also tended to be greater than the response observed in the Denver dogs (+20 ± 1 mm Hg).

Heart worm infestation ($n = 3$) increased both the normoxic pulmonary arterial pressure (21 ± 3 mm Hg) and pulmonary vascular resistance (6.4 ± 1.4 mm Hg/liter/min). The absolute increases during hypoxia (+12 ± 1 mm Hg, and +2.5 ± 1.3 mm Hg/liter/min) were similar to those for the remainder of the lowland group; however, the responses expressed as percentage change were smaller.

Discussion. This study demonstrates that both in terms of pulmonary arterial pressure and calculated resistance the highland dogs had greater responses to hypoxia than lowland dogs, suggesting that chronic low-grade hypoxia may alter hypoxic reactivity. The greater response of the highland dogs to hypoxia is in contrast to our experience in rats (5) and cattle (6). Lungs isolated from rats which had been exposed at 4270 m for 5 weeks showed less pulmonary hypertension in response to acute alveolar hypoxia than those from control rats maintained at 1600 m. Hypoxic pulmonary hypertension, with associated right heart failure (brisket disease) is less common in cattle native to altitudes above 2133 m than in lowland cattle

taken to high altitude. We have shown that the characteristic to susceptibility or resistance to hypoxic vasoconstriction is inherited (7). This is true of the acute or chronic response to hypoxia (8). It is thought that natural selection through a number of generations may have rendered the highland cattle more resistant to the pulmonary vascular effects of hypoxia (9). Dogs do not develop chronic pulmonary hypertension at high altitude (10), and increased responsiveness of the pulmonary vascular bed would not therefore be a detrimental factor in natural selection. Whatever the change may be, increased vascular reactivity appears to be either acquired over a long period of time (certainly in excess of 4 weeks), or else inherited.

The pressor response to prostaglandin $F_{2\alpha}$ tended to be greater in the dogs from 1600 m than in those from sea level, and was even greater in dogs from 2700 m than in those from the two lower altitudes. This suggests an increasing responsiveness to prostaglandin $F_{2\alpha}$ with increasing altitude of residence. The observation is consistent with the greater responsiveness to prostaglandin $F_{2\alpha}$ in lungs from high vs low altitude rats (5).

It is evident from this study that the altitude from which dogs are obtained is yet another variable which should be considered when hemodynamic results from various laboratories are compared. Perhaps the different pulmonary vascular pressor responses seen in the highland and lowland dogs will provide a stimulus and a model for the study of the mechanism of hypoxic pulmonary vasoconstriction.

Summary. Greater pulmonary vascular resistance increases in response to acute hypoxia have been observed in the anesthetized dog at 1600-m altitude than in dogs studied at sea level. Consequently, the hemodynamic response to hypoxia was studied in 11 "lowland" dogs flown to Denver and compared to the response of 11 dogs obtained locally. The local "highland" dogs had mean increases in pulmonary arterial pressure and pulmonary vascular resistance during hypoxia of +17 ± 1 mm Hg and +5.3 ± 0.9 mm Hg/liter/min, respectively, in contrast to the increases of +12 ± 1 mm Hg and +2.8 ± 0.2 mm Hg/liter/min observed in the lowland dogs. The increase in pulmonary arterial pressure induced by prostaglandin $F_{2\alpha}$ was not significantly different in the two groups. The pulmonary pressor response to hypoxia in seven lowland dogs restudied after 3- to 4-weeks residence at 1600 m was not altered. The difference in responsiveness of the pulmonary vascular bed to hypoxia in the two groups suggests that chronic low-grade hypoxia may alter hypoxic reactivity, and that the resident altitude should be considered when comparing data from various laboratories.

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