

ARTERIAL OXYGEN SATURATION IN TIBETAN AND HAN INFANTS BORN IN LHASA, TIBET

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Abstract Background. Reduced oxygen availability at high altitude is associated with increased neonatal and infant mortality. We hypothesized that native Tibetan infants, whose ancestors have inhabited the Himalayan Plateau for approximately 25,000 years, are better able to maintain adequate oxygenation at high altitude than Han infants, whose ancestors moved to Tibet from lowland areas of China after the Chinese military entered Tibet in 1951.

Methods. We compared arterial oxygen saturation, signs of hypoxemia, and other indexes of neonatal well-being at birth and during the first four months of life in 15 Tibetan infants and 15 Han infants at 3658 m above sea level in Lhasa, Tibet. The Han mothers had migrated from lowland China about two years previously. A pulse oximeter was placed on each infant's foot to provide measurements of arterial oxygen saturation distal to the ductus arteriosus.

Results. The two groups had similar gestational ages (about 38.9 weeks) and Apgar scores. The Han infants had lower birth weights (mean [\pm SE], 2773 \pm 92 g) than the Tibetan infants (3067 \pm 107 g), higher concentrations of cord-blood hemoglobin (18.6 \pm 0.8 g per deciliter, vs. 16.7 \pm 0.4 in the Tibetans), and higher hematocrit values

(58.5 \pm 2.4 percent, vs. 51.4 \pm 1.2 percent in the Tibetans). In both groups, arterial oxygen saturation was highest in the first two days after birth and was lower when the infants were asleep than when they were awake. Oxygen saturation values were lower in the Han than in the Tibetan infants at all times and under all conditions during all activities. The values declined in the Han infants from 92 \pm 3 percent while they were awake and 90 \pm 5 percent during quiet sleep at birth to 85 \pm 4 percent while awake and 76 \pm 5 percent during quiet sleep at four months of age. In the Tibetan infants, oxygen saturation values averaged 94 \pm 2 percent while they were awake and 94 \pm 3 percent during quiet sleep at birth and 88 \pm 2 percent while awake and 86 \pm 5 percent during quiet sleep at four months. Han infants had clinical signs of hypoxemia — such as cyanosis during sleep and while feeding — more frequently than Tibetans.

Conclusions. In Lhasa, Tibet, we found that Tibetan newborns had higher arterial oxygen saturation at birth and during the first four months of life than Han newborns. Genetic adaptations may permit adequate oxygenation and confer resistance to the syndrome of pulmonary hypertension and right-heart failure (subacute infantile mountain sickness). (N Engl J Med 1995;333:1248-52.)

REDUCED oxygen availability at high altitude is associated with increased neonatal and infant mortality. Two groups of people have lived at high altitude (3000 to 4500 m) in the Tibet Autonomous Region, People's Republic of China, for different lengths of time. Native Tibetans have inhabited the Himalayan Plateau for approximately 25,000 years.^{1,2} People of Han ancestry moved to Tibet from lowland central and southeastern China in large numbers after the Chinese military entered Tibet in 1951. Our hypothesis was that Tibetan infants, whose ancestors had resided at high altitude longer, are better able to maintain adequate oxygenation than Han infants.

Subacute infantile mountain sickness, characterized by dyspnea, cyanosis, facial edema, oliguria, pulmonary hypertension, and right-heart failure, has been described primarily in Han infants in Lhasa, Tibet.^{3,4} There is anecdotal information that some Han infants born at high altitude become ill in the first weeks to months of life, fail to thrive, and require relocation to a low altitude, where they recover completely. We therefore examined arterial oxygen saturation, signs of hypoxemia, and other indexes of neonatal well-being at

birth and during the first four months of life in 15 Tibetan infants and 15 Han infants at 3658 m above sea level in Lhasa.

METHODS

Subjects

We enrolled 15 Tibetan and 15 Han infants delivered consecutively at the People's Hospital of the Tibet Autonomous Region. All the mothers resided in Lhasa throughout their pregnancies. The only identified complications during pregnancy were light, first-trimester vaginal bleeding in one Han mother and second-trimester vaginal bleeding in one Tibetan mother. No mothers reported the use of medications or smoking during their pregnancies. One Tibetan infant was delivered by cesarean section. Another was delivered through meconium-stained amniotic fluid. All the infants were born at gestational ages of \geq 37 weeks,⁵ with normal cardiopulmonary physical examinations, no major congenital anomalies, and five-minute Apgar scores of \geq 7. The study protocol was approved by the Tibet Institute of Medical Science and the Institutional Review Board of the University of Colorado Health Sciences Center. Verbal informed consent from the parents was obtained for each neonate. Studies were performed from June through November 1991.

Study Techniques

Pulse oximetry was performed with the use of a Biox 3740 oximeter with a Flex II probe (Ohmeda, Louisville, Colo.) placed on the lateral aspect of the foot to provide measurements of arterial oxygen saturation distal to the ductus arteriosus. The pulse rate and arterial oxygen saturation were recorded continuously on a dedicated Series 37 printer (Ohmeda), which also documented signal strength from the plethysmographic wave form.

Pulse oximetry was performed 6 to 24 hours, 24 to 48 hours, one week, one month, two months, and four months after birth. The mean (\pm SE) actual measurement times were 15 \pm 6 hours, 39 \pm 7 hours, 7 \pm 1 days, 30 \pm 6 days, 55 \pm 4 days, and 120 \pm 7 days for the Tibetans and 16 \pm 5 hours, 38 \pm 8 hours, 7 \pm 1 days, 30 \pm 3 days, 59 \pm 5 days, and 123 \pm 4 days for the Han infants. Arterial oxygen saturation was meas-

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ured while the infants were quietly awake, feeding, in active sleep, and in quiet sleep. Infants were screened for intercurrent illness before each home study; fever or signs of lower respiratory infection excluded an infant from study, but nasal congestion alone was not grounds for exclusion. From the continuous recording of arterial oxygen saturation and pulse rate, steady-state values were recorded at 1-minute intervals for a total of 10 minutes during each of the four activities, as previously described.^{6,7} Measurements of awake infants were taken when they had open eyes and were not crying. Sleep states were defined by the clinical criteria of Prechtl.⁸ Active sleep was characterized by closed eyes with eye movements; small and frequent movements of the limbs, face, and head; irregular respirations; and variable pulse rate. Quiet sleep was defined as a relaxed state with eyes closed and still, regular respirations and pulse rate, and no gross body movements except occasional startles. Feeding was defined as actively sucking and swallowing from a breast or a bottle.

Respiratory rate was counted by auscultation for a one-minute period during sleeping and waking states. Tachypnea was defined as a respiratory rate of ≥ 60 breaths per minute from birth to two months of age and of ≥ 50 breaths per minute from two months to one year.⁹

Hemoglobin was measured in cord blood with a spectrophotometer (HemoCue, Mission Viejo, Calif.) calibrated with samples analyzed spectrophotometrically by the cyanmethemoglobin technique.¹⁰ The hematocrit was determined with a microcentrifuge.

Supplemental oxygen is not routinely used in the resuscitation of newborns in Lhasa. In the nursery, its use was limited to infants who consistently appeared cyanotic. Infants were breathing room air during all oximetry studies. A low-flow nasal cannula was used to administer oxygen to one Han infant for 30 minutes after birth and to another at 38 to 43 hours of age, after the second oximetry study. No Han infant received supplemental oxygen after discharge from the hospital. No Tibetan infant received supplemental oxygen.

Statistical Analysis

Values for arterial oxygen saturation and pulse rate were averaged for each infant during each activity at each study time. Data are reported as group means \pm SE. Arterial oxygen saturation and respiratory rates were compared among groups, activities, and study times with the use of repeated-measures analysis of variance (SAS Institute, Cary, N.C.).¹¹ The characteristics of the Han and Tibetan groups were compared with the use of Student's *t*-test or the Kruskal-Wallis test, as appropriate. Frequencies were compared between groups with the chi-square test or Fisher's exact test. Two-tailed *P* values of <0.05 were considered to indicate statistical significance.

RESULTS

The Han and Tibetan mothers differed in the altitude at which they had been born and in the length of time they had lived at high altitude (Table 1). These differences reflected the study design. The two groups of neonates had similar gestational ages and Apgar scores (Table 1). The Han infants had lower birth weights (2773 ± 92 g) than the Tibetan infants (3067 ± 107 g), although values in both groups were lower than would be considered normal for full-term white infants born at sea level in the United States (3521 ± 480 g).¹² Two Han newborns, but none of the Tibetan newborns, were small for their gestational ages.^{13,14} Cord-blood hemoglobin concentrations and hematocrit values were significantly higher in the Han infants (18.6 ± 0.8 g per deciliter and 58.5 ± 2.4 percent, respectively) than in the Tibetan infants, who had values for hemoglobin (16.7 ± 0.4 g per deciliter) and hematocrit (51.4 ± 1.2 percent) that were similar to normal values for full-term infants in the United States (16.8 g per deciliter and 53 percent, respectively).¹⁵

In both groups, arterial oxygen saturation was highest in the first two days after birth (Han infants: 92 ± 3

Table 1. Group Characteristics of 15 Han and 15 Tibetan Mother-and-Infant Pairs.*

CHARACTERISTIC	HAN	TIBETAN
Mother		
Age range (yr)	20–28	20–30
Parity	1.3 \pm 0.1	1.3 \pm 0.1
Altitude of birthplace (m)	<500	>3000†
Years of residence at >3000 m	2 \pm 1	25 \pm 1†
Infant		
Birth weight (g)	2773 \pm 92	3067 \pm 107‡
Gestational age (wk)	38.9 \pm 0.4	38.9 \pm 0.4
Sex (F/M)	8/7	9/6
Apgar score		
1 min	8	8
5 min	10	9
Cord-blood hemoglobin (g/dl)	18.6 \pm 0.8	16.7 \pm 0.4‡
Cord-blood hematocrit (%)	58.5 \pm 2.4	51.4 \pm 1.2§

*Plus-minus values are means \pm SE.

†*P*<0.001.

‡*P*=0.04.

§*P*=0.01.

percent while awake at one day and 91 ± 4 percent at two days; Tibetan infants: 94 ± 2 percent while awake at one day and 93 ± 2 percent at two days). By the end of the first week after birth these values had fallen to 87 ± 6 percent while awake for the Han infants and 89 ± 3 percent for the Tibetan infants (Fig. 1). At one week, arterial oxygen saturation during quiet sleep was 84 ± 9 percent in the Han infants and 87 ± 5 percent in the Tibetans (*P*<0.001). Respiratory frequency in awake Han infants declined from 57 breaths per minute at one month to 45 breaths per minute at four months (Fig. 2). The Tibetan infants had an elevated respiratory rate (58 breaths per minute) at two months of age. There was no correlation between arterial oxygen saturation and respiratory frequency in either group.

Arterial oxygen saturation was lower in the Han infants than in the Tibetan infants in all states at all times (*P*<0.001 by repeated-measures analysis of variance). It declined in the Han infants during quiet sleep from 84 ± 9 percent at one week after birth to 76 ± 5 percent at four months. For the Tibetans, arterial oxygen saturation was 87 ± 5 percent at one week and 86 ± 5 percent at four months (Fig. 1). Differences between values for waking and sleeping infants were greater in the Han group than in the Tibetan group (*P*=0.009).

In the first four months of life, Han infants had clinical signs of hypoxemia more frequently than Tibetan infants (Table 2). Fourteen of 15 Han infants repeatedly had cyanosis during sleep, when feeding, and with minor respiratory illnesses. A transient murmur and gallop developed in one Han infant on day 2 of life but resolved after oxygen was administered. Pedal edema developed in another Han infant at one month; central cyanosis, marked acrocyanosis, and cold hands and feet developed in a third Han infant. Cyanosis developed in one Tibetan infant during periodic breathing while she was asleep at one, two, and four months; four Tibetan infants were observed to be cyanotic on a single occasion each while they were asleep or feeding. No signs of pulmonary hypertension or right-heart failure developed in any Tibetan infant.

Six Han and two Tibetan infants were lost to follow-up. Four Han infants were sent to a lower altitude be-

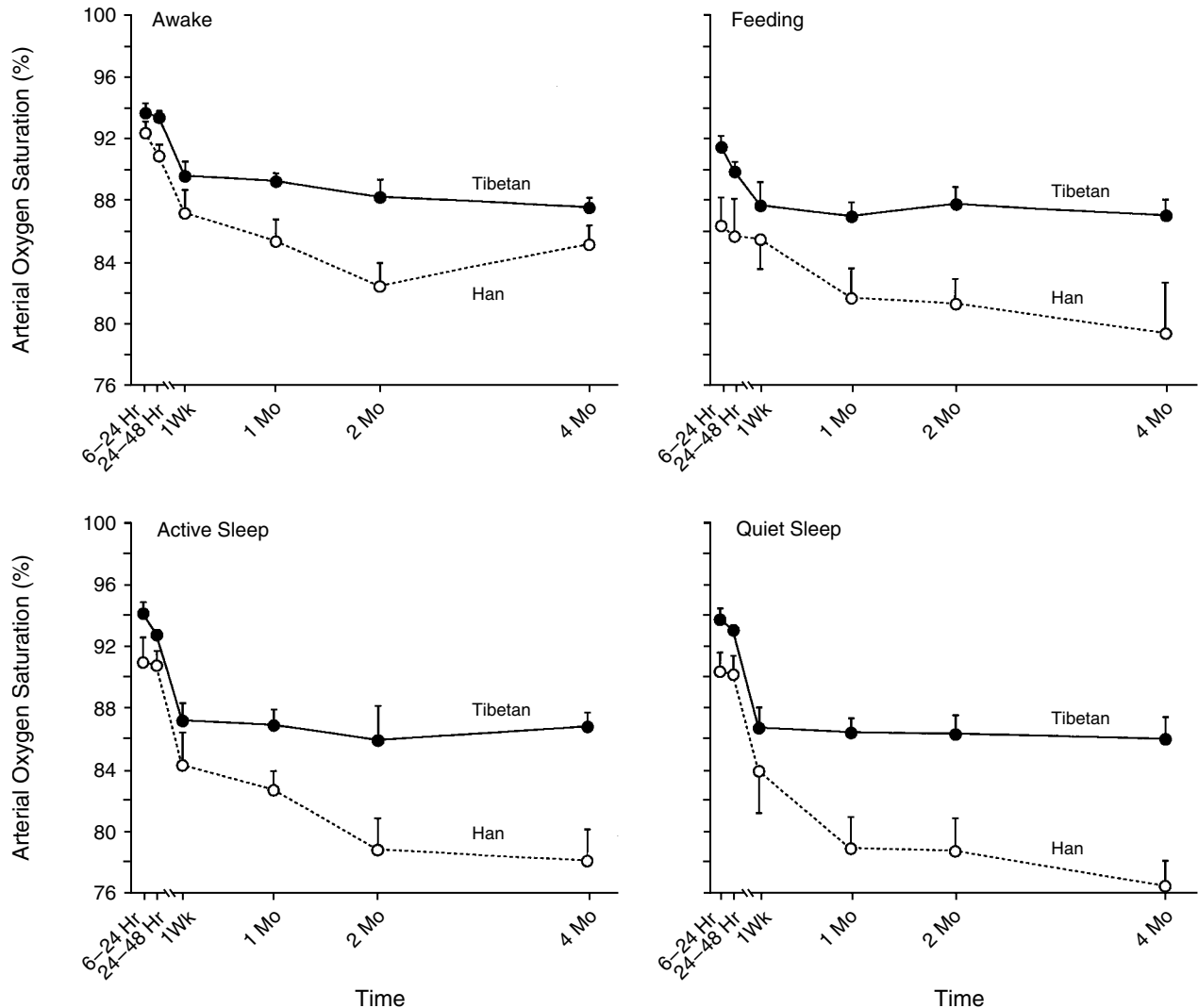


Figure 1. Mean (\pm SE) Arterial Oxygen Saturation in Tibetan and Han Infants at Each Study Time while Awake, Feeding, in Active Sleep, and in Quiet Sleep.

The values for the Tibetan infants were significantly greater than those for the Han infants ($P < 0.05$ by Student's *t*-test for all comparisons) at one month of age and later in all states except waking and feeding at four months. Observations were made in 15 Han infants and 15 Tibetan infants from birth through one month of age, in 11 Han and 13 Tibetan infants at two months of age, and in 9 Han and 13 Tibetan infants at four months of age.

tween one and two months after birth; two more departed between two and four months after birth. Their parents cited family reasons for returning to their home districts but also expressed concern about poor feeding and growth and chronic diarrhea. Three of these infants had values for arterial oxygen saturation of 76 to 78 percent during quiet sleep before departure, but other Han infants who remained in Lhasa had values as low as 63 to 66 percent. No Han infants with complete follow-up died during the study period. One Tibetan infant died of meningitis at six weeks of age. Another moved outside Lhasa and was unavailable for study after one month.

DISCUSSION

In this study of 30 infants born in Lhasa, we found that Tibetan newborns had higher values for arterial

oxygen saturation at birth and during the first four months of life than Han newborns. The results of pulse oximetry correlate well with direct measurements of oxygen saturation obtained in blood specimens by co-oximetry in neonates and infants,¹⁶ even at very low oxygen-saturation values, if the pulse amplitude is adequate.¹⁷ Measurements were made only when the pulse wave form displayed on the oximeter was clear and full. The oximeter probe was placed on the foot to measure postductal arterial oxygen saturation. Fetal and adult hemoglobin differ little in their light absorption at the wavelengths used. Therefore, the change in the predominance of hemoglobin type from fetal to adult in the first several months of life is likely to have introduced negligible error.¹⁸

The differences in arterial oxygen saturation between the Han and Tibetan infants increased between one

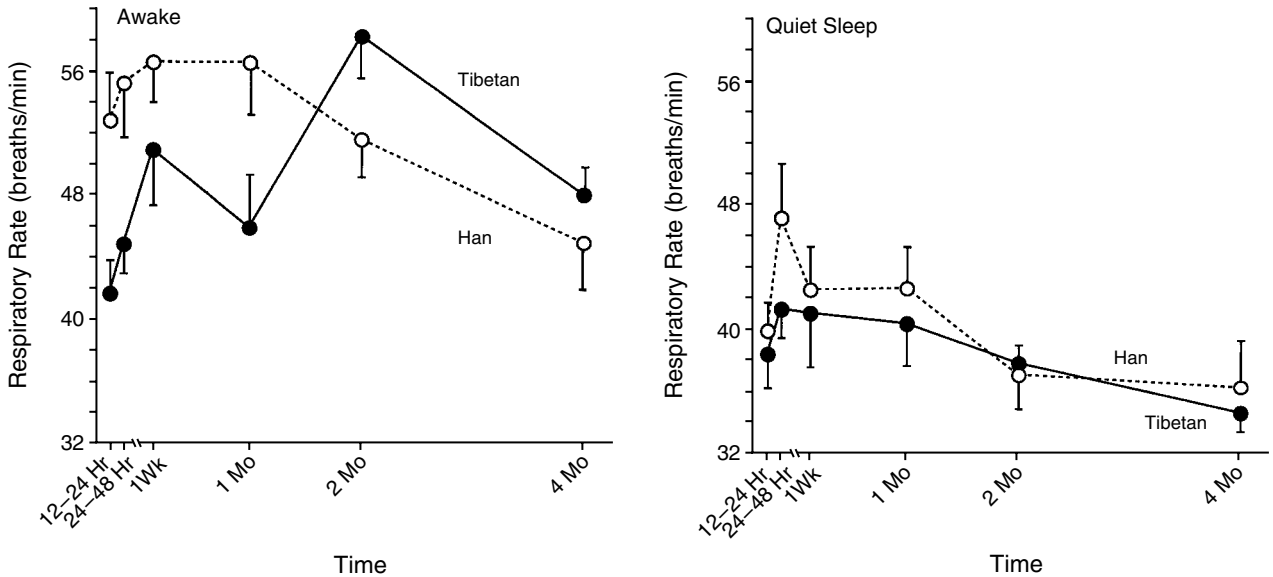


Figure 2. Mean (\pm SE) Respiratory Rate in Tibetan and Han Infants while Awake and during Quiet Sleep at Each Study Time. The values for the Han infants were significantly greater than those for the Tibetan infants ($P < 0.05$) during the first 48 hours and at one month in the waking state. Observations were made in 15 Han and 15 Tibetan infants from birth through one month of age, in 11 Han and 13 Tibetan infants at two months of age, and in 9 Han and 13 Tibetan infants at four months of age.

week and four months after birth. The fall in these values in Han and Tibetan neonates by the end of the first week of life was consistent with observations in Colorado infants at 3100 m above sea level⁶ but differed from the pattern of stable or increasing oxygen saturation reported in infants at sea level¹⁹ or 1610 m above sea level.⁷ Longitudinal studies in Colorado residents at 3100 m showed a subsequent rise in these values throughout the early months of infancy.⁶ The lower values observed in sleeping infants than in waking ones after one week of age are consistent with observations at sea level¹⁹ and at 1610 m and 3100 m above sea level.^{6,7}

Signs of hypoxemia were more prevalent in Han infants than in Tibetan infants; however, the assessment of health status was limited to clinical examinations and interval histories taken from parents. Serial growth measurements and formal developmental evaluations were not performed. Lower birth weights and higher hemoglobin concentrations and hematocrits among the

Han infants suggested relative fetal hypoxemia.²⁰ The protection of Tibetans from altitude-associated intrauterine growth retardation²¹ may reflect an increased fetal oxygen supply achieved in pregnant Tibetan women by redirection of pelvic blood flow to the uteroplacental circulation.²²

The physiologic mechanisms responsible for the observed differences in arterial oxygen saturation could involve one or more of the initial steps in the oxygen-transport system: ventilation, alveolar-arterial oxygen diffusion, hemoglobin-oxygen affinity, or pulmonary perfusion. Decreased minute ventilation or increased periodic breathing may underlie the fall in arterial oxygen saturation observed at one week of life and values that are lower during sleep than during the waking state. Periodic breathing is increased in infants at high altitude.^{23,24} Studies in adults at high altitude have shown a relation between periodic breathing and low oxygen saturation.²⁵ Although periodicity was noted in

Table 2. Clinical Signs in Han and Tibetan Infants from Birth to Four Months of Age.

SIGN	24-48 HOURS		1 WEEK		1 MONTH		2 MONTHS		4 MONTHS	
	HAN (N = 15)	TIBETAN (N = 15)	HAN (N = 15)	TIBETAN (N = 15)	HAN (N = 15)	TIBETAN (N = 15)	HAN (N = 11)	TIBETAN (N = 13)	HAN (N = 9)	TIBETAN (N = 13)
	<i>number of observations</i>									
Respiratory										
Cyanosis during sleep	1	—	4	1	8	1	6	2	7	1
Cyanosis when feeding	3	—	3	1	5	—	2	—	2	1
Cyanosis with upper respiratory infection	—	—	—	—	1	—	2	—	—	—
Circulatory										
Pedal edema	—	—	—	—	1	—	—	—	—	—
Acrocyanosis and cold hands and feet	—	—	—	—	1	—	—	—	—	—
Gallop rhythm	1	—	—	—	—	—	—	—	—	—
General										
Poor feeding or failure to thrive	—	—	—	—	—	—	1	—	—	—

both Tibetan and Han infants, this was not systematically quantitated, nor was minute ventilation measured.

A shift in the oxyhemoglobin-binding curve can change arterial oxygen saturation without changing the partial pressure of arterial oxygen. A postnatal increase in the level of 2,3-diphosphoglycerate promotes the release of oxygen from hemoglobin and thus lowers arterial oxygen saturation for a given partial pressure of arterial oxygen in the first week of life at sea level.²⁶ Adults who were born at high altitude and remained there have elevated 2,3-diphosphoglycerate levels^{27,28}; we are unaware of any available information on levels of this chemical or on the position of oxyhemoglobin dissociation curves for infants at high altitude.

Right-to-left shunting may lower arterial oxygen saturation. Persistence of right-to-left shunting across the foramen ovale and the ductus arteriosus has been documented in people at high altitude.²⁹ We did not perform echocardiography to evaluate the possible persistence of intracardiac and extracardiac shunts or to estimate pulmonary-artery pressure.

Differences in pulmonary-artery pressure may underlie the differences in arterial oxygen saturation and in clinical outcomes between Han and Tibetan infants at high altitude. Oxygen saturation approaching 80 percent, as recorded in Han infants during sleep, has been shown to produce hypoxic pulmonary hypertension in susceptible infants.³⁰ Newborns at 4540 m above sea level in Peru showed a persistence of near-systemic values for pulmonary-artery pressure for several days,³¹ in contrast to the rapid postnatal fall in pulmonary-artery pressure at sea level.³² Children under five years of age at 4330 m and 4540 m in Peru had elevated pulmonary-artery pressures and increased pulmonary vascular resistance as compared with children at sea level.³³

Histologic and clinical data from infants in Lhasa support differences between the two groups in susceptibility to the development of pulmonary-artery hypertension. Fifteen infants (14 Han and 1 Tibetan) who died with symptoms of subacute infantile mountain sickness had medial hypertrophy of small pulmonary arteries, muscularization of pulmonary arterioles, and severe right ventricular hypertrophy and dilation.³ A control group of Tibetan infants had normal thin-walled pulmonary arteries and arterioles after four months of age.

In summary, in a comparison of two groups of infants in Lhasa at 3658 m above sea level, arterial oxygen saturation was significantly higher from birth to four months of age in native Tibetan infants than in Han infants. Differences in the pulmonary vasoconstrictor response to hypoxia, known to be influenced by genetic factors, may underlie the observed differences in arterial oxygen saturation between the two groups. Our data suggest that heritable characteristics selected through long residence at high altitude result in adequate arterial oxygen saturation in native people during neonatal life and early infancy.

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