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Cardiac Output Is Decreased and Hypoxic Vasoconstriction Is Intact in Chronically Hypoxic Sheep[1] (40924)

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Abstract. Previous studies have shown that although sheep have a pulmonary pressor response to acute hypoxia, they fail to develop pulmonary hypertension during chronic exposure to high altitude. We wondered if this failure was due to decreased cardiac output or to blunted hypoxic pulmonary vasoconstriction. After 12 days at a simulated altitude of 4573 m, six sheep developed mild pulmonary hypertension with increased pulmonary arterial pressure (17 ± 1 before to 25 ± 2 mm Hg after), decreased cardiac output (6.0 ± 0.4 before to 5.1 ± 0.6 liters/min after), and increased pulmonary vascular resistance (1.6 ± 0.2 before to 3.4 ± 0.5 mm Hg/liter/min after). The pulmonary vasoconstrictor response to acute hypoxia was studied before and after 12 days of exposure to 4573 m by exposing the sheep to increasing altitudes in a dose–response manner. During acute hypoxia, pulmonary arterial pressures were the same before and after chronic hypoxia, but cardiac outputs were decreased after chronic high altitude exposure. Thus, after 12 days at 4573 m, pulmonary vascular resistances were higher at each of four levels of acute hypoxia, although the magnitude of the resistance increase in going from 1524 to 4573 m was not changed (Δ = 1.0 ± 0.3 before and 1.2 ± 0.3 mm Hg/liter/min after). We conclude that pulmonary vasoconstrictor responses to acute hypoxia were not blunted after 12 days of exposure to high altitude. Decreased cardiac output may be an important factor in the adaptation of the pulmonary circulation of sheep to chronic hypoxia.

Acute airway hypoxia causes pulmonary arterial constriction and chronic hypoxia results in pulmonary hypertension (1). However, there is variation among species and individuals in the severity of pulmonary hypertension after chronic hypoxia, suggesting that the pulmonary circulation of some organisms adapts to chronic hypoxia (1). Knowledge of the mechanism of this adaptation may aid in the prevention and treatment of pulmonary hypertension in chronically hypoxic humans with lung disease.

Sheep have a moderate pulmonary pressor response to acute hypoxia (2–4), but do not develop pulmonary hypertension during exposure to high altitude (2, 5). One possible mechanism for this adaptation to chronic hypoxia is decreased cardiac output, as described in men living at high altitude (6). Another possibility is that pulmonary vascular reactivity could be reduced by chronic hypoxia. For example, McMurtry *et al.* (7) found that lungs isolated from rats exposed to high altitude for 4 to 6 weeks had blunted pulmonary vasoconstriction to acute hypoxia, while vasoconstriction in response to other agents was enhanced. The aim of the present study was to determine whether sheep had a decrease in cardiac output and/or pulmonary vascular reactivity to acute hypoxia after 12 days at high altitude.

Materials and methods. Six castrated, mixed breed, male sheep between 5 and 10 months of age and weighing from 35 to 51 kg were obtained locally. Both carotid arteries were exteriorized during halothane anesthesia several weeks before the study. On the day of study, under local anesthesia, an 18-gauge Long-dwell catheter (Becton, Dickinson, Raritan, N.J.) was placed per-

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cutaneously in a carotid artery. A polyethylene catheter (PE-160, Clay-Adams, Parsippany, N.J.) was placed in the superior vena cava through percutaneous puncture of an external jugular vein by a 14-gauge catheter (Jelco Laboratories, Raritan, N.J.). A Swan-Ganz catheter (Edwards Laboratory, Santa Ana, Calif.) was placed in a pulmonary artery through an external jugular vein, using a percutaneous introducer (Bard, Billerica, Mass.).

The animals were awake and resting upright in a sling throughout each study. Heart rate was obtained from the surface electrocardiogram. Mean systemic arterial, pulmonary arterial, and pulmonary capillary wedge pressures were measured using Statham transducers (Oxnard, Calif.). Heart rate and systemic arterial and pulmonary arterial pressures were monitored continuously. Cardiac output was determined by the indocyanine green dye (Cardio-Green, Hynson, Westcott, and Dunning, Baltimore, Md.) dilution method (8). Arterial blood gases were measured with Radiometer microelectrodes (Model 27, Copenhagen).

The experimental design is summarized in Fig. 1. We found that the hemodynamic variables were not affected by the direction of change in altitude. Therefore, the sheep were subjected to increasing altitudes in a dose–response manner both before and after chronic high altitude exposure.

Baseline measurements of blood pressures, cardiac output, heart rate, and arterial blood gases were made at the laboratory altitude of 1524 m (P_B 630 mm Hg, P_IO_2 122 mm Hg). The animals were then exposed in a hypobaric chamber to simulated altitudes of 3049 m (P_B 523 mm Hg, P_IO_2 100 mm Hg), 3658 m (P_B 483 mm Hg, P_IO_2 92 mm Hg), and 4573 m (P_B 430 mm Hg, P_IO_2 80 mm Hg). The above measurements were repeated after at least 10 min at each altitude when blood pressures and heart rate had stabilized.

After completion of the study, the catheters were removed, and the sheep were given an intramuscular injection of 1.2 M units of benzathine penicillin and procaine penicillin G (Bicillin Fortified, Wyeth, Philadelphia, Penn.). The entire procedure lasted about 3 hr. The sheep were then placed in another hypobaric chamber and kept at a simulated altitude of 4573 m for 12 days. They were given feed and water *ad libitum* during this time. This duration of chronic hypoxic exposure was chosen because Reeves *et al.* (2) found that sheep failed to develop pulmonary hypertension after 2 weeks at high altitude. Thus, any adaptive mechanism should be apparent after about 2 weeks of hypoxia.

At the end of the 12-day exposure to 4573 m, the sheep were kept at that simulated high altitude and catheterized as described above. Hemodynamic measurements were made at 4573 m before the animals were returned to 1524 m. The sheep were then studied at 1524, 3049, 3658, and 4573 m, as described above.

The care and use of the sheep followed the University of Colorado Medical Center guidelines for use of animals in research.

The data are expressed as means ± SE.

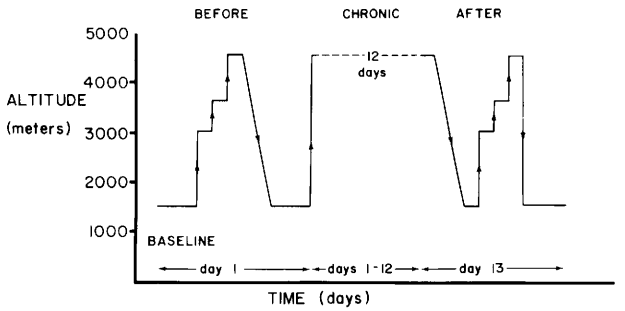

FIG. 1. The experimental design is shown. Arterial blood gas and hemodynamic variables were measured at 1524, 3049, 3658, and 4573 m, in the order shown, before and after 12 days of exposure to 4573 m. The arrows indicate the direction of change in altitude.

The data collected at 1524 m before altitude exposure were compared with data collected at 4573 m after 12 days of high altitude exposure using the paired Student's *t* test. Changes with acute high altitude exposures were analyzed using two-way analyses of variance and the Student–Newman–Keuls multiple comparison test (9). Data collected at a given altitude were analyzed for differences between the studies before and after chronic high altitude exposure using the paired Student's *t* test. Differences were considered significant at $P < 0.05$.

Results. Effect of 12 days of exposure to 4573 m. The initial measurements at 1524 m were compared to measurements after 12 days at 4573 m, before re-exposure to low altitude. Chronic hypoxia decreased arterial partial pressure of O_2 (P_aO_2) from 71 ± 2 to 44 ± 2 mm Hg ($P < 0.05$). Hematocrit increased from 32 ± 1 at 1524 m to 39 ± 1% after 12 days at 4573 m ($P < 0.05$). Mean pulmonary arterial pressure increased from 17 ± 1 mm Hg at 1524 m to 25 ± 2 mm Hg ($P < 0.05$) after 12 days at high altitude, cardiac output decreased from 6.0 ± 0.4 to 5.1 ± 0.6 liters/min ($P < 0.05$), pulmonary vascular resistance increased from 1.6 ± 0.2 to 3.4 ± 0.5 mm Hg/liters/min ($P < 0.05$), and stroke volume decreased from 74 ± 4 to 54 ± 4 ml/beat ($P < 0.05$). Total systemic resistance, heart rate, mean systemic pressure, and mean pulmonary capillary wedge pressure were not significantly changed after chronic high altitude exposure.

Response to acute hypoxia. Acute exposure to increasing altitudes caused progressive arterial hypoxemia (Table I). Arterial oxygen tension tended to be higher at a given altitude after than before chronic high altitude exposure, while pH and P_aCO_2 tended to be lower after chronic exposure (Table I), indicating slightly increased ventilation after chronic hypoxia and renal compensation for chronic hypocapnia.

Cardiac output at each altitude was lower after than before chronic high altitude exposure (Fig. 2) due to decreases in stroke volume (Table I).

Acute exposure to increasing altitudes in a dose–response manner caused progres-

TABLE I. ARTERIAL BLOOD GAS AND HEMODYNAMIC VARIABLES IN SHEEP AT DIFFERENT ALTITUDES BEFORE AND AFTER 12 DAYS AT 4573 m

Altitude (m)		P_aO_2 (mm Hg)	P_aCO_2 (mm Hg)	pH	Stroke volume (ml/beat)	Total systemic vascular resistance (mm Hg/liters/min)	Heart rate (beats/min)	Mean systemic arterial pressure (mm Hg)	Mean pulmonary capillary wedge pressure (mm Hg)
1524	B	71 ± 2	39 ± 1[a]	7.45 ± 0.01	74 ± 4[a]	17.3 ± 0.6[a]	81 ± 8	101 ± 5	9 ± 2
	A	74 ± 2	35 ± 1	7.43 ± 0.01	60 ± 5	23.4 ± 2.4	77 ± 4	103 ± 5	9 ± 1
3049	B	54 ± 1[a]	39 ± 1[a]	7.46 ± 0.01[a]	76 ± 6	16.4 ± 1.1[a]	87 ± 3	105 ± 4	8 ± 1
	A	57 ± 1	36 ± 1	7.43 ± 0.01	60 ± 5	21.7 ± 2.5	85 ± 4	104 ± 2	8 ± 1
3658	B	47 ± 1	38 ± 1	7.47 ± 0.01[a]	69 ± 6	17.8 ± 0.7[a]	89 ± 8	105 ± 6	9 ± 1
	A	49 ± 1	37 ± 1	7.43 ± 0.01	56 ± 3	22.3 ± 1.9	88 ± 5	106 ± 2	8 ± 1
4573	B	40 ± 1	36 ± 1	7.47 ± 0.01[a]	65 ± 5[a]	17.4 ± 1.2[a]	101 ± 11	108 ± 5	9 ± 1
	A	40 ± 1	36 ± 1	7.45 ± 0.01	52 ± 1	23.3 ± 2.7	95 ± 6	108 ± 2	9 ± 1

Note. Data are means ± SE, $n = 6$. B is before and A is after 12 days at 4573 m.
[a] Difference between B and A means at $P < 0.05$.

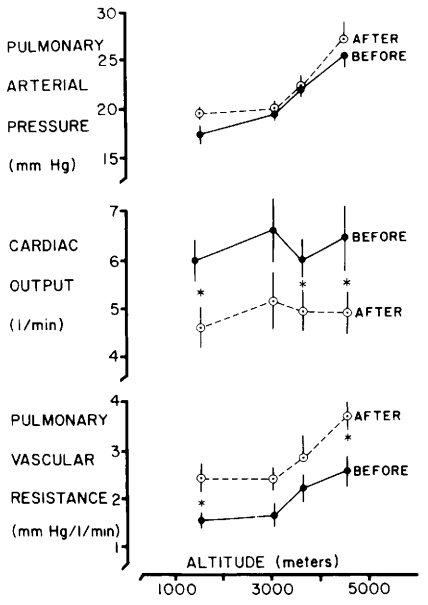

FIG. 2. Responses to acute hypoxia are presented as mean pulmonary arterial pressure, cardiac output, and pulmonary vascular resistance at 4 altitudes before (●) and after (⊙) 12 days at 4573 m. Data are expressed as means ± SE; $n = 6$ sheep. The asterisks (*) indicate significant differences between before and after means at $P < 0.05$, using the paired Student's t test.

sive increases in mean pulmonary arterial pressure and pulmonary vascular resistance, such that the values at 4573 m were significantly different from values at 1524 and 3049 m (Fig. 2, $P < 0.05$). Mean pulmonary arterial pressures were the same at each altitude before and after 12 days at 4573 m (Fig. 2). Pulmonary vascular resistances were higher at a given altitude after than before chronic high altitude exposure (Fig. 2). However, the absolute and percentage increases in pulmonary vascular resistance in going from 1524 to 4573 m were not different before and after 12 days at 4573 m (1.0 ± 0.3 before and 1.2 ± 0.3 mm Hg/liters/min after and 70 ± 22% before and 59 ± 17% after; P = NS). The threshold at which pulmonary vascular resistance increased was also unchanged after chronic high altitude exposure, remaining between 3049 and 3658 m (Fig. 2).

Total systemic vascular resistance was higher at each altitude after than before 12 days at 4573 m (Table I). Heart rates and mean systemic arterial and pulmonary capillary wedge pressures were similar before and after chronic high altitude exposure (Table I).

Discussion. We have found that sheep develop and maintain mild pulmonary hypertension during 12 days at high altitude, with values for pulmonary arterial pressure similar to those reported in previous studies of chronically hypoxic sheep (2, 5). Like men and goats at high altitude (6, 10), the chronically hypoxic sheep in this study had decreased cardiac output and stroke volume. Other investigators have noted that acute relief of hypoxia by O_2 administration at high altitude did not reverse depressed myocardial function due to chronic hypoxia, suggesting that the decreased cardiac output is not due to a simple, direct effect of lowered P_aO_2 on the heart (6, 10). The present study showed that cardiac output remained depressed immediately after return to low altitude, suggesting that hypobaria alone was not the cause of the decrease. Hypocapnic alkalosis can cause decreased cardiac output after chronic hypoxia (11), but arterial pH was the same or lower in the sheep after chronic high altitude exposure. Reduced ventricular filling pressure probably did not account for the decreased cardiac output since pulmonary capillary wedge pressures were unchanged after chronic hypoxia. Increased hematocrit could contribute to the decreased cardiac output (12), although the magnitude of the rise in hematocrit was small in these sheep. Other factors which have been reported to decrease cardiac output during chronic hypoxia are reduced myocardial contractility (10) and attenuated cardiac responsiveness to adrenergic stimulation (13).

It is difficult to assess changes in vascular reactivity in the face of decreased cardiac output. However, it appears that acute hypoxic vasoconstriction was intact after 12 days at 4573 m. Mean pulmonary arterial pressure and vascular resistance increased between 1524 and 4573 m both before and after chronic exposure to simulated high altitude. The magnitudes of the increases were similar to those reported in acutely

hypoxic sheep by other investigators (2–4). Pulmonary vascular resistances were higher after chronic high altitude exposure, but there were no changes in the relative magnitude of resistance increases between 1524 and 4573 m. Thus, the blunting of acute hypoxic vasoconstriction found in lungs isolated from chronically hypoxic rats (7) was not seen in intact sheep. Species differences may account for this, or it may be that isolation of lungs from rats somehow caused or exposed the blunted hypoxic vasoconstriction response.

From these studies it seems that sheep have a modest increase in pulmonary arterial pressure and resistance with acute hypoxia and hypoxic vasoconstriction remains intact after 12 days of high altitude exposure. However, the decrease in cardiac output may minimize the pulmonary hypertension observed at high altitude and may account for the reputation that the sheep has attained as a "hyporeactor" to chronic hypoxia.

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