Functional and structural adaptation of the yak pulmonary circulation to residence at high altitude

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Durmowicz, Anthony G., Stephen Hofmeister, T. K. Kadyraliev, Almas A. Aldashev, and Kurt R. Stenmark. Functional and structural adaptation of the yak pulmonary circulation to residence at high altitude. J. Appl. Physiol. 74(5): 2276-2285, 1993.—The high-altitude (HA) native yak (Bos grunniens) has successfully adapted to chronic hypoxia (CH) despite being in the same genus as domestic cows, which are known for their great hypoxic pulmonary vasoconstrictor responses (HPVRs), muscular pulmonary arteries, and development of severe pulmonary hypertension on exposure to CH. To determine possible mechanisms by which the pulmonary circulation may adapt to CH, yak pulmonary vascular reactivity to both vasoconstrictor and vasodilator stimuli and yak pulmonary artery structure were assessed. Hypoxia caused a small but significant HPVR, and norepinephrine infusion caused a greater rise in pulmonary arterial pressure (Ppa) than did hypoxia. Acetylcholine, an endothelium-dependent vasodilator, had no effect on Ppa but lowered pulmonary resistance (Rp) by causing an increase in cardiac output. Sodium nitroprusside, an endothelium-independent vasodilator, decreased both Ppa and Rp significantly. Yak small pulmonary arteries had a 4.1 ± 0.1% medial thickness, with vessels ≤100 µm devoid of smooth muscle. Yak pulmonary artery endothelial cells were much longer, wider, and rounder in appearance than those of domestic cows. Thus the yak has successfully adapted to HA conditions by maintaining both a blunted HPVR and thin-walled pulmonary vessels. Differences in both endothelial cell morphology and response to acetylcholine between the yak and those reported in the domestic cow suggest the adaptation to HA may include changes not only in the amount of pulmonary vascular smooth muscle but in endothelial cell function and structure as well.

pulmonary hypertension; chronic hypoxia; Bos grunniens; vascular reactivity; vasodilators

THE MAINTENANCE OF low pulmonary arterial pressures at high altitude as an adaptation to chronic hypoxia occurs over many generations and appears to be genetically transmitted within populations. A slow evolutionary process is suggested by the relatively high pulmonary pressures in human populations that have recently moved to altitude (6) compared with populations that have lived at altitude for thousands of years (5, 8, 13). Although the mechanism(s) by which adaptation to chronic hypoxia occurs remains unknown, the fact that the mechanism is genetically transmitted is best illustrated in cattle that are either “susceptible” or “resistant” to the development of severe pulmonary hypertension and cor pulmonale (brisket disease) on exposure to a chronic hypoxic environment (4, 19, 22). Domestic cattle (Bos taurus) native to high altitudes and their offspring have a low incidence of brisket disease (2%), whereas herds recently transported from sea level have incidences as high as 40–50%, a finding strongly suggestive of genetic selection of resistant animals (6, 21).

The native high-altitude yak (Bos grunniens) has successfully adapted over many generations to the chronic hypoxia of high altitude despite belonging to the genus Bos in which the closely related domestic bovine members are known for their large hypoxic pulmonary vasoconstrictor responses, muscular pulmonary arteries, and the development of severe pulmonary hypertension (brisket disease) when exposed to chronic hypoxia. The factor(s) responsible for the remarkable ability of the yak to not only live but to work as a beast of burden at very high altitudes is unknown. However, the maintenance of both low pulmonary arterial pressures and thin-walled pulmonary arteries appears to contribute. Previous studies have demonstrated that yaks in the London Zoo have similar pulmonary pressures to those residing at high altitude in Nepal (3) and that one adult female yak possessed thin-walled pulmonary arteries (10). However, no data exist on the assessment of pulmonary vascular reactivity and structure in the same set of animals.

Inherent differences in the pulmonary vascular smooth muscle itself, such as a blunted contractile response to hypoxia or an absolute lack of smooth muscle in the pulmonary arteries, could account for the maintenance of low pulmonary arterial pressures and thin-walled pulmonary arteries in high-altitude-adapted species. Alternatively, differences in the function of the pulmonary vascular endothelium, which plays a major role in the regulation of pulmonary vascular tone and pressure, could contribute to a species' ability to adapt to a high-altitude environment. We hypothesized that adaptation to a high-altitude environment results in significant changes in endothelial cell function. Thus, in an effort to examine the role of the pulmonary vascular endothelium in the adaptation of the yak's pulmonary arteries to a chronic hypoxic environment, the present study was undertaken to assess pulmonary pressures, pulmonary vascular reactivity, and pulmonary vascular structure in the native high-altitude bovine species Bos grunniens. Pulmonary vasoconstriction was measured by the use of both alveo-
lary hypoxia and the \( \alpha \)-agonist norepinephrine. Both endothelium-dependent and endothelium-independent vasoconstrictors were infused in the pulmonary arteries under baseline conditions and under conditions of increased tone (hypoxia) to help assess the relative role of the endothelium in determining vascular reactivity in the high-altitude yak. In addition, morphometric analysis of yak pulmonary arteries was done to determine the thickness of the muscular media of small pulmonary arteries, and endothelial cell surface structure and size were assessed in both the yak and domestic calf by scanning electron microscopy.

**MATERIALS AND METHODS**

**Animals.** Three juvenile (5–7 mo old) active and healthy appearing male yaks weighing ~100 kg each were used in this study. These animals were born and lived in a semi-wild yak herd at 3,200 m altitude in the Talas region of the Republic of Kyrgyzstan. The yaks were transported to the Kyrgyz Institute of Cardiology in the city of Bishkek (previously Frunze), Republic of Kyrgyzstan (altitude 730 m) and were studied in Bishkek <12 h after their arrival. The care and treatment of the study animals were in full compliance with the Kyrgyz and Soviet National Animal Care Committee policies.

**Hemodynamic studies.** All physiological studies were performed in unanesthetized animals in the left lateral recumbent position. Although initially the animals had to be physically restrained, after a period of acclimatization to their surroundings, they remained quiet when held by the investigators. A dual-thermistor 7-Fr Swan-Ganz catheter (Nova Dual Therm, Berlin, NJ) and a separate pulmonary artery catheter for drug infusion (PE-160, Clay Adams, Parsippany, NJ) were placed percutaneously via the external jugular vein by the Seldinger technique with the use of local lidocaine anesthesia. Correct placement was determined by pressure wave tracing. An aortic catheter (PE-200, Clay Adams, Parsippany, NJ) was introduced via the left saphenous artery that had been surgically exposed after local lidocaine anesthesia. Pressures were measured with disposable transducers (Sorenson Transpac, North Chicago, IL) and continuously recorded on a two-channel recorder (model 402, Soltec, Sun Valley, CA) with zero pressure set 4–5 cm above floor level to approximate the level of the heart with the animal in left lateral recumbency. Cardiac output was measured by the thermodilution method by use of the dual-thermistor pulmonary artery catheter with a 10-ml injectate volume of normal saline and a T-110-D cardiac output computer (Nova Medical Specialties, Berlin, NJ). Measurements were made at least three times in each animal under both basal and experimental conditions. Total pulmonary and systemic arterial resistances were calculated by dividing mean pressure values by cardiac output and were expressed as millimeters of mercury per liter per minute.

The animals were exposed to hypoxic conditions by blending oxygen and nitrogen in a 100-liter meteorological balloon to achieve the desired oxygen concentration as determined by a Fyrite \( O_2 \) concentration test kit (Bacharach, Pittsburgh, PA). Administration of the hypoxic gas was accomplished with a custom-made cattle face mask equipped with one-way valves to prevent rebreathing expired gases. Arterial blood gas determinations (Radiometer, Copenhagen, Denmark) were made under normoxic and hypoxic conditions to document \( pH \) and arterial \( P_{O_2} \) and \( P_{CO_2} \). Measurements of heart rate, pulmonary and systemic arterial blood pressures, and cardiac output were made in room air and while the animals were breathing a hypoxic gas mixture (fractional concentration of inspired \( O_2 = 0.11–0.13 \)). The animals breathed the hypoxic gas mixture continuously for ~80–90 min, which was the length of time required to measure and record pulmonary arterial pressures and cardiac outputs both at baseline and during drug infusions. Approximately 5–7 min were allowed between each drug dose for a steady state to be achieved.

Acetylcholine and sodium nitroprusside (Sigma Chemical, St. Louis, MO) were dissolved in 0.9% NaCl at concentrations of 300 \( \mu g/ml \) and were administered by continuous infusion by utilizing Harvard infusion pumps at rates of 1, 3, 6, and 9 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) in the pulmonary artery during both room air and hypoxic conditions. Data were collected after 5 min of drug infusion, at which time hemodynamic measurements appeared stable. Drug doses were administered serially without interruption beginning with the smallest dose. Two animals received the acetylcholine infusion first followed by nitroprusside, and one animal received the nitroprusside infusion followed by acetylcholine. Sufficient time (10–15 min) was allowed between drugs for arterial pressures and heart rates to return to predrug values.

Norepinephrine was administered undiluted by continuous infusion directly in the pulmonary artery after recovery from both acetylcholine and nitroprusside at a rate of 20 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) for a period of 3 min under normoxic conditions, with data collected during the period of maximum norepinephrine effect.

**Histology and morphological analysis.** After completion of the hemodynamic studies, the yaks were anticoagulated by administration of 10,000 U of intravenous porcine heparin, anesthetized with 1.2 g of intravenous pentobarbital sodium, and killed by exsanguination. The heart and lungs were removed en bloc. The left caudal lobe was dissected free and prepared for histological examination as reported previously (16). Briefly, the lung lobe was perfusion fixed via the left caudal lobe bronchus (25–30 cmH\(_2\)O) and left lobar pulmonary artery (at the measured in vivo mean pulmonary arterial pressure) with 10% phosphate-buffered formaldehyde, \( pH \) 7.40. After 20–24 h of fixation, the lobar pulmonary artery was perfused and lobar bronchus was lavaged with 70% ethanol to remove the formaldehyde, and the lung was then stored in fresh 70% ethanol at room temperature until the time of histological processing. At least six tissue blocks were taken randomly from the left caudal lobe of each lung, embedded in paraffin, cut into 4-\( \mu m \)-thick sections, and stained with hematoxylin and eosin, trichome, or Verhoeff van Gieson (VVG) stains by use of standard histological techniques. The percent medial thickness (medial wall thickness/external vessel diameter \( \times 100 \)) of \( \geq 50 \) small pulmonary arteries (100–300 \( \mu m \) in diameter) was calculated for each animal. The external vessel diameter was taken as the mean of two mea-
measurements made at right angles to each other, and medial thickness was estimated as the mean of four measurements around the circumference of each vessel (17). The number of complete elastic lamellae present in elastic pulmonary arteries 4,000 μm in diameter was counted. Lung and conducting pulmonary artery sections from an age-matched Hereford calf that had lived at 3,000 m altitude in South Park, CO and suffered from brisket disease were prepared in a similar fashion and served as a comparison altitude-sensitive bovine species (see Figs. 1B, 2B, and 3B).

Right ventricular mass was determined as a criterion for sustained pulmonary arterial hypertension during life. The heart was dissected free from the great vessels, and the atria were removed. The weights of the heart, right ventricular free wall (RV), and left ventricle plus intraventricular septum (LV + S) were obtained after careful removal of fat and cardiac valves. From these data the RV/LV + S and right ventricular-to-total ventricular weight (RV/T) ratios were calculated.

Scanning electron microscopy. Yak and cow lungs to be examined by scanning electron microscopy were obtained from 26 male yaks and 10 domestic male cows ~1 yr old. The lungs were perfused fixed via the lobar pulmonary artery at a pressure of 25–30 mmHg with a 2.5% buffered glutaraldehyde solution. Small intralobar pulmonary arteries 300–500 μm in diameter were then dissected free from surrounding lung tissue and cut longitudinally. The vessels were dehydrated in increasing concentrations of ethanol, air-dried, and covered with palladium, and the pulmonary artery endothelial surface examined with a Philips PSEN-500 scanning electron microscope (12).

Statistical analysis. Dose-response curves were analyzed by analysis of variance (ANOVA). Comparisons between doses were made by Fisher’s protected least-significant difference test at the 95% significance level. Blood gas values in room air and hypoxic conditions were compared with values from same animals breathing either 11–13% O2 or room air during an infusion of norepinephrine or nitroprusside into the pulmonary artery.

### Results

#### Hemodynamic studies.**

During room air breathing, mean pulmonary arterial pressures in the yak (Table 1) were slightly lower than either the 29 mmHg reported for yearling steers at 1,600 m or the 28 mmHg reported for cattle <1 yr old at sea level (7, 24). However, cardiac output values of 11.3 l/min in the 100-kg yaks (Table 1) were similar to values of 11.3 l·min⁻¹·100 kg body wt⁻¹ in the steers (7). The administration of hypoxic gas decreased arterial P0₂ but did not change arterial PCO₂ or pH (Table 1). Pulmonary arterial pressure (+42%) and cardiac output (+22%) were both noted to increase with hypoxic exposure (Table 1). The increase in pulmonary resistance, however, was only 17%. Systemic blood pressure was unchanged. Total systemic resistance decreased by 22%. Norepinephrine infused at a dose of 20 μg·kg⁻¹·min⁻¹ in the pulmonary artery under room air conditions to induce vasoconstriction increased pulmonary arterial pressure and decreased cardiac output and stroke volume (Table 1). Total pulmonary resistance more than tripled. Systemic blood pressure, heart rate, and total systemic resistance increased.

Infusion of acetylcholine in the yak pulmonary artery under room air conditions had no effect on mean pulmonary or systemic blood pressures at any infusion rate studied (Table 2). However, cardiac output increased at the higher infusion rates, resulting in decreases in total pulmonary and systemic resistances. Under hypoxic conditions, acetylcholine infusion did not change pulmonary arterial pressure. Cardiac output did increase, however, resulting in a decrease in calculated pulmonary resistance (Table 2). A decrease in systemic resistance was also observed. Heart rate increased.

Nitroprusside infusion into the pulmonary artery under room air conditions did not change mean pulmonary arterial pressure or cardiac output, but there was a small (22%) decrease in calculated pulmonary resistance at the highest dose (Table 3). Systemic resistance also decreased by 22% at the highest infusion rate. Under hypoxic conditions, nitroprusside infusion decreased mean pulmonary arterial pressure but cardiac output did not change. Pulmonary resistance decreased by 37% (Table 3). Systemic pressure also decreased, and systemic resistance decreased 33%.

#### Heart weight determinations.**

The weight of RV was 130 ± 6 g, and that of LV + S was 327 ± 16 g. The calculated RV/LV+S was 0.40 ± 0.02. RV/T was 0.29 ± 0.02.

#### Histology and morphometric analysis.**

Histochemical analysis of trichrome- and VVG-stained sections of yak lung demonstrated the small pulmonary arteries (100–300 μm) to be extremely thin walled with a single layer of smooth muscle and little extracellular matrix (Fig. 1A). In comparison, lung sections from an age-matched calf that had died of brisket disease while living near South Park, CO (altitude 3,000 m) showed the small pulmonary arteries (100–300 μm) to be extremely thin walled with a single layer of smooth muscle and little extracellular matrix deposition (Fig. 1B).

### Table 1. Measurements of hemodynamic and blood gas responses to vasoconstrictors

<table>
<thead>
<tr>
<th>Room Air</th>
<th>Hypoxia (11-13% O₂)</th>
<th>Norepinephrine (20 μg·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>93 ± 8</td>
<td>107 ± 7</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>11.3 ± 0.7</td>
<td>13.8 ± 0.7*</td>
</tr>
<tr>
<td>SV, ml</td>
<td>122 ± 6</td>
<td>129 ± 12</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>24 ± 1</td>
<td>34 ± 1*</td>
</tr>
<tr>
<td>Psys, mmHg</td>
<td>171 ± 4</td>
<td>168 ± 6*</td>
</tr>
<tr>
<td>TPR, mmHg·l⁻¹·min⁻¹</td>
<td>2.8 ± 0.2</td>
<td>2.6 ± 0.9*</td>
</tr>
<tr>
<td>TPR, mmHg·l⁻¹·min⁻¹</td>
<td>15.9 ± 1.7</td>
<td>13.0 ± 1.4*</td>
</tr>
<tr>
<td>pH</td>
<td>7.55 ± 0.02</td>
<td>7.55 ± 0.01</td>
</tr>
<tr>
<td>Paco₂, Torr</td>
<td>90 ± 11</td>
<td>42 ± 3*</td>
</tr>
<tr>
<td>Pao₂, Torr</td>
<td>32 ± 1.5</td>
<td>30 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE for heart rate (HR), cardiac output (CO), stroke volume (SV), mean pulmonary arterial pressure (Ppa), mean systemic arterial pressure (Psys), total pulmonary resistance (TPR), total systemic resistance (TSR), arterial O₂ and CO₂ partial pressures (Pao₂ and Paco₂), and arterial pH (pH) in blood sampled from left saphenous artery. Hemodynamic and blood gas measurements in native high altitude yak breathing room air at 730 m altitude are compared with values from same animals breathing either 11–13% O₂ or room air during an infusion of norepinephrine or nitroprusside into the pulmonary artery.

† Significantly different compared with room air (P < 0.05, ANOVA for hemodynamics, paired Student’s t test for blood gas values).

* Significantly different compared with hypoxia (P < 0.05, ANOVA).
TABLE 2. Hemodynamic measurements related to acetylcholine infusion

<table>
<thead>
<tr>
<th>Acetylcholine Dose, μg · kg⁻¹ · min⁻¹</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>Hypoxia</td>
<td>Room air</td>
<td>Hypoxia</td>
<td>Room air</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>90 ± 9</td>
<td>96 ± 6</td>
<td>99 ± 3</td>
<td>125 ± 13*</td>
<td>131 ± 10</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>25 ± 2</td>
<td>34 ± 2</td>
<td>24 ± 2</td>
<td>33 ± 2</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>10.6 ± 0.8</td>
<td>13.4 ± 1.0</td>
<td>12.6 ± 0.7</td>
<td>13.9 ± 1.0</td>
<td>15.3 ± 0.9*</td>
</tr>
<tr>
<td>TPR, mmHg · l⁻¹ · min</td>
<td>2.0 ± 0.2</td>
<td>2.6 ± 0.1</td>
<td>1.9 ± 0.1*</td>
<td>2.3 ± 0.1*</td>
<td>1.6 ± 0.1*</td>
</tr>
<tr>
<td>CO₂, l/min</td>
<td>10.8 ± 0.8</td>
<td>13.4 ± 1.0</td>
<td>12.6 ± 0.7</td>
<td>13.9 ± 1.0</td>
<td>15.3 ± 0.9*</td>
</tr>
<tr>
<td>TPR, mmHg · l⁻¹ · min</td>
<td>16.8 ± 1.4</td>
<td>13.2 ± 1.0</td>
<td>13.2 ± 0.9*</td>
<td>12.6 ± 0.9</td>
<td>10.5 ± 1.0*</td>
</tr>
</tbody>
</table>
| Values are means ± SE. * Significantly different compared with baseline values (0 infusion rate) under room air and hypoxia conditions (P < 0.05, ANOVA).

The present study indicates that the native high-altitude yak has a minimal increase in pulmonary arterial pressure and resistance in response to alveolar hypoxia administered at an altitude of 730 m. Furthermore, morphological analysis demonstrates that these animals have a thin pulmonary vascular medial layer and virtually no smooth muscle in the small pulmonary arterioles <100 μm in diameter. The pressures, resistances, and vessel structure found in the yak are similar to those found in humans who have adapted to high altitude over thousands of years (8, 9) but are in contrast to those of the closely related domestic cow that typically doubles its pulmonary arterial pressure with hypoxia, has pulmonary arteries with a thick muscular coat (Fig. 2B), and has smooth muscle present in pulmonary arteries as small as 20 μm (1, 16, 22; Fig. 2B). In addition, the native high-altitude yak has no evidence of chronically increased pulmonary arterial pressures as evidenced by low RV/LV + S and RV/T ratios and the maintenance of thin-walled muscular and elastic pulmonary arteries. In fact, RV/LV + S and RV/T in the yak were approximately equal to those of the closely related domestic cow residing in Denver (RV/LV + S of 0.47, RV/T of 0.26) and much less than those of cattle living at high altitudes (2, 7, 11, 16).

The adaptive mechanism(s) responsible for the diminished hypoxic pulmonary vasoconstrictor response in high-altitude-adapted animals is unknown, although the fact that it is genetically transmitted has been best described in bovine species. Will et al. (22) and Weir et al. (19) demonstrated that offspring of cattle that were determined to be either susceptible or resistant to the development of brisket disease retained their respective susceptible or resistant trait for at least two generations. Also, Cruz et al. (4) performed cattle embryo experiments in which susceptible animal embryos that were transplanted into resistant female cows retained the susceptible trait postnatally. The yak's small hypoxic pulmonary vasoconstrictor response also appears to be trans-

TABLE 3. Hemodynamic measurements related to sodium nitroprusside infusion

<table>
<thead>
<tr>
<th>Sodium Nitroprusside Dose, μg · kg⁻¹ · min⁻¹</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>Hypoxia</td>
<td>Room air</td>
<td>Hypoxia</td>
<td>Room air</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>97 ± 15</td>
<td>115 ± 10</td>
<td>101 ± 14</td>
<td>123 ± 19</td>
<td>115 ± 13</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>22 ± 1</td>
<td>35 ± 2</td>
<td>22 ± 1</td>
<td>32 ± 9</td>
<td>21 ± 9</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>172 ± 7</td>
<td>172 ± 5</td>
<td>169 ± 4</td>
<td>188 ± 3*</td>
<td>166 ± 4*</td>
</tr>
<tr>
<td>TPR, mmHg · l⁻¹ · min</td>
<td>2.0 ± 0.2</td>
<td>3.0 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>3.0 ± 0.1</td>
<td>1.8 ± 0.1*</td>
</tr>
</tbody>
</table>
| Values are means ± SE. * Significantly different compared with baseline values (0 infusion rate) under room air and hypoxia conditions (P < 0.05, ANOVA).
FIG. 1. A: photomicrograph of small pulmonary artery (185 µm diam) from native high-altitude 6-mo-old yak with its accompanying airway. Mean pulmonary arterial pressure while breathing room air at 750 m altitude was 24 mmHg. Note thin vessel wall with little smooth muscle or extracellular matrix [Verhoeff van Gieson stain (VVG), ×100]. B: photomicrograph of size-matched (210-µm diam) small pulmonary artery from 6-mo-old calf that died of brisket disease at altitude of 3,000 m. Note increases in medial thickness and elastin deposition and presence of distinct adventitial layer compared with yak vessel (VVG, ×100).
mitted genetically. Anand et al. (3), in cross-breeding studies of yaks and cows, have suggested that the genetic transmission of an attenuated hypoxic vasoconstrictor response is via simple autosomal dominant inheritance.

In cattle resistant to the development of pulmonary hypertension and in the native high-altitude yak, the principal factor determining altitude resistance appears to be the maintenance of low pulmonary pressures with hypoxia. This hypothesis is supported by the work of Ou et al. (15), who have shown that rather than the actual
FIG. 3. A: photomicrograph of wall of elastic pulmonary artery 4,000 µm in diameter in 6-mo-old yak. Note presence of ~17-18 elastic lamellae (VVG, ×100). B: photomicrograph of wall of elastic pulmonary artery 4,000 µm in diameter from 6-mo-old calf that died of brisket disease. Note approximately equal number of elastic lamellae as in size- and age-matched yak elastic pulmonary artery despite greatly increased thickness of calf pulmonary arterial wall (VVG, ×100).
amount of pulmonary vascular smooth muscle present, it is the existence of a mechanism to blunt the hypoxic pulmonary vasoconstrictor response to chronic hypoxia that is the most important factor in the adaptation of a species to high altitude. This is suggested by the ability of the Madison strain of the Sprague-Dawley rat to survive when exposed to chronic hypoxic conditions even though it has a greater acute hypoxic pulmonary vasoconstrictor response than the Hilltop strain, which shows signs of chronic mountain sickness and has a high mortality on exposure to high altitudes. The Madison strain's hypoxic pulmonary vasoconstrictor response is, unlike the Hilltop strain's, attenuated on exposure to chronic hypoxia (15).
The findings presented here clearly demonstrate that the yak has a markedly attenuated hypoxic vasoconstrictor response compared with either a general domestic calf population or high-altitude-resistant domestic calves (16, 20, 23). Possible reasons for the blunting of the hypoxic pulmonary vasoconstrictor response during the process of adaptation to high altitude could include cellular changes in the smooth muscle cell itself, such as differences in calcium flux, actin-myosin linkages, or a change in responsiveness to vasodilator and/or vasoconstrictor substances. Indeed, pulmonary hypertension rat pulmonary vascular smooth muscle has a decreased responsiveness to nitroprusside possibly due to desensitization of the soluble guanylate cyclase fraction in the pulmonary vascular smooth muscle cell (18). Alternatively, changes in endothelial cell release of vasoactive substances could affect the underlying smooth muscle, resulting in blunting of the hypoxic pulmonary vasoconstrictor response.

Our data imply that endothelial regulation of pulmonary vascular tone may, indeed, be different in the yak than in cattle. Although the endothelium-independent vasodilator nitroprusside lowered pulmonary arterial pressure in both the hypoxic yak (present study) and calf (14), the failure of acetylcholine to lower pulmonary arterial pressure in the hypoxic yak was in striking contrast to its marked pressure lowering effect in the closely related altitude-sensitive hypoxic calf (14). This observation is consistent with a different role for endothelium-dependent vasodilation in these two members of the Bos genus. Further evidence that the pulmonary endothelium, rather than smooth muscle, might be important in the differences between yak and cow was the striking difference in endothelial morphology between the two animal species. For example, one might speculate that the larger, more metabolically active yak endothelial cells that possess an increased number of ribosomes and have more prominent mitochondrial cristae than those of domestic bulls (19) were somehow related both to low resting pulmonary vascular tone and lack of reactivity with alveolar hypoxia.

Morphologically, we have shown that yak pulmonary arterial walls remain very thin despite their exposure to chronic hypoxic conditions. The factor(s) responsible for either the maintenance of thin-walled pulmonary vessels or, alternatively, the increase in wall thickness in pulmonary hypertensive animals is unknown. Because the yak lives under chronically hypoxic conditions and yet has thin-walled pulmonary arteries, data presented here would suggest that hypoxia per se is not the principal stimulus for the increases in pulmonary artery wall cell proliferation and extracellular matrix production seen in hypoxic pulmonary hypertension. Hemodynamic forces such as increased pressure and flow thus appear to play a more important role in the structural changes (or lack thereof) seen in pulmonary vasculature exposed to chronic hypoxia. The yak pulmonary vasculature, by maintaining low pulmonary pressures under hypoxic conditions, is not subjected to increased hemodynamic forces and so may lack the stimulus for vascular cell proliferation and matrix protein production.

Interestingly, despite the yak having a vessel wall thickness less than one-third that of the domestic calf with brisket disease, the number of elastic lamellae in the conducting pulmonary arteries of the yak and calf was similar. This finding is consistent with those of Wolinsky and Glagov (25), who reported the number of elastic lamellar units in the aorta was proportional to the radius of the vessel regardless of wall thickness or animal species. Thus, in the process of both adaptation (yak) and extreme maladaptation (calf with brisket disease) to the chronic hypoxia of high altitude, the basic architecture of large pulmonary arteries is maintained even though pulmonary artery wall thickness may change dramatically.

In summary, this study demonstrates the exceptional adaptation of the species Bos grunniens to high altitude as demonstrated by its greatly diminished hypoxic pulmonary vasoconstrictive response, its thin-walled pulmonary arteries with little smooth muscle, and its lack of right ventricular hypertrophy, all of which are uncharacteristic for the closely related domestic cow member of the genus Bos when exposed to high-altitude environments (1–3, 11, 14, 16, 20, 21, 24). Differences in both endothelial cell morphology and response to the endothelium-dependent vasodilator acetylcholine between the high-altitude yak and low-altitude domestic calf suggest the evolutionary process of adaptation to chronically hypoxic environments may include changes not only in the amount of pulmonary vascular smooth muscle present but also in endothelial cell function and structure. These changes could subsequently contribute to the differences in pulmonary vascular tone and reactivity that exist between high-altitude-adapted and sensitive populations.

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