

Cardiopulmonary Hemodynamics of Blue-Sheep, *Pseudois nayaur*, as High-Altitude Adapted Mammals

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Abstract: The blue-sheep, pika, and yak live in the Tibetan highlands at an altitude of 6,100 m and are typical mammals adapted to high-altitudes. These animals have a long history of habitation at high-altitudes and are considered to be “animals completely adapted to high-altitudes” because of their physiological and morphological traits that are well adapted to high-altitude environments. To evaluate the physiological characteristics of high-altitude adaptation in the blue-sheep, changes in the pulmonary hemodynamics during exposure to simulated-altitudes at 0, 2,300, and 4,500 m were examined by means of a climatic chamber in Qinghai Province, China (altitude 2,300 m). Seven blue-sheep inhabiting the mountains (3,000 m) of Qinghai Province, China, were compared with 5 pigs raised in the same area as controls. The primary items of measurement were the body weight (BW), systemic arterial pressure (*P*_{sa}), pulmonary artery pressure (*P*_{pa}), hematocrit (Ht), left ventricular

weight (LVW), right ventricular weight (RVW), and blood gas profile. The principal findings of this study are: (1) Ht, an index of right ventricular hypertrophy (RVW/LVW), and oxygen consumption ($\dot{V}O_2$) were significantly lower in the blue sheep compared with the pigs; (2) When the animals were exposed to simulated-altitudes at 0, 2,300, and 4,500 m, *P*_{pa} increased significantly in tandem with altitude elevation in both species, but the increases were significantly smaller in the blue-sheep; and (3) *P*_{pa}/*P*_{sa}, an index of the right ventricular load, increased with the altitude in both species, but the increases were smaller in the blue sheep. From these observations, low Ht and RVW/LVW and significant attenuation of hypoxic pulmonary vasoconstriction (HPV) in the blue-sheep is considered to be characteristics of animals completely adapted to high-altitudes, such as the pika. [The Japanese Journal of Physiology 53: 377–384, 2003]

Key words: blue-sheep, high-altitude, pulmonary hypertension, right ventricular hypertrophy.

The blue-sheep, pika, and yak live in the Tibetan highlands at an altitude of 6,100 m and are typical animals adapted to high-altitude among mammals of the world [1]. These animals have a long history of habitation at high-altitudes and are considered to be “animals completely adapted to high-altitude” because of their physiological and morphological traits that are

well adapted to high-altitude environments.

When animals are exposed to a high-altitude environment over a long period, the pulmonary artery pressure increases because of an increase in the hematocrit (Ht) associated with an increase in the red blood cell count and hypoxic pulmonary vasoconstriction (HPV), causing pulmonary hypertension and right

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ventricular hypertrophy. These responses show marked individual and species differences [2]. HPV and pulmonary vascular remodeling are completely different in regard to the response to hypoxia in pulmonary circulation. Also, acute and chronic hypoxia is different stimuli to pulmonary circulation. Our previous experiments using the pika characteristically showed minimal pulmonary hypertension, minimal right ventricular hypertrophy, lower Ht, and weaker HPV among various kinds of animals [3]. We accomplished this study to assess our hypothesis that blue-sheep, a larger animal than a pika, has other mechanism(s) than those of pika to adapt to high-altitudes in regard to pulmonary circulatory response. We also used pigs as controls for comparably strengthening the hypoxic response of blue-sheep.

MATERIALS AND METHODS

Adult seven male blue-sheep weighing 33.3 ± 1.3 kg and adult five male pigs weighing 50.2 ± 1.8 kg were used. The animals, which were living in Qinghai Province (3,000 m above sea level), were transported to the Qinghai High Altitude Medical Science Institute (2,300 m above sea level), Xining, China. After the measurement of the body weight, the animals were anesthetized with an intramuscular administration of xylazine hydrochloric acid (0.3 ml/kg, Bayer Pharmaceutical Co.). Through a right neck incision, a No. 8 cordis catheter sheath introducer and a silicon catheter were inserted for later passage of a Swan-Ganz catheter and systemic arterial pressure (P_{sa}) measurement, respectively. A 7F Swan-Ganz catheter was advanced via the cordis to measure the pulmonary artery pressure (P_{pa}), pulmonary artery wedge pressure (Wedge P), and cardiac output (CO).

Experiments were started after a full recovery from the anesthetic state. All physiological measurements were made with the animals awake and standing. Catheters for measurements of P_{pa} and P_{sa} were connected to a pressure amplifier (UNIPULSE, Japan) via a blood pressure transducer (P10Ez-1, Nihon Kohden Co., Japan). The zero level for transducers was taken at the level of the left atrium. CO was measured by a thermo dilution technique of at least three injections of 5 ml of cooled normal saline and the use of a cardiac output computer (9520A, American Edwards Laboratories, USA). Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated by the following equation. $PVR = (P_{pa} - \text{Wedge } P) / CO$ and $SVR = P_{sa} / CO$, respectively. P_{pa} / P_{sa} was also calculated. It is clear in the following equation that P_{pa} / P_{sa} indicates the ratio of the

right ventricular work rate ($RV\dot{W}$) to the left ventricular work rate ($LV\dot{W}$). $RV\dot{W} / LV\dot{W} \approx P_{pa} \times CO / P_{sa} \times CO = P_{pa} / P_{sa}$.

Arterial and mixed venous blood pH, PO_2 , PCO_2 , and SO_2 were measured on a blood gas analyzer (iSTAT Co., USA) with an EG7 cartridge. Blood samples were drawn from the systemic artery and Swan-Ganz catheter. Oxygen consumption ($\dot{V}O_2$) was calculated from the results of blood gas analysis by using the following equation based on Fick's methods, $\dot{V}O_2 = CO \times (CaO_2 - CvO_2)$ and CO_2 (ml/dl) = $1.34 \times Hb$ (g/dl) $\times SO_2$ (%) / 100 + $0.0031 \times PO_2$ (mmHg). In these equations, CaO_2 is the arterial blood oxygen content, CvO_2 is the venous blood oxygen content, Hb is the hemoglobin concentration, SO_2 is the oxygen saturation, and PO_2 is the partial oxygen pressure.

The animals were placed in a large climatic chamber (9.3 m long and 68 m³) in which the atmospheric pressure could simulate altitudes of 0, 2,300, and 4500 m above sea level. Baseline measurements were performed in a resting state at 2,300 m. The environmental conditions were then adjusted to 0, 2,300, and 4,500 m. The animals were exposed first to 0 m and sequentially returned to 2,300 m. Finally, the animals went up to 4,500 m from 2,300 m. The simulated-altitude was changed at a rate of 150 m/min. The interval for reaching another simulated altitude was about 20 min. Hemodynamic measurements and blood gas analyses were performed at least 20 min after each of the three altitudes was reached.

After physiological measurements, the heart was excised and the ventricles were separated into the left ventricle (including the septum) and into the right ventricle according to Fulton's method [4]. The left ventricular weight (LVW) and right ventricular weight (RVW) were then measured. The total ventricular weight (TVW) was calculated by $LVW + RVW$ and the ventricular weight ratio (RVW / LVW) was also calculated as an index of right ventricular hypertrophy.

During the experiment, the temperature and relative humidity in the climatic chamber were maintained at $20 \pm 1^\circ\text{C}$ and $50 \pm 3\%$, respectively.

The animal care and experimental protocol were approved by a committee of the Qinghai High Altitude Medical Institute.

In statistical analyses, the values obtained were expressed as the mean \pm standard error (SE), and the data were compared by a *t*-test and an analysis of variance (ANOVA) at the 5% level of significance.

RESULTS

Comparison of ventricular weights, Ht, and oxygen consumption

Table 1 shows the ventricular weights, Ht and oxygen consumption in blue-sheep and pigs at 2,300 m. The body weight (BW) was 33.29 ± 1.26 kg in the blue-sheep significantly smaller than the 50.20 ± 1.82 kg in the pigs. The weight ratio of the right ventricle to the left ventricle (RVW/LVW) was 0.29 ± 0.003 in the blue-sheep and 0.37 ± 0.02 in the pigs, indicating that the degree of right ventricular hypertrophy was significantly smaller in the blue-sheep. The Ht was $36.14 \pm 0.35\%$ in the blue sheep but $38.26 \pm 0.95\%$ in the pigs, and the oxygen consumption ($\dot{V}O_2$) was 4.75 ± 0.36 ml/min/kg in the blue-sheep but 6.69 ± 0.39 ml/min/kg in the pigs, both also significantly smaller in the blue sheep.

Table 1. Comparison of ventricular weights, hematocrit, and oxygen consumption between blue-sheep and pig at 2,300 m.

	Species	
	Sheep (n=7)	Pig (n=5)
Altitude (m)	2,300	2,300
BW (kg)	33.29 ± 1.26	$50.20 \pm 1.82^*$
LVW (g)	112.51 ± 4.61	99.74 ± 5.73
RVW (g)	33.59 ± 1.25	36.60 ± 1.86
TVW (g)	146.1 ± 5.89	136.34 ± 7.60
RVW/LVW	0.29 ± 0.003	$0.37 \pm 0.02^*$
Ht (%)	36.14 ± 0.35	$38.26 \pm 0.95^*$
$\dot{V}O_2$ (ml/min//kg)	4.75 ± 0.36	$6.69 \pm 0.39^*$

Values are means \pm SE. BW, body weight; LVW, left ventricular weight; RVW, right ventricular weight; TVW, total ventricular weight; RVW/LVW, ratio of RVW to LVW; $\dot{V}O_2$, O_2 uptake; Ht, hematocrit. * $p < 0.05$ vs. sheep.

0.95% in the pigs, and the oxygen consumption ($\dot{V}O_2$) was 4.75 ± 0.36 ml/min/kg in the blue-sheep but 6.69 ± 0.39 ml/min/kg in the pigs, both also significantly smaller in the blue sheep.

Comparison of effects of exposure to high-altitude conditions on the pulmonary hemodynamics

Table 2 shows changes in the pulmonary hemodynamics when the animals were exposed to simulated-altitudes at 0, 2,300, and 4,500 m in the climatic chamber.

P_{pa} increased progressively to 15.89, 17.52, and 25.26 mmHg in the blue-sheep as the altitude elevated from 0 to 2,300 m and then to 4,500 m and a significant difference was observed between 0 and 4,500 m ($p < 0.05$). It also increased from 23.80 to 29.95 and to 41.40 mmHg in the pigs revealing a significant difference between 0 and 4,500 m ($p < 0.05$). Furthermore, it was significantly lower ($p < 0.05$) in the blue-sheep than in the pigs at all altitudes (Table 2). Figure 1 shows changes in ΔP_{pa} associated with elevations of the altitude relative to the values at 0 m. As this figure clearly shows, ΔP_{pa} increased with elevations of the altitude in both species, but the increase (slope) was milder in the blue-sheep. Consequently, significant differences ($p < 0.05$) were observed in P_{pa} between the two species (Table 2). P_{sa} showed no change associated with elevations of the altitude in either species. However, it was significantly smaller ($p < 0.05$) in the blue-sheep than in the pigs at all altitudes. The change in ΔP_{sa} associated with an elevation of the altitude relative to the value at 0 m showed no change with the

Table 2. A comparison of the effects of exposure to simulated-altitude on pulmonary hemodynamics.

	Species					
	Sheep (n=7)			Pig (n=5)		
	0 m	Simulated altitude 2,300 m	4,500 m	0 m	Simulated altitude 2,300 m	4,500 m
P_{pa} (mmHg)	15.89 ± 0.91	17.52 ± 1.18	$25.26 \pm 2.58^{\#}$	$23.80 \pm 2.71^*$	$29.95 \pm 3.77^*$	$41.40 \pm 5.12^{*,\#}$
P_{sa} (mmHg)	97.72 ± 2.25	96.22 ± 3.49	101.15 ± 3.94	$138.20 \pm 5.67^*$	$143.17 \pm 7.54^*$	$132.82 \pm 10.65^*$
P_{pa}/P_{sa}	0.163 ± 0.01	0.184 ± 0.014	$0.253 \pm 0.029^{\#}$	0.171 ± 0.014	0.208 ± 0.019	$0.313 \pm 0.033^{\#}$
CO (l/min)	4.74 ± 0.4	4.72 ± 0.39	5.17 ± 0.61	5.59 ± 0.39	5.7 ± 0.44	5.67 ± 0.69
HR (beats/min)	65 ± 5.3	70 ± 4.9	79 ± 5.3	$129 \pm 13.3^*$	$132 \pm 4.9^*$	$141 \pm 7.9^*$
SV (ml/beat)	74.4 ± 6.2	68.6 ± 6.2	66.2 ± 6.9	$44.0 \pm 2.7^*$	$43.2 \pm 3.1^*$	$42.3 \pm 5.1^*$
Wedge P (mmHg)	8.08 ± 0.88	7.27 ± 0.66	8.30 ± 1.24	$3.75 \pm 0.71^*$	$4.25 \pm 0.97^*$	4.39 ± 1.60
PVR (mmHg//min)	1.66 ± 0.18	2.24 ± 0.27	$3.54 \pm 0.55^{\#}$	$3.79 \pm 0.31^*$	$4.74 \pm 0.32^*$	$6.52 \pm 0.45^{*,\#}$
SVR (mmHg//min)	21.53 ± 1.82	20.93 ± 1.18	20.80 ± 1.79	25.78 ± 2.96	26.35 ± 3.57	23.93 ± 3.45

Values are means \pm SE. P_{pa} , pulmonary arterial mean pressure; P_{sa} , systemic arterial mean pressure; P_{pa}/P_{sa} , ratio of P_{pa} to P_{sa} ; CO, cardiac output; HR, heart rate; SV, stroke volume; Wedge P , mean pulmonary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance. * $p < 0.05$ vs. sheep; $\#$ $p < 0.05$ vs. altitude at 0 m.

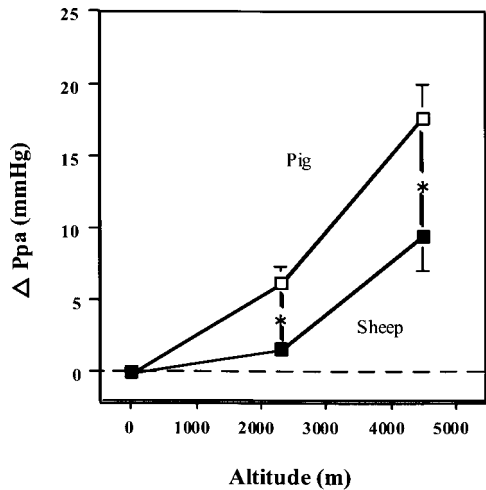


Fig. 1. Changes in ΔPpa associated with elevation of the altitude in blue-sheep and pigs. The increase with elevation of the altitude (slope) was milder in the blue sheep. Values are means \pm SE. * $p < 0.05$ between the two species; ΔPpa : difference of the values at 0 m.

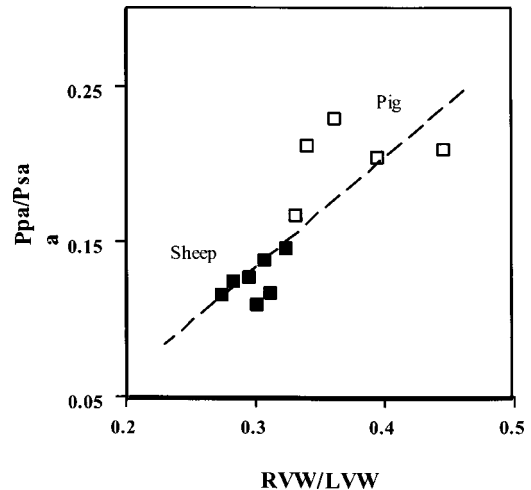


Fig. 3. Relationship between RVW/LVW and Ppa/Psa in the blue-sheep and pigs at 2,300 m. A close correlation ($r = 0.80$, $p < 0.01$) was observed between RVW/LVW and Ppa/Psa . The blue-sheep were distributed around the lower part of this regression line.

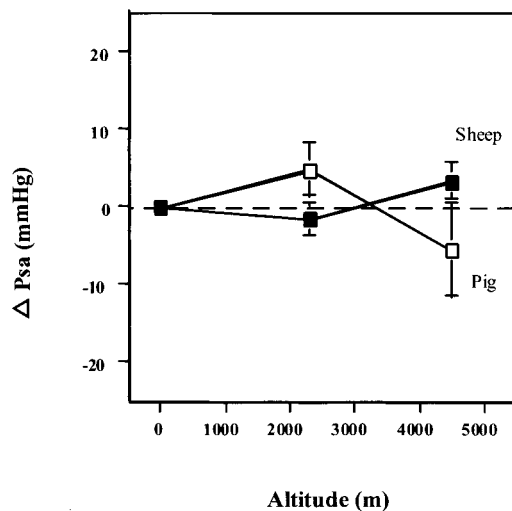


Fig. 2. Changes in ΔPsa associated with an elevation of the altitude in blue-sheep and pigs. ΔPsa showed no change with the altitude or difference between the species. Values are means \pm SE. ΔPsa : difference of the values at 0 m.

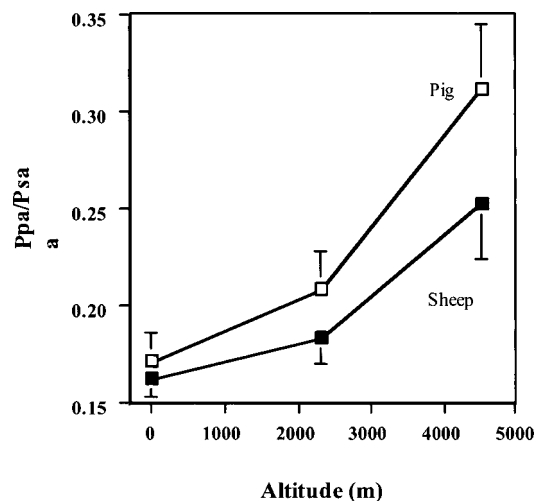


Fig. 4. Changes in Ppa/Psa associated with elevation of the altitude in blue-sheep and pigs. The increase with elevation of the altitude (slope) was milder in the blue sheep. Values are means \pm SE.

altitude or difference between the species (Fig. 2). Figure 3 shows the relationship between RVW/LVW and Ppa/Psa in the blue-sheep and pigs at 2,300 m. As described in relation to an equation in the methods section, Ppa/Psa represents the ratio of the right ventricular work rate to the left ventricular work rate. A close correlation ($r = 0.80$, $p < 0.01$) was observed between RVW/LVW and Ppa/Psa . However, the blue-sheep were distributed around the lower part on this regression line, indicating that Ppa/Psa and RVW/LVW were both smaller in the blue sheep than in the pigs. Figure 4 shows changes in Ppa/Psa as the

altitude changed. It increased with elevation in both species, but the values of the blue-sheep were smaller than those of the pigs at all altitudes. Also, the slope of its increase was milder in the blue-sheep. CO and HR increased slightly with altitude elevations in both species but absolute HR was significantly smaller ($p < 0.05$) in the blue-sheep at all altitudes. SV tended to decrease with altitude elevation reflecting changes in CO and HR. However, its absolute values were significantly greater ($p < 0.05$) in the blue-sheep at all altitudes. PVR increased from 1.66 ± 0.18 mmHg//min at 0 m to 2.24 ± 0.27 mmHg//min at 2,300 m, and to 3.54 ± 0.55 mmHg//min at 4,500 m in the blue-sheep,

Table 3. A comparison of exposure to simulated-altitude on blood gas analyses.

	Species					
	Sheep (n=7)			Pig (n=5)		
	0 m	Simulated altitude 2,300 m	4,500 m	0 m	Simulated altitude 2,300 m	4,500 m
Hba (g/dl)	10.57 ± 0.48	10.71 ± 0.36	11.57 ± 0.20	13.00 ± 0.41*	12.50 ± 0.50	13.25 ± 0.48*
Hbv (g/dl)	10.71 ± 0.42	11.14 ± 0.26	10.86 ± 0.46	14.00 ± 0.41*	12.50 ± 0.29*	14.00 ± 0.00*
PaO ₂ (mmHg)	90.00 ± 3.62	56.86 ± 1.12 [#]	36.43 ± 1.59 [#]	73.00 ± 2.48*	47.25 ± 1.49* [#]	30.00 ± 1.29* [#]
PvO ₂ (mmHg)	36.43 ± 2.09	31.00 ± 1.00	24.86 ± 1.32 [#]	31.75 ± 1.44	27.00 ± 1.78	19.25 ± 1.55 [#]
SaO ₂ (%)	97.86 ± 0.26	92.86 ± 0.46 [#]	79.86 ± 1.97 [#]	96.25 ± 0.48	88.25 ± 1.25* [#]	71.50 ± 2.90* [#]
SvO ₂ (%)	71.29 ± 2.34	67.00 ± 2.19	54.00 ± 2.89 [#]	66.25 ± 2.78	52.5 ± 3.23* [#]	39.50 ± 5.48* [#]
PaCO ₂ (mmHg)	29.91 ± 1.39	27.70 ± 1.07	24.64 ± 0.90 [#]	32.45 ± 0.48	30.30 ± 0.57 [#]	24.93 ± 1.58 [#]
PvCO ₂ (mmHg)	33.91 ± 1.75	33.44 ± 1.33	28.10 ± 1.68 [#]	38.98 ± 1.19	36.83 ± 0.97	31.50 ± 1.17 [#]
pHa	7.53 ± 0.02	7.55 ± 0.02	7.58 ± 0.02	7.54 ± 0.01	7.56 ± 0.01	7.61 ± 0.02 [#]
pHv	7.48 ± 0.02	7.51 ± 0.01	7.53 ± 0.02	7.49 ± 0.01	7.51 ± 0.01	7.56 ± 0.02
VO ₂ (ml/min)	183.73 ± 33.70	158.02 ± 13.83	226.62 ± 22.53	242.24 ± 25.52*	339.23 ± 31.09*	305.11 ± 47.09*

Values are means ± SE. Hba, arterial Hb; Hbv, mixed venous Hb; PaO₂, arterial PO₂; PvO₂, mixed venous PO₂; SaO₂, arterial SO₂; SvO₂, mixed venous SO₂; PaCO₂, arterial PCO₂; PvCO₂, mixed venous PCO₂; pHa, arterial pH; pHv, mixed venous pH; VO₂, O₂ uptake. * $p < 0.05$ vs. sheep; # $p < 0.05$ vs. altitude at 0 m.

which revealed a significant difference between 0 and 4,500 m ($p < 0.05$). In the pigs it also increased with altitude elevation, from 3.79 ± 0.31 to 4.74 ± 0.32 and to 6.52 ± 0.45 at the respective altitudes, and the difference between 0 and 4,500 m was significant ($p < 0.05$). The values in the blue sheep were significantly smaller ($p < 0.05$) than those in the pigs at all altitudes, and the rates of their increases with altitude (slope) elevation were also smaller in the blue-sheep. SVR, however, showed no change at different altitudes in species or difference between the species.

Results of blood gas analyses

Table 3 shows the results of blood gas analyses in the animals exposed to simulated altitudes at 0, 2,300, and 4,500 m.

Hb showed no change associated with the altitude in the blue-sheep or pigs. However, its absolute values were significantly lower in the blue-sheep, reflecting the significantly lower hematocrit. PaO₂ decreased markedly with altitude elevations in both species. In the blue-sheep, it decreased from 90.00 to 56.86 mmHg and to 36.43 mmHg as the altitude elevated from 0 to 2,300 m and 4,500 m. In the pigs, it also decreased significantly ($p < 0.05$) from 73.00 to 47.25 mmHg and to 30.00 mmHg. Between the species, it was significantly higher ($p < 0.05$) in the blue-sheep at all altitudes. SaO₂ also decreased markedly with altitude elevations. It decreased significantly ($p < 0.05$) from 97.86 to 92.86% and to 79.86% in the blue-sheep and from 96.25 to 88.25% and to 71.50% in the

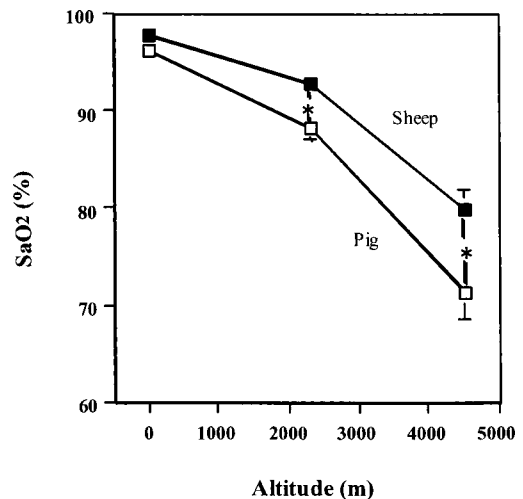


Fig. 5. Changes in SaO₂ associated with an elevation of the altitude in blue-sheep and pigs. SaO₂ decreased markedly with an altitude elevation in both species. But the values of each altitude were always greater in the blue-sheep. Values are means ± SE. * $p < 0.05$ between the two species.

pigs. The difference in SaO₂ between the species was small at 0 m but it widened as the altitude elevated to 4.6% at 2,300 m and to 8.4% ($p < 0.05$) at 4,500 m, and the values were always higher in the blue-sheep (Fig. 5). pHa was 7.53 in the blue-sheep and 7.54 in the pigs at 0 m, but it increased to 7.58 and 7.61, respectively, with elevation of the altitude to 4,500 m. These increases in pHa were 0.05 in the blue-sheep and significantly greater, 0.07 in the pigs ($p < 0.05$) (Fig. 6).

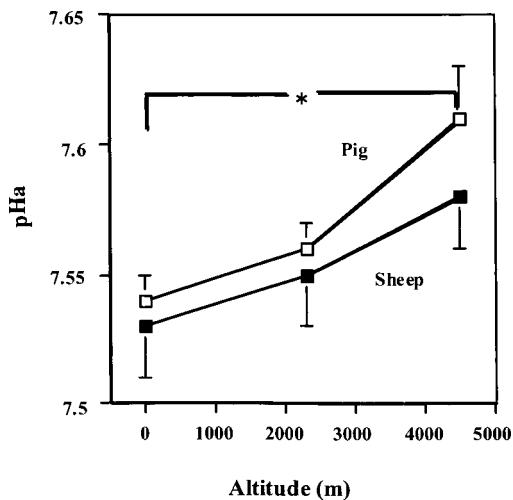


Fig. 6. Changes in arterial blood pH (pHa) associated with an elevation of the altitude in blue-sheep and pigs. pHa increased with an altitude elevation in both species, but increases were greater in the pig. Values are means \pm SE. * $p < 0.05$ vs. altitude at 0 m.

DISCUSSION

Since the blue-sheep are distributed in the highlands to an altitude of 6,100 m [1], and at high-altitudes has been long, they are considered to be completely adapted to high-altitudes. Therefore, to evaluate the characteristics of the adaptation of blue-sheep to high-altitudes, we exposed them to simulated-altitudes of 0, 2,300, and 4,500 m, using the climatic chamber at the High Altitude Medical Institute (2,300 m), Qinghai, China. The following results were obtained. (1) The Ht, heart size, degree of right ventricular hypertrophy, and oxygen consumption were significantly smaller in the blue-sheep compared with pigs inhabiting at the same altitude (3,000 m). (2) When the animals were exposed to simulated-altitudes of 0, 2,300, and 4,500 m, marked differences were observed in the pulmonary circulation, such as pulmonary artery pressure, pulmonary vascular resistance, and ratio of the pulmonary arterial pressure to the systemic artery pressure. However, no change was observed in either species in the systemic circulation, such as cardiac output, systemic arterial pressure, and systemic vascular resistance. The altitude-dependent changes in pulmonary circulation were always smaller, and their increases as the altitude increased were smaller in the blue sheep. These results suggest that HPV is markedly weaker in the blue-sheep than in the pig. (3) The arterial blood partial oxygen pressure and arterial blood oxygen saturation decreased with altitude elevation in both species, but their absolute values were higher in the blue-sheep at all altitudes. The pH in-

creased with an elevation of the altitude in both species, but its increases were smaller in the blue-sheep, suggesting that the effect of respiratory alkalosis resulting from hyperventilation under a hypoxic condition was smaller. Thus, blue-sheep has almost the same mechanism for adaptation to high altitude as that of the pika [3] and of Tibetans [5].

Generally, when animals are exposed to a high-altitude environment, pulmonary hypertension, and right ventricular hypertrophy are induced. The following two factors are considered to be possible causes of these phenomena: (1) constriction of the pulmonary capillaries because of hypoxia (hypoxic pulmonary vasoconstriction, HPV) and (2) an increase in the Ht as a result of an increase in red blood cells. HPV, confirmed in 1946 by an experiment by Von Euler [6] that used cats, is marked pulmonary hypertension resulting from constriction of the pulmonary artery during pulmonary ventilation at a low oxygen concentration. Many reports have since appeared, and HPV was shown to be observed regardless of the animal species, induced also by the migration of animals to high-altitude regions as well as by exposure to a low atmospheric pressure. Although HPV plays an important role in the control of pulmonary circulation during hypoxia, the mechanism of its occurrence remains unknown. On the other hand, the increase in the Ht because of an increase in red blood cells mentioned in (2) increases the blood viscosity, and this increased viscosity is considered to affect the pulmonary circulation to induce pulmonary hypertension. This view is supported by reports that the degree of right ventricular hypertrophy depends on the ambient temperature in animals inhabiting at the same altitude and were correlated with changes in the Ht [7], that the pulmonary arterial pressure increases more markedly than the systemic blood pressure when the hematocrit is increased artificially by red cell transfusion [8], and that polycythemia caused by the administration of cobalt chloride induces right ventricular hypertrophy [9].

As observed above, the interaction between HPV and an increase in the blood viscosity because of an increase in the Ht appears certain to be involved in pulmonary hypertension and right ventricular hypertrophy observed at high-altitudes. Therefore analysis of these two factors is considered to be needed for elucidation of high-altitude pulmonary hypertension and right ventricular hypertrophy.

The increased pulmonary artery pressure or right ventricular hypertrophy at high-altitudes has been reported to vary widely among species and individuals of the same species even when they are exposed to the

same altitudes [2, 5, 10–16]. Reeves *et al.* [2] reported species differences in the increase in the pulmonary artery pressure resulting from chronic exposure to a high-altitudes; although pulmonary hypertension induced by exposure to high-altitudes was remarkable in the cow and horse, it was minimal in the llama, dog, sheep, and rabbit. It was also shown that there are two types of cows, i.e., the susceptible type, which shows marked increases in the pulmonary artery pressure when exposed to high-altitudes and the resistant type, which is less responsive to changes in the altitude [2]. Genetic factors have been suggested to play important roles in this sensitivity to exposure to a high-altitude, and cows of the susceptible type die after developing right heart failure because of marked pulmonary hypertension. Similar differences in the responsiveness to hypoxia are observed also in humans, and some individuals develop marked pulmonary hypertension, but others do not at the same altitude [16]. Those who do such individuals are quite likely to develop high-altitude pulmonary edema, a form of advanced altitude disease [18]. When these observations are considered together, a smaller degree of pulmonary hypertension or right ventricular hypertrophy at a high-altitude indicates better adaptability to it. In fact, the Ht is significantly lower, the degree of pulmonary hypertension or right ventricular hypertrophy is markedly smaller, and the oxygen consumption is less in the pika, which is an animal completely adapted to a high-altitude, than it is in the rat [3]. Moreover, HPV is significantly smaller in the pika than in the rat [19]. In this study, the blue-sheep has significantly low levels of the hematocrit and pulmonary artery pressure and a low degree of right ventricular hypertrophy compared with pigs. HPV and oxygen consumption are also significantly smaller in the blue-sheep than in the pigs.

In terms of oxygen consumption, which was significantly smaller in the blue-sheep and the pika [3] than in the rat and pigs, the acquisition of such ability is considered to be a major characteristic of high-altitude adaptation. Physiological homeostasis must be maintained by a smaller oxygen intake to maintain life in a high-altitude environment with sparse oxygen. The high arterial blood oxygen saturation and PaO_2 in the blue-sheep at high altitudes are considered to be characteristics of animals completely adapted to high altitudes. To strengthen our results, we also have had interest in the thickness of the pulmonary vascular wall of the blue-sheep at low altitudes since Tucker *et al.* [20] documented a strong positive correlation between the thickness of pulmonary arterial smooth muscle at low altitudes and the development of pulmonary hypertension at high-altitudes. We don't know

if the blue sheep fits Tucker's concept.

In conclusion, among mammals, the blue-sheep and the pika, animals living in the highest altitudes in the world, have developed almost the same physiological adaptation mechanism for a high-altitude environment as a result of their long history of habitation in highlands through a natural selection of better-adapted individuals.

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REFERENCES

1. Heath D: Physical and geography, High altitude fauna and flora. *In: Man at High Altitude*, ed. Heath D and Williams DR, Churchill Livingstone, Edinburgh London Melbourne, and New York, pp 13–23, 1981
2. Reeves JT, Wagner WW, McMurtry IF, and Grover RF: Physiological effects of high altitude on the pulmonary circulation. *In: International Review of Physiology, Environmental Physiology III*, ed. Robertshaw D, University Press, Baltimore, Vol 120, pp 289–310, 1979
3. Sakai A, Ueda G, Yanagidaira Y, Takeoka M, Tang G, and Zang Y: Physiological characteristics of Pika, Ochotona, high-altitude adapted animals. *In: High-Altitude Medical Science*, ed. Ueda G and Voelkel NF, Shinshu University Press, Matsumoto, pp 99–107, 1988
4. Fulton RN, Hutchinson EC, and Jones AM: Ventricular weight in cardiac hypertrophy. *Br Heart J* 14: 413–420, 1952
5. Groves BM, Droma T, Sutton JR, and McCullough RG: Minimal hypoxic pulmonary hypertension in normal Tibetans at 3,658 m. *J Appl Physiol* 74(1): 312–318, 1993
6. Von Euler US and Lijestrang G : Observation on pulmonary arterial blood pressure in the cat. *Acta Physiol Scand* 12: 301–320, 1946
7. Sakai A: Hematocrit and right ventricular weight. Seasonal and latitudinal changes in hematocrit and right ventricular weights of wood mice, *Apodemus argenteus*. *Jpn J Physiol* 36 : 8–16, 1974 (in Japanese)
8. Sakai A, Ueda G, Kobayasi T, and Kubo K: Effects of elevated-hematocrit levels on pulmonary circulation in conscious sheep. *Jpn J Physiol* 34: 871–882, 1984
9. Swigart RH: Polycythemia and right ventricular hypertrophy. *Circ Res* 17: 30–38, 1965
10. Petit RD, Warburton RR, Ou LC, Brink-Johnson T, and Hill NS: Exogenous erythropoietin fails to augment hypoxic pulmonary hypertension in rats. *Respir Physiol* 91: 271–282, 1993
11. Colice GL, Hill N, Lee YJ, and Du H: Exaggerated pulmonacrotaline in rats susceptible to chronic mountain sickness. *J Appl Physiol* 83: 25–31, 1997
12. He L, Chang SW, and Voelkel NF: Pulmonary vascular reactivity in Fischer rats. *J Appl Physiol* 70: 1861–1866, 1991

13. Ou LC and Smith RP: Probable strain differences of rats in susceptibilities and cardiopulmonary responses to chronic hypoxia. *Respir Physiol* 53: 367–377, 1983
14. Salameh G, Karamesetty MR, Warburton RR, Klinger JR, Ou LC, and Hill NS: Differences in acute hypoxic pulmonary vasoresponsiveness between rat strains: role of endothelium. *J Appl Physiol* 87: 356–362, 1999
15. Walker BR, Voelkel NF, McMurtry IF, and Adams EM: Evidences for diminished sensitivity of the hamster pulmonary vasculature to hypoxia. *J Appl Physiol* 52: 1571–1574, 1982
16. Walker BR, Berend N, and Voelkel NF: Comparison of muscular pulmonary arteries in low and high altitude hamsters and rats. *Respir Physiol* 56: 45–50, 1984
17. Grover RF: Pulmonary circulation in animals and man at high altitude. *Ann NY Acad Sci* 127: 632–639, 1965
18. Kawashima A, Kubo K, Kobayashi T, and Sekiguchi M: Hemodynamic responses to acute hypoxia, hypobaria, and exercise in subjects susceptible to high-altitude pulmonary edema. *J Appl Physiol* 67: 1982–1989, 1989
19. Ge R, Kubo K, Kobayashi T, Sekiguchi M, and Honda T: Blunted hypoxic pulmonary vasoconstrictive response in the rodent *Ochotona cuizoniae* (pika) at high altitude. *Am J Physiol* 274: H1729–H1799, 1998
20. Tucker A, McMurtry IF, Reeves JT, Alexander AF, Will DH, and Grover RF: Lung vascular smooth muscle as a determinant of pulmonary hypertension at high altitude. *Am J Physiol* 228: 762–767, 1975