

Higher Arterial Oxygen Saturation During Submaximal Exercise in Bolivian Aymara Compared to European Sojourners and Europeans Born and Raised at High Altitude

TOM D. BRUTSAERT,^{1*} MAURICIO ARAOZ,² RUDY SORIA,²
HILDE SPIELVOGEL,² AND JERE D. HAAS¹

¹Department of Anthropology, Cornell University, Ithaca, New York
²Instituto Boliviano de Biología de Altura, La Paz, Bolivia

KEY WORDS hypoxia; Amerindian; lung diffusion capacity; developmental adaptation; genetic adaptation; Tibet

ABSTRACT Arterial oxygen saturation (SaO₂) was measured at 3,600–3,850 m by pulse oximetry at rest and during submaximal exercise in three study groups: 1) highland Aymara natives of the Bolivian altiplano (n = 25); 2) lowland European/North American sojourners to the highlands with at least 2 months of acclimatization time to 3,600 m (n = 27); and 3) subjects of European ancestry born and raised at 3,600 m (n = 22). Aymara subjects maintained ~1 percentage point higher SaO₂ during submaximal work up to 70% of their maximal work capacity, and showed a smaller rate of decline in SaO₂ with increasing work compared to both European study groups. The higher-exercise SaO₂ of Aymara compared to Europeans born and raised at 3,600 m suggests genetic adaptation. The two European study groups, who differed by exposure to high altitude during their growth and development period, did not show any significant difference in either resting or exercise SaO₂. This suggests that the developmental mode of adaptation is less important than the genetic mode of adaptation in determining exercise SaO₂. A weak correlation was detected (across study groups only) between the residual forced vital capacity (FVC) and the residual SaO₂ measured at the highest level of submaximal work output (P = 0.024, R = 0.26). While firm conclusions based on this correlation are problematic, it is suggested that a part of the higher SaO₂ observed in Aymara natives is due to a larger lung volume and pulmonary diffusion capacity for oxygen. Results from this study are compared to similar studies conducted with Tibetan natives, and are interpreted in light of recent quantitative genetic analyses conducted in both the Andes and Himalayas. *Am J Phys Anthropol* 113:169–181, 2000.

© 2000 Wiley-Liss, Inc.

There are numerous comparative studies showing that high altitude (HA) native populations in the Andes and Himalayas maintain higher arterial oxygen saturation (SaO₂) during exercise at HA compared to acclimatized lowland groups (Sun et al., 1990; Ge et al., 1993, 1995; Zhuang et al., 1996; Chen et al., 1997; Schoene et al., 1990; Favier et al., 1995). In addition, Tibetan native neonates born at HA have higher

resting SaO₂ compared to neonates born to acclimatized lowland mothers (Niermeyer et al., 1995). The ability to maintain SaO₂ should be considered an important measure of adaptation to hypoxic stress, given the

*Correspondence to: Tom Brutsaert, Ph.D., Department of Anthropology, University at Albany, SUNY, 1400 Washington Ave., Albany, NY 12222. E-mail: tbrutsa@atasc.albany.edu
Received 3 November 1999; accepted 26 April 2000.

reduced ambient partial pressure of oxygen (PO_2) at HA and the increased challenge of providing sufficient O_2 for cellular metabolic processes, particularly during exercise. At least three modes of adaptation may explain the higher exercise SaO_2 of Andeans and Himalayans, including: physiological acclimatization (short-term and reversible), developmental adaptation (fixed traits acquired during the period growth and development), and genetic adaptation (Lasker, 1969). However, developmental and/or genetic mechanisms appear most likely in the case of the exercise SaO_2 phenotype, i.e., while physiological acclimatization to HA does result in a modest improvement in resting and exercise SaO_2 (Bender et al., 1989; Huang et al., 1984), even fully acclimatized lowland groups do not attain the high SaO_2 during exercise typically seen in Andeans and Himalayans (Ge et al., 1995; Zhuang et al., 1996; Favier et al., 1995).

Recent quantitative genetic studies of resting SaO_2 in Andean Aymara and Tibetan populations have raised the issue of genetic adaptation (Beall et al., 1994, 1997a, 1999a). In these studies, resting SaO_2 was measured within families, and the phenotypic variance was partitioned into additive genetic, shared household, and random environmental components. In the two Tibetan studies conducted thus far, a significant proportion of the age- and sex-adjusted variance measured in resting SaO_2 (from 21–39%) was attributed to additive genetic factors, with the overall pattern of variance best explained by a major gene conferring a 5–6 percentage point increase in resting SaO_2 . In contrast, in an Andean Aymara population, no significant proportion of the variance measured was attributed to additive genetic factors, i.e., the heritability of resting SaO_2 was not significantly different from zero. This is puzzling, given that other measures of the O_2 transport system, including chest dimensions, pulmonary function measures, hemoglobin concentration, and the hypoxic ventilatory response all show significant heritabilities in Andean, North American, and Himalayan populations (Moore et al., 1976; Saunders et al., 1976; Beall et al., 1994, 1999a; Mueller et al., 1980; Kramer, 1992). Three possibilities should be

considered with respect to this Andean study: 1) pleiotropic effects have masked the ability to detect additive genetic variance for the resting SaO_2 phenotype in Andeans; 2) environmental effects have masked the ability to detect additive genetic variance in Andeans; or 3) Andean populations are near fixation for an allelic variant that influences the resting SaO_2 phenotype (Beall et al., 1999a). If the latter is true, then two further possibilities should be considered: 1) fixation has occurred in the Andes for an adaptive allele by natural selection, or 2) fixation has occurred for a non-adaptive allele by genetic drift or some other historical process.

There is no present knowledge concerning a genetic polymorphism that influences resting SaO_2 . Thus, it is not straightforward to distinguish between the various possibilities given above. However, phenotypic comparisons between carefully selected population groups according to a migrant study design (Harrison, 1966) can yield information favoring one possibility over another. Specifically, if allele fixation has occurred by natural selection for an adaptive allele, then Andean populations should have higher resting and exercise SaO_2 when compared to populations who have had a lifetime of exposure to HA, but who are not native to HA. In the present study we focus on the exercise SaO_2 phenotype rather than resting SaO_2 , but these two phenotypes may be expressions of the same underlying genetic system, as the two measures are significantly correlated (Beall et al., 1999b). We show here that rural Aymara in Bolivia have higher exercise SaO_2 compared to acclimatized European sojourners to HA, and compared to Europeans born and raised at HA. These results suggest genetic adaptation, but firm conclusions in this regard will only be possible with the resolution of an underlying genetic system. At present it is not clear where attention should be focused, as the exercise SaO_2 phenotype is complex and depends on the functional interaction of ventilatory, pulmonary, cardiovascular, and hematological factors. Thus, it may be as important to focus on the question of how adaptation has occurred rather than if adaptation is genetic, developmental, or due to acclimatization. Schoene et al. (1990) ar-

gued that the higher SaO₂ in Andeans is made possible because of a larger pulmonary diffusion capacity for oxygen (DLO₂). While DLO₂ is problematic to measure, many studies of highland natives show larger pulmonary diffusion capacities for carbon monoxide (DLCO), which is easier to measure and strongly related to DLO₂ (Jones et al., 1992; Remmers and Mithoeffer, 1969; Dempsey et al., 1971; Vincent et al., 1978). Such findings, as well as the reduced alveolar-arterial oxygen partial pressure gradient (A-a) O₂ found in highland natives during exercise (Dempsey et al., 1971; Zhuang et al., 1996), point strongly to an increased DLO₂ as the factor responsible for higher exercise SaO₂ in Andeans. This in turn argues that the basis for genetic adaptation influencing SaO₂ lies with factors affecting lung volume or lung functional development at HA. We previously reported on the developmental and genetic components of one measure of lung volume, i.e., forced vital capacity (FVC), in these same subject groups (Brutsaert et al., 1999a). In the present study, we take advantage of the fact that FVC can be used as a proxy measure of lung diffusion capacity (see Cerney et al., 1973; DeGraff et al., 1970; Dempsey et al., 1971; Guleria et al., 1971; Johnson et al., 1985), and test the hypothesis that a larger DLO₂ explains the higher SaO₂ during exercise in Aymara by correlation analysis.

METHODS

Subjects and study design

Nonsmoking male subjects between ages 18–35 years were recruited by newspaper advertisement and contact with health professionals, university administrators, and community leaders. All subjects were screened to determine that they were in good health and gave consent after being informed of the risks and benefits associated with the study. The study protocol was approved by the Cornell University Human Subjects Committee, and the Human Subjects Committee of the Instituto Boliviano de Biología de Altura (IBBA, La Paz, Bolivia). The following are descriptions of the three subject groups studied:

1. High-altitude natives were rural Aymara-speaking Amerindians living on the Bolivian altiplano near the village of Pucarani, ~10 miles from the southern shore of Lake Titicaca (n = 25). These subjects were subsistence farmers, raising food crops and tending flocks of domesticated animals. These subjects may be considered the descendants of Amerindians who have had an approximately 10,000-year history in the high Andes (Cardich, 1994), although historic and genetic data make clear that such populations have experienced admixture with European populations since the time of the Spanish conquest (Chakraborty et al., 1985, 1989).
2. Acclimatized lowland sojourners to HA were expatriate European and North American professionals, born and raised at low altitude, and living and working in La Paz, Bolivia (n = 24). These subjects were studied after at least 2 months of acclimatization to high altitude, sufficient for full ventilatory, renal, and hematological acclimatization (Huang et al., 1984). Hemoglobin levels measured in these subjects confirmed hematological acclimatization to HA. The majority of these subjects had been at high altitude for longer than 2 months, with a mean exposure in the sample of 20.3 ± 6.9 (S.E.) months.
3. Europeans born and raised at high altitude (n = 22) came from established migrant communities in La Paz. While some of these migrants were the children or grandchildren of recent European migrants, the majority could trace at least one ancestral line back to Spanish migrants who arrived in Bolivia more than three generations ago. Family history interviews were used to establish no admixture with Amerindian populations. As an indicator of population admixture, four surnames were obtained from each subject (see Greksa, 1992; Chakraborty et al., 1989). No subject in this group had a surname of either Aymara or Quechua origin.

Subject characteristics

Standard anthropometric techniques (Weiner and Lourie, 1981) were used by the same investigator to measure height, weight,

and skinfolds (subscapular, suprailiac, biceps, and triceps) for each subject. Percentage of body fat (%body fat) and fat-free mass (FFM) were calculated from skinfold measurements according to equations given by Durnin and Womersley (1974). Hemoglobin concentration (Hb) was measured by a photometric method from capillary blood obtained by finger prick (Hemocue, Angellholm, Sweden). The Hemocue was calibrated according to specifications given by the manufacturer. Forced vital capacity (FVC) and peak oxygen consumption ($\text{VO}_{2\text{peak}}$) were measured according to methods described previously (Brutsaert et al., 1999a,b). $\text{VO}_{2\text{peak}}$, according to convention, was defined as the highest level of oxygen consumption at volitional fatigue occurring at the end of a graded exercise test.

Exercise testing

Aymara subjects were tested in the village of Pucarani, Bolivia (3,850 m, mean barometric pressure 471 mm Hg, mean temperature 17°C). Lowland subjects were tested at IBBA in La Paz, Bolivia (3,600 m, mean barometric pressure 499 mm Hg, mean temperature 19°C).

Each subject was given two identical submaximal exercise tests on separate days on a mechanically braked cycle ergometer. Each test began with a 5-min resting period with the subject seated on the cycle ergometer. Exercise bouts were 5 min in duration in order to achieve steady-state, and were separated by 5-min rest periods. Work levels were set at 1, 1.5, 2, and 2.5 kg resistance on the cycle ergometer, with subjects instructed to maintain a pedal cadence near 60 rpm. These are referred to as work levels 1–4 in the analyses which follow. During testing, heart rate (HR) was continuously monitored with a Polar HR monitor (Vantage XL, Electric Oy, Sweden), and arterial oxygen saturation (SaO_2) was monitored by a pulse oximeter with a sensor attached to an ear lobe which was massaged prior to exercise to stimulate blood flow (Criticare SO1+, Criticare Systems, Inc., Waukesha, WI). The steady-state HR and SaO_2 were determined as the average of readings taken every 30 sec during the last 2 min of each work period. During exercise testing, subjects inspired room air through a low-

resistance breathing valve, and the expired fractions of O_2 and CO_2 were measured continuously from a mixing chamber by gas analyzers calibrated to gas standards before each exercise test: an Applied Electrochemistry S-3A O_2 analyzer (AEI Technologies, Pittsburg, PA), and a Beckman LB-2 CO_2 analyzer (Beckman Instruments, Inc., Schiller Park, IL). Inspired minute ventilation ($V_{\text{E-ATP}}$) was measured by a dry gas meter calibrated with a 3-l syringe. These data were processed by an automated O_2 uptake system (REP-200B, Rayfield Electronics) to produce 30-sec-interval calculations of oxygen consumption ($\text{VO}_{2\text{t}}$), carbon dioxide production ($\text{VCO}_{2\text{t}}$), and minute ventilation ($V_{\text{E-BTPS}}$). The steady-state values for all exercise variables were determined as the average over the last 2 min of each 5-min exercise period. The respiratory exchange ratio (RER) and the ventilatory equivalent ($V_{\text{E}}/\text{VO}_{2\text{t}}$) at steady-state were calculated from these data. The steady-state work was calculated from the resistance setting on the cycle ergometer and the distance pedaled, again as an average over the last 2 min of work at each work level. Data from the two tests were combined for the analyses described below.

Analytic models, statistics, and repeatability

Group differences in anthropometric measures were tested by analysis of variance (ANOVA). Similarly, group differences in measured resting and exercise variables, including SaO_2 , were tested by ANOVA or analysis of covariance (ANCOVA) at rest and for each level of submaximal exercise from levels 1–4. ANOVA for repeated measures was used to test for SaO_2 differences between groups across all levels of exercise. Analytic models were as follows: ancestral (genetic) effects of HA exposure on SaO_2 were tested by comparing the Aymara natives to the Europeans born and raised at HA. Developmental effects of HA exposure were tested by comparing the two European subject groups who differed by the environment in which they were born and raised. The effect of FVC on exercise SaO_2 was tested by least squares linear regression. FVC and SaO_2 residuals were used in this

TABLE 1. Subject characteristics¹

	Aymara	Acclimatized European sojourners to HA ²	Europeans born and raised at HA
N	25	27	22
Age (years)	23.3 ± 0.9 ³	26.8 ± 0.9B	23.5 ± 1.3
Stature (cm)	162.8 ± 1.5 ^{3,4}	175.8 ± 1.3	175.3 ± 1.6
Weight (cm)	56.4 ± 1.0 ^{3,4}	70.3 ± 1.4	67.8 ± 2.2
FFM (kg)	47.8 ± 0.7 ^{3,4}	56.4 ± 1.0	54.3 ± 1.3
% body fat	15.2 ± 1.0 ^{3,4}	19.6 ± 0.8	19.2 ± 1.2
FVC (liters)	5.34 ± 0.14 ⁴	5.69 ± 0.15	5.81 ± 0.18
FVC adjusted for stature (liters)	5.96 ± 0.14 ^{3,4}	5.26 ± 0.12	5.52 ± 0.13
Hb g · dl ⁻¹	17.5 ± 0.2	17.6 ± 0.2	17.8 ± 0.3
VO _{2peak} ml · min ⁻¹ · kg ⁻¹	51.9 ± 1.7 ^{3,4}	41.8 ± 1.5	41.2 ± 2.2

¹ Values given as mean ± standard error.

² HA, high altitude.

³ Significantly different from acclimatized European sojourners to HA, $P \leq 0.05$.

⁴ Significantly different from Europeans born and raised at HA, $P \leq 0.05$.

analysis from the residual values obtained from the regression of FVC on height, and SaO₂ on V_E and VO₂. For all statistics, significance for main effects was assumed at $P \leq 0.05$. All statistics were performed using the GLM procedure of Systat Statistical Software, version 5.2 (Evanston, IL).

Repeat measurements of SaO₂ during exercise were made on one subject on 8 different days. The coefficient of repeatability was calculated as 1.2%, and defines the 95% confidence interval of expected difference between any two measurements of SaO₂ made on separate days (Bland and Altman, 1986).

RESULTS

Subject characteristics

Subject characteristics are given in Table 1. In general, Aymara subjects differed greatly from European subject groups. The Aymara were shorter, lighter, and had a lower FFM and %body fat compared to acclimatized sojourners and Europeans born and raised at HA. According to the study design, and to eliminate the effect of acclimatization, sojourners to HA were fully acclimatized to HA. In this regard, Hb levels were similar between groups, indicating full acclimatization to HA by all study groups. In two previous papers we reported on the FVC and the VO_{2peak} in these same subject groups (Brutsaert et al., 1999a,b). Presently, the FVC (adjusted for stature) and VO_{2peak} ml · min⁻¹ · kg⁻¹ are reported again to emphasize that these Aymara subjects have larger mass-specific measures of lung

volume and aerobic capacity at HA compared to Europeans. The reader is referred to the previous papers for details. Briefly, data suggest that both genetic and developmental factors explain the larger body size-specific lung volumes of Andean natives, while developmental factors alone explain the higher body size-specific VO_{2peak} in Andean natives.

Submaximal exercise

Although submaximal work levels (1–4) were given at a fixed external resistance, variations in pedaling frequency (from 50–70 rpm) explain the small work output (Watt) differences between study groups at any given level of work (Table 2). Because Aymara subjects tended to pedal slower due to unfamiliarity with the cycle ergometer, they did slightly less external work at each work level compared to the European subject groups. However, work efficiency between subject groups did not differ (unpublished results), i.e., the linear relationship between the metabolic cost of work (VO₂) and external work performed on the cycle ergometer was identical for all groups. Thus, the slightly lower VO₂ and VCO₂ at each work level in Aymara subjects is accounted for by the lower work rates they performed, and this fact likely explains part of the lower HR and RER seen in these subjects as well. Additionally, because of differences between groups in VO_{2peak}, there were differences between groups in the relative work output (percentage of VO_{2peak}) at any give submaximal work level

TABLE 2. Submaximal exercise results¹

	Rest	Work level 1	Work level 2	Work level 3	Work level 4
Aymara					
Watts ²	0	54 ± 1 ^{3,4}	85 ± 1 ^{3,4}	108 ± 2 ^{3,4}	137 ± 2 ^{3,4}
VO ₂ l · min ⁻¹	0.30 ± 0.01 ^{3,4}	1.00 ± 0.02 ^{3,4}	1.34 ± 0.02 ^{3,4}	1.58 ± 0.02 ^{3,4}	1.93 ± 0.03 ^{3,4}
VCO ₂ l · min ⁻¹	0.30 ± 0.02	0.90 ± 0.02 ^{3,4}	1.23 ± 0.02 ^{3,4}	1.51 ± 0.03 ^{3,4}	1.93 ± 0.03 ^{3,4}
RER	0.99 ± 0.03	0.90 ± 0.01 ⁴	0.92 ± 0.01 ^{3,4}	0.95 ± 0.01 ^{3,4}	1.00 ± 0.01 ⁴
V _E l · min ⁻¹	7.1 ± 0.5 ⁴	16.5 ± 0.3 ^{3,4}	22.3 ± 0.5 ^{3,4}	26.5 ± 0.6 ^{4,4}	34.6 ± 0.9 ^{3,4}
V _E /VO ₂	23.3 ± 1.1	16.5 ± 0.5 ^{3,4}	16.6 ± 0.4 ^{3,4}	16.7 ± 0.4 ^{3,4}	17.9 ± 0.4 ^{3,4}
HR bpm	76 ± 2 ³	98 ± 1.5 ^{3,4}	114 ± 2 ^{3,4}	121 ± 1 ^{3,4}	139 ± 2 ^{3,4}
% peak VO ₂	11 ± 1 ^{3,4}	36 ± 1 ⁴	48 ± 1 ⁴	56 ± 1 ⁴	69 ± 2 ⁴
Acclimatized European sojourners					
Watts ²	0	60 ± 2	93 ± 2	119 ± 3	154 ± 3
VO ₂ l · min ⁻¹	0.35 ± 0.01	1.07 ± 0.02	1.43 ± 0.03 ⁴	1.68 ± 0.03	2.18 ± 0.05
VCO ₂ l · min ⁻¹	0.33 ± 0.01	0.98 ± 0.02 ⁴	1.38 ± 0.03	1.70 ± 0.04 ⁴	2.04 ± 0.04 ⁴
RER	0.92 ± 0.02	0.92 ± 0.01 ⁴	0.96 ± 0.01	1.01 ± 0.01	1.07 ± 0.01
V _E l · min ⁻¹	8.0 ± 0.4	19.2 ± 0.4	27.4 ± 0.8	32.3 ± 0.9	43.1 ± 1.3
V _E /VO ₂	22.9 ± 1.1	18.0 ± 0.4	19.1 ± 0.4	19.2 ± 0.4	21.0 ± 0.4
HR bpm	85 ± 3	105 ± 1.8 ⁴	123 ± 2 ⁴	129 ± 2 ⁴	148 ± 2 ⁴
% peak VO ₂	12 ± 1	37 ± 1 ⁴	50 ± 1 ⁴	59 ± 1 ⁴	71 ± 2 ⁴
Europeans born and raised at HA					
Watts ²	0	59 ± 2	95 ± 2	121 ± 3	153 ± 4
VO ₂ l · min ⁻¹	0.35 ± 0.01	1.12 ± 0.03	1.52 ± 0.03	1.76 ± 0.03	2.42 ± 0.11
VCO ₂ l · min ⁻¹	0.34 ± 0.01	1.06 ± 0.04	1.46 ± 0.03	1.83 ± 0.04	2.14 ± 0.05
RER	0.99 ± 0.03	0.94 ± 0.01	0.96 ± 0.01	1.04 ± 0.01	1.14 ± 0.05
V _E l · min ⁻¹	8.6 ± 0.4	20.4 ± 1.0	27.9 ± 1.1	32.8 ± 1.0	42.8 ± 1.5
V _E /VO ₂	25.4 ± 1.2	18.4 ± 0.5	18.3 ± 0.4	18.7 ± 0.4	20.0 ± 0.5
HR bpm	82 ± 3	111 ± 3	132 ± 3	139 ± 3	159 ± 3
% peak VO ₂	13 ± 1	41 ± 1	56 ± 2	64 ± 2	78 ± 2

¹ Values given as mean ± standard error.

² Watts is a measure of work output during exercise on a cycle ergometer.

³ Significantly different from acclimatized European sojourners to HA, $P \leq 0.05$.

⁴ Significantly different from Europeans born and raised at HA, $P \leq 0.05$.

(Table 2). While Aymara subjects and European sojourners did not differ in this respect, both of these groups worked at lower relative work outputs during submaximal exercise compared to Europeans born and raised at HA (Table 2).

V_E during exercise was clearly lower in the Aymara subjects compared to Europeans, independent of variations in absolute or relative external work. The relative hypoventilation of Aymara during exercise is revealed by the significantly lower V_E/VO_2 , which as an index measure is independent of work rate. Europeans born and raised at HA and acclimatized European sojourners did not differ with respect to V_E or V_E/VO_2 during exercise.

Figure 1 shows the SaO₂ of study groups during submaximal exercise (levels 1–4), up to about 70% of maximal work capacity. SaO₂ decreased in all groups with increasing work output. Figure 1A (genetic model) is the comparison of Aymara with Europeans born and raised at HA. The Aymara

maintain a significantly higher SaO₂ during exercise, and also show a smaller rate of decline in SaO₂ with increasing exercise, compared to Europeans born and raised at HA (by ANOVA for repeated measures). Figure 1B (developmental model) is the comparison of European sojourners to HA with Europeans born and raised at HA. There are no significant differences in exercise SaO₂ between these two groups. Overall results did not change when the small differences in relative work output between groups were taken into consideration, i.e., controlling for the percentage of VO_{2peak} by ANCOVA had no effect on the model results.

Because SaO₂ is a functional variable which depends in large part on V_E , covariance models were constructed, holding constant the effect of V_E during exercise (Tables 3 and 4). In effect, these models test the hypothesis that developmental and/or genetic effects allow for a higher functional output (SaO₂) in the Aymara for the same

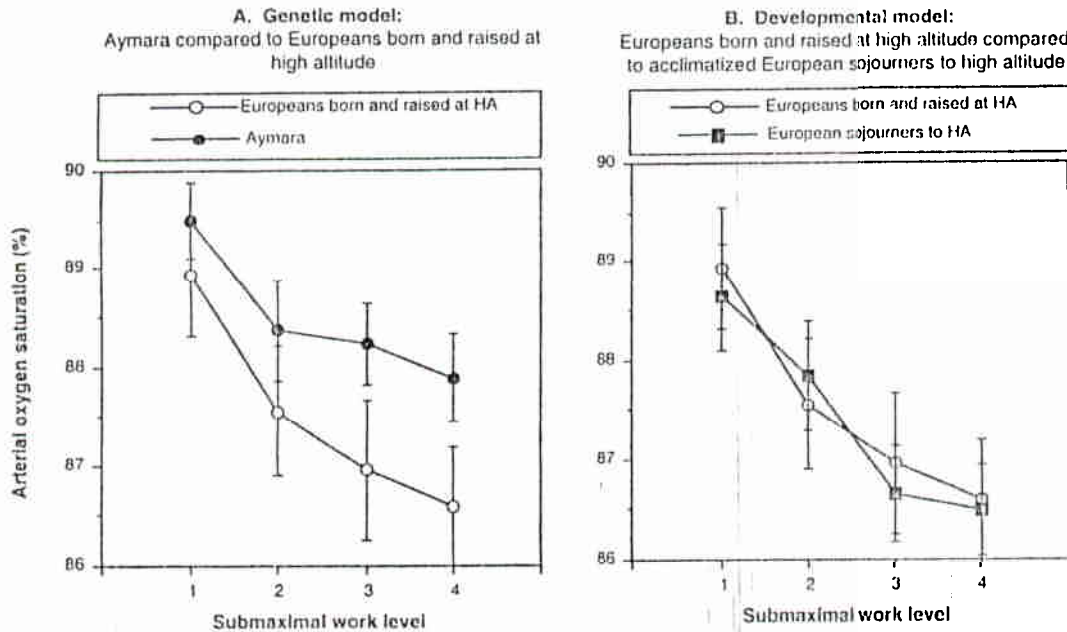


Fig. 1. Arterial oxygen saturation (%) with increasing submaximal work at 3,600–3,850 m in (A) Aymara compared to Europeans born and raised at 3,600 m, and (B) Europeans born and raised at 3,600 m compared to acclimatized European sojourners to 3,600 m. Aymara maintain a higher exercise SaO₂ compared to both European groups by ANOVA for repeated measures. Work levels 1–4 correspond to approximately 60, 90, 120, and 150 Watts, respectively. Error bars are SEM.

TABLE 3. Genetic effect models: mean and adjusted mean arterial oxygen saturation (SaO₂) at each of four submaximal workloads¹

	Aymara	Europeans born and raised at HA	P-value
Rest			
SaO ₂ (%), unadjusted mean	92.5 ± 0.6	91.9 ± 0.7	0.468 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	92.7 ± 0.6	91.7 ± 0.6	0.275 (ns)
Work level 1			
SaO ₂ (%), unadjusted mean	89.5	88.9	0.441 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	89.9 ± 0.5	88.5 ± 0.5	0.049*
Work level 2			
SaO ₂ (%), unadjusted mean	88.4	87.6	0.321 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	88.8 ± 0.6	87.1 ± 0.6	0.047*
Work level 3			
SaO ₂ (%), unadjusted mean	88.2	87.0	0.113 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	88.3 ± 0.6	86.9 ± 0.6	0.133 (ns)
Work level 4			
SaO ₂ (%), unadjusted mean	87.9	86.6	0.084 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	88.1 ± 0.5	86.3 ± 0.6	0.028*

¹ Adjusted means are from covariance analysis, holding constant the effect of oxygen consumption (VO₂) and ventilation (V_E) at each work level. Means ± standard error are given. P values are given for the comparison of Europeans born and raised at HA with acclimatized European sojourners to HA. ns, not significant. Unadjusted means are the same as those given in Figure 1B. HA, high altitude.

* P-values less than 0.05.

physiological input (V_E). Unadjusted mean SaO₂s at each exercise level are presented in Tables 3 and 4, as are the adjusted means from covariance analyses controlling for V_E

and VO₂. VO₂ was controlled to account for the small variations in work output between study groups discussed previously. In all models, at each workload, V_E was signifi-

TABLE 4. Developmental effect models: mean and adjusted mean arterial oxygen saturation (SaO₂) at each of four submaximal workloads¹

	Europeans born and raised at HA	Acclimatized European sojourners to HA	P-value
Rest			
SaO ₂ (%), unadjusted mean	91.9 ± 0.7	92.0 ± 0.7	0.855 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	92.3 ± 0.6	91.7 ± 0.7	0.454 (ns)
Work level 1			
SaO ₂ (%), unadjusted mean	88.6	88.9	0.714 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	88.7 ± 0.5	88.8 ± 0.6	0.866 (ns)
Work level 2			
SaO ₂ (%), unadjusted mean	87.8	87.6	0.739 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	87.7 ± 0.6	87.7 ± 0.6	0.995 (ns)
Work level 3			
SaO ₂ (%), unadjusted mean	86.7	87.0	0.713 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	86.1 ± 0.6	87.1 ± 0.7	0.291 (ns)
Work level 4			
SaO ₂ (%), unadjusted mean	86.5	86.6	0.883 (ns)
SaO ₂ (%), adjusted for VO ₂ (l · min ⁻¹) and V _E (l · min ⁻¹)	86.3 ± 0.5	86.8 ± 0.5	0.436 (ns)

¹ Adjusted means are from covariance analysis, holding constant the effect of oxygen consumption (VO₂) and ventilation (V_E) at each work load. Means ± standard error are given. P values are given for the comparison of Europeans born and raised at HA with acclimatized European sojourners to HA. ns, not significant. Unadjusted means are the same as those given in Figure 1B. HA, high altitude.

cantly related to SaO₂. Table 3 shows the genetic effect models, comparing Aymara with Europeans born and raised at HA. While higher in the Aymara, unadjusted mean SaO₂s were not significantly different between these two groups at any individual work level. However, adjusted mean SaO₂s were from 1–1.8 percentage points higher in Aymara compared to Europeans born and raised at HA at work levels 1, 2, and 4. Table 4 shows the developmental effect models, comparing European sojourners to HA with Europeans born and raised at HA. Both the unadjusted and adjusted mean SaO₂s were similar at rest and during exercise between these two groups.

To test the hypothesis that higher SaO₂ during exercise is made possible by larger lungs (and thus presumably by a larger DLO₂) in the Aymara vs. Europeans, a regression model was constructed relating the residual FVC (controlling for stature) with the residual SaO₂ (controlling for VO₂ and V_E) (Fig. 2). SaO₂ values from work level 4 were used in this analysis, where group differences in SaO₂ were greatest. FVC residuals were used because they give a non-biased expression of relative lung size for a subject in this study. SaO₂ residuals remove the effect of V_E on SaO₂, and allow for a more direct test of the FVC-SaO₂ hypothesis. Figure 2 shows a significant positive

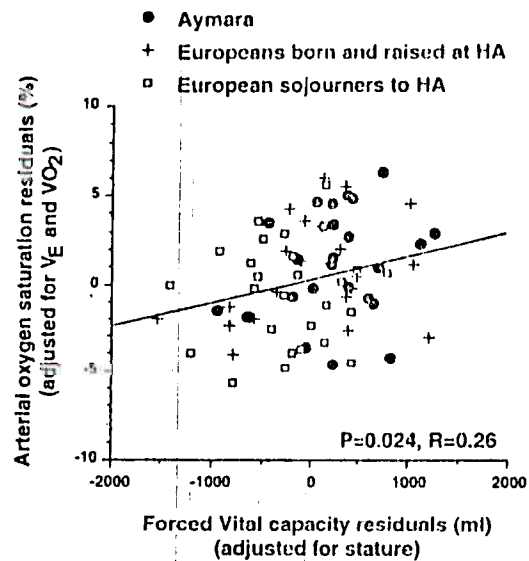


Fig. 2. Relationship between arterial oxygen saturation (SaO₂) residuals and forced vital capacity (FVC) residuals for the combined sample of the three subject groups in this study. While significant across all study groups, the relationship between SaO₂ and FVC is not significant within any specific study group.

relationship between SaO₂ residuals and FVC residuals when all three study groups are combined ($P = 0.024$, $R = 0.26$). However, this relationship only exists across groups and not within groups. Independent regressions within groups show no relation-

ship between SaO₂ and FVC residuals within Aymara ($P = 0.205$), European sojourners to HA ($P = 0.814$), or Europeans born and raised at HA ($P = 0.142$).

DISCUSSION

In this comparative study conducted in the Bolivian Andes, we confirm previous findings which show that Aymara high-altitude natives are able to maintain higher SaO₂ during exercise compared to acclimatized lowland groups (Schoene et al., 1990; Favier et al., 1995). The SaO₂ phenotype is independent of body size considerations, unlike many other exercise phenotypes measured in the Andes which depend greatly on body size, e.g., aerobic capacity. With respect to exercise SaO₂, Aymara highland natives are similar to Himalayan highland natives who also show higher exercise SaO₂ compared to well-acclimatized lowland controls (Ge et al., 1995; Zhuang et al., 1996; Sun et al., 1990). The two most important findings of this study are the following: 1) Aymara natives maintain a significantly higher SaO₂ during exercise when compared to Europeans born and raised at 3,600 m, suggesting genetic adaptation (Fig. 1A and Table 3); 2) European groups, born and raised at different altitudes, have the same resting and exercise SaO₂, suggesting that developmental adaptation is less important than genetic adaptation in determining the high exercise SaO₂ of the Aymara (Fig. 1B and Table 4). To address the question of how the Aymara have adapted to express a higher SaO₂ during exercise, a weak but significant correlation ($P = 0.024$, $R = 0.262$) is presented between exercise SaO₂ (controlling for V_E and work rate) and FVC (controlling for stature). This correlation existed across study groups only, and not within a specific study group (Fig. 2). While this correlation can be used to suggest that the higher SaO₂ of the Aymara native is made possible because of a larger DLO₂ (the lung diffusion-SaO₂ hypothesis), a straightforward interpretation in this regard is problematic for reasons that will be discussed below. The remainder of this paper will discuss: 1) the validity of the general study design and the analytic models; 2) the contrast between these results and those

found in Tibetans; 3) the lung diffusion-SaO₂ hypothesis; and 4) the current findings within the context of previous statistical genetic work.

Validity of the study design and analytic models

The ability to infer genetic and/or developmental adaptation in a comparative study depends upon the validity of the study design used to isolate these effects. The migrant study approach is useful, but validity depends upon the proper designation of individuals into study groups. The potential problem in the Andes is admixture between European and Amerindian populations. It may not be possible to find Amerindian natives with no European admixture, given the historical reality of this region (Chakraborty et al., 1985, 1989), but the probability of finding relatively unadmixed Aymara subjects was optimized by recruiting rural subsistence farmers rather than urban La Paz residents. European sojourners to HA recently arrived from outside Bolivia, so admixture was not an issue in this group. European natives, born and raised in La Paz, were carefully screened to minimize the probability of admixture with Aymara or Quechua natives.

Even with a valid study design, the comparative study approach can be problematic. Differences between study groups in health, nutrition, activity level, or some other factor can confound study results. Potential confounders with respect to the SaO₂ phenotype include subject age and training state. While resting SaO₂ decreases slightly with age up to the seventh decade of life in Andean populations (Beall et al., 1999a), this decrease was not evident across the narrow 18–35-year age range studied here. Training state is also not a likely confounder in this study. While previous studies show no differences in resting SaO₂ with training (Williams et al., 1986), trained individuals show a slightly lower SaO₂ during submaximal exercise compared to untrained individuals (Williams et al., 1986). The training effect is probably due to a decrease in metabolic acidosis during exercise and a concomitant decrease in the stimulus to hyperventilate (Gledhill et al., 1980). The

Aymara subjects were more physically active (i.e., better trained) than the European subjects in this study due to the labor demands imposed by their subsistence lifestyle. This was confirmed in these subjects previously by physiological measurements made to assess training status (see Brutsaert et al., 1999b), and is also supported by a study which used the doubly labeled water technique to show heavy levels of physical activity associated with agropastoral activities in Andean populations (Kashiwazaki et al., 1995). Nevertheless, physical activity level should not be considered a confounder in the present study, because training differences would decrease, not increase, the observed difference in the exercise SaO_2 between Aymara and European groups. Similarly, although the Aymara were tested at a slightly higher altitude (3,850 m) compared to Europeans (3,600 m), this would tend to decrease, not increase, the observed SaO_2 difference between these study groups.

The Aymara are able to maintain a higher SaO_2 during exercise compared to either European study group (Fig. 1). When exercise SaO_2 is adjusted for V_E differences between groups, differences between Aymara and European subjects increase (Tables 3 and 4). These adjusted values of exercise SaO_2 provide additional insight into possible physiological mechanisms of adaptation in the Aymara. SaO_2 is a physiological outcome representing the interaction of structural and functional parameters. SaO_2 depends upon the alveolar ventilation (V_A), the blood flow through the lung (Q_L), the matching of V_A to Q_L within the lung (V_A/Q_L mismatch), the extent of intrapulmonary shunt, the affinity of Hb for O_2 , and the DLO_2 (which itself depends on the size of the alveolar capillary interface, the properties of the alveolar and capillary membranes, and the pulmonary capillary blood volume). To express exercise SaO_2 while controlling for V_E is to describe the output of a physiological system (SaO_2) while holding constant one important input or cost (V_E). Thus the Aymara, despite relative hypoventilation (defined here as the level of V_E per metabolic rate, VO_2) during exercise compared to Europeans, maintain higher SaO_2 . As would be expected, observed differences

in SaO_2 increase between Aymara and Europeans when V_E is held constant. These findings are similar to those of Schoene et al. (1990), who suggest that the Aymara have a high pulmonary gas exchange efficiency and higher exercise SaO_2 due to a large lung diffusion capacity.

Andeans vs. Tibetans

The Aymara adaptive response during exercise should be contrasted to the Tibetan adaptive response, which is different in some respects. At rest and during exercise, Tibetans ventilate as much or more than acclimatized newcomers to HA, and clearly ventilate more compared to Andeans (Beall et al., 1997b; Sun et al., 1990; Zhuang et al., 1993; Huang et al., 1984; Moore et al., 1992). In addition, Tibetans have hypoxic and hypercapnic ventilatory responsiveness at least as great as acclimatized newcomers, and likely greater than that in Andeans (Zhuang et al., 1993; Curran et al., 1995). Paradoxically, despite greater V_E in Tibetans, Beall et al. (1997a, 1999a) report lower resting SaO_2 compared to Aymara when both groups were measured at the same altitude and with the same equipment. This may indicate different patterns of adaptation to the same environmental stress (see Beall, 2000), or indeed that Tibetans are better adapted than Andeans (see Moore et al., 1992). Whichever the case, what is functionally important is that both groups (Andeans and Tibetans) maintain approximately 1 percentage point higher SaO_2 during exercise and show a smaller rate of decline in SaO_2 with increasing exercise compared to acclimatized controls.

The lung diffusion- SaO_2 hypothesis

Again, it has been argued that functional adaptation to maintain higher SaO_2 in Andean natives is made possible by a larger lung diffusion capacity (Schoene et al., 1990). Clearly, if Aymara natives have higher SaO_2 for the same level of V_E compared to Europeans, then some other factor besides V_E (from the list of factors influencing SaO_2 given above) must account for the difference between groups. There is no information about V_A/Q_L mismatch or intrapulmonary shunt in Andean natives, al-

though these could be important factors. Hb-O₂ affinities are apparently not different between Aymara and lowland groups at rest (Winslow et al., 1981). This leaves diffusion capacity as the likeliest factor, especially considering: 1) that DLCO at rest is larger in Andean highland natives (DeGraff et al., 1970; Dempsey et al., 1971; Guleria et al., 1971; Vincent et al., 1978; Remmers and Mithoeffer, 1969; Johnson et al., 1985), and 2) that (A-a)O₂ is smaller during exercise in Andean, Tibetan, and North American highland natives (Dempsey et al., 1971; Zhuang et al., 1996).

One way to test the lung diffusion-SaO₂ hypothesis is to test for correlation between FVC (as a proxy for DLO₂) and exercise SaO₂. A significant correlation between residual FVC and residual SaO₂ was evident across the three subject groups (i.e., for the combined sample of study subjects), but not within any specific study group (Fig. 2). The residual values plotted in this figure give unbiased expressions of both exercise SaO₂ and the relative lung sizes of individuals in this study. Support for the lung diffusion SaO₂ hypothesis based on this analysis is problematic because of: 1) the problem of inferring causality from correlation, 2) the low correlation coefficient, and 3) the fact that the correlation was not observed within any specific study group. Also, the European subjects, born and raised at HA, despite having larger FVCs compared to the European sojourners (see Brutsaert et al., 1999a), did not have higher exercise SaO₂ compared to European sojourners. Perhaps other adaptive changes are necessary to bring about an increase in exercise SaO₂, in addition to changes which clearly increase the lung volume (and presumably the DLO₂) with exposure to HA. Alternately, the weak correlation observed may be due to the fact that the FVC is a poor proxy for lung diffusion capacity. Indeed, one would expect stronger correlations between residual lung volume or DLCO with SaO₂ during exercise. Unfortunately, these comparisons do not exist in the literature. Also consider that static lung volumes (and DLCO) are typically measured at rest, not during exercise. To fully address the lung diffusion-SaO₂ hypothesis, measures of DLO₂ should

be made during exercise, where functional benefit is postulated.

Interpretation of results within the context of previous statistical genetic work

Both the comparative and statistical genetic approaches to study human adaptation to HA have limitations. Ideally, they should be used together to provide an explanation for the observed phenotypic variability within and between population groups native to both high and low altitude. In the Andes, heritability is apparently not significant for the resting SaO₂, at least in the one Aymara group studied (Beall et al., 1999a). This conclusion assumes that pleiotropic and/or environmental effects are not masking additive genetic variance in this population. If true, then there is currently no potential for natural selection to work on this phenotype in the Andes. However, this does not imply that natural selection has not been at work in the past. Indeed, if past selection pressure was strong, leading to fixation of an allelic variant (or variants) influencing resting SaO₂s in the Andes, then the Aymara should have higher resting SaO₂s compared to developmentally adapted Europeans. While resting SaO₂ were only marginally higher in Aymara subjects, exercise SaO₂ were more than 1 percentage point higher compared to both European groups. Beall et al. (1999b) have shown that there is a significant correlation between resting and exercise SaO₂, and this may justify treating both phenotypes as expressions of the same underlying genetic system. It should also be recalled that the resting SaO₂ in the present study was measured with subjects seated on a cycle ergometer immediately prior to exercise. Thus, our resting SaO₂ measurements are likely not comparable to those measured in a true resting state.

For the purpose of comparison, assume that the same adaptive allele inferred from previous quantitative genetic studies in Tibetans also exists in the Andes (i.e., a dominant allele conferring a 5-6 percentage point increase in resting SaO₂ for homozygotes and heterozygotes, and at 45% frequency; Beall et al., 1994, 1997a). If we also assume allele fixation in the Andes (100%

frequency), then Andean populations would have a ~1.7 percentage point higher phenotypic mean resting SaO₂ compared to Tibetans, based on Hardy-Weinberg predictions. This is not far from the 2.6 percentage point difference reported in previous studies (Beall et al., 1997a, 1999a). However, the exercise SaO₂ reported here is similar between Andeans and Tibetans (discussed previously). This is difficult to reconcile with the idea of allele fixation in the Andes, unless it is the case that resting and exercise SaO₂ are not genetically correlated, or that environmental effects act differently on these phenotypes in the two regions. A clearer understanding of these issues necessitates: 1) further statistical genetic study, especially of SaO₂ during exercise and of SaO₂ in lowland native populations with no history of ancestral exposure to HA; and 2) further comparative study, especially focused on the question of how adaptation has taken place in both Tibetans and Andeans.

CONCLUSIONS

This comparative study shows that Aymara HA natives in the Bolivian Andes have a higher exercise SaO₂ compared to European groups tested at HA. It is unclear whether this phenotype can be fully explained by an adaptive increase in lung size with HA exposure. SaO₂ during exercise in the Aymara is higher than that observed in Europeans born and raised at HA, suggesting genetic adaptation. SaO₂ during exercise is similar between European groups differing in developmental exposure to HA, suggesting that developmental adaptation plays little role in determining the exercise SaO₂ phenotype difference between Aymara and Europeans. The higher SaO₂ during exercise in the Aymara compared to acclimatized European groups is similar to the higher SaO₂ seen in Tibetans compared to acclimatized Han Chinese during exercise. Despite a similar exercise SaO₂ phenotype between these two highland native groups, Tibetans achieve higher exercise SaO₂ by ventilating as much or more than acclimatized controls, while the Aymara achieve higher SaO₂ by ventilating less. It is not clear why these interpopulation differences exist, but the higher SaO₂ in the Aymara,

despite lower V_E, as well as their narrow (A-a)O₂ during exercise, certainly argues for a greater DLO₂ in this population. Further studies should compare DLO₂ (ideally) or DLCO during exercise with the exercise SaO₂ in these population groups.

LITERATURE CITED

- Beall CM. 2000. Tibetan and Andean patterns of adaptation to high-altitude hypoxia. *Hum Biol* 72:201-228.
- Beall CM, Blangero J, Williams-Blangero S, Goldstein MC. 1994. Major gene for percent of oxygen saturation of arterial hemoglobin in Tibetan highlanders. *Am J Phys Anthropol* 95:271-276.
- Beall CM, Strohl KP, Blangero J, Williams-Blangero S, Decker MJ, Brittenham GM, Goldstein MC. 1997a. Quantitative genetic analysis of arterial oxygen saturation in Tibetan highlanders. *Hum Biol* 69:597-604.
- Beall CM, Brittenham GM, Strohl KP, Decker MJ, Goldstein MC, Blangero J, Williams-Blangero S, Almasay L, Worthman CM. 1997b. Ventilation and hypoxic ventilatory response of Tibetan and Aymara high altitude natives. *Am J Phys Anthropol* 104:427-447.
- Beall CM, Almasay LA, Blangero J, Williams-Blangero S, Decker MJ, Brittenham GM, Strohl KP, Decker MJ, Vargas E, Villena M, Soria R, Alarcon AM, Gonzales C. 1999a. Percent of oxygen saturation or arterial hemoglobin among Bolivian Aymara at 3,900 m-4,000 m. *Am J Phys Anthropol* 108:41-51.
- Beall CM, Worthman CM, Stallings J. 1999b. Oxygen saturation and the response to sub-maximal exercise among Tibetans at 3,900 m. *Am J Phys Anthropol* [Suppl] 28:88.
- Bender PR, McCullough RE, McCullough RG, Huang SY, Wagner PD, Cymerman A, Hamilton AJ, Reeves JT. 1989. Increased exercise SaO₂ independent of ventilatory acclimatization at 4,300 m. *J Appl Physiol* 66:2733-2738.
- Bland JM, Altman DG. 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1:307-310.
- Brutsaert TD, Soria R, Caceres E, Spielvogel H, Haas JD. 1999a. Effect of developmental and ancestral high altitude exposure on chest morphology and pulmonary function in Andean and European/North American natives. *Am J Hum Biol* 11:383-395.
- Brutsaert TD, Spielvogel H, Soria R, Caceres E, Buzenet G, Haas JD. 1999b. Effect of developmental and ancestral high altitude exposure on VO_{2max} of Andean and European/North American natives. *Am J Phys Anthropol* 110:435-455.
- Cardich A. 1994. The origin of the Andean civilization. *Anthropologie* 98:173-189.
- Cerney FC, Dempsey JA, Reddan EWG. 1973. Pulmonary gas exchange in non-native residents of high altitude. *J Clin Invest* 52:2993-2999.
- Chakraborty R, Gershowitz H, Ferrell RE, Barton SA, Schull WJ. 1985. Immunoglobulin GM and KM allotypes in the Aymara of Chile and Bolivia. *Ann Hum Biol* 12:533-544.
- Chakraborty R, Barton SA, Ferrell RE, Schull WJ. 1989. Ethnicity determination by names among the Aymara of Chile and Bolivia. *Hum Biol* 61:159-178.
- Chen QH, GE RI, Wang XZ, Chen HX, Wu TY, Kobayashi T, Yoshimura K. 1997. Exercise performance of Tibetan and Han adolescents at altitudes of 3,417 and 4,300 m. *J Appl Physiol* 83:661-667.

- Currán LS, Zhuang J, Droma T, Land L, Moore LG. 1995. Hypoxic ventilatory responses in Tibetan residents of 4400 m compared with 3658 m. *Respir Physiol* 100:223-230.
- DeGraff AC, Grover RF, Johnson RL, Hammond JW, Miller JM. 1970. Diffusing capacity of the lung in Caucasians native to 3,100 m. *J Appl Physiol* 29:71-76.
- Dempsy JA, Reddan WG, Birnbaum ML, Forster HV, Thoden JS, Grover RF, Rankin J. 1971. Effects of acute through life-long hypoxic exposure on exercise pulmonary gas exchange. *Respir Physiol* 13:62-89.
- Durnin JV, Wormersley J. 1974. Body fat assessed from total body density and its estimation from skin fold thickness: measurements on 481 men and women aged 16 to 72 years. *Br J Nutr* 32:77-79.
- Favier R, Spielvogel H, Desplanches D, Ferretti G, Kayser B, Hoppeler H. 1995. Maximal exercise performance in chronic hypoxia and acute normoxia in high altitude natives. *J Appl Physiol* 78:1868-1874.
- Ge RL, Chen QH, Wang LH, Gen D, Yang P, Kubo K, Fujimoto K, Matsuzawa Y, Yoshimura K, Takeoka M, Kobayashi T. 1993. Higher exercise performance and lower $\dot{V}O_{2max}$ in Tibetan than Han residents at 4,700 m altitude. *J Appl Physiol* 77:684-691.
- Ge RL, He Lun GW, Chen QH, Li HL, Gen D, Kubo K, Matsuzawa Y, Fujimoto K, Yoshimura K, Takeoka M, Kobayashi T. 1995. Comparisons of oxygen transport between Tibetan and Han residents at moderate altitude. *Wilderness Environ Med* 6:391-400.
- Gledhill N, Spriet LL, Froese AB, Wilkes DL, Meyers EC. 1980. Acid base status with induced erythroemia and its influence on arterial oxygenation during heavy exercise [Abstract]. *Med Sci Sports Exerc* 12:122.
- Greksa LP. 1992. Surnames as indicators of European admixture in Andean Indians. *Int J Anthropol* 7:41-49.
- Guleria JS, Pande JN, Sethi PK, Roy SB. 1971. Pulmonary diffusing capacity at high altitude. *J Appl Physiol* 31:536-543.
- Harrison GA. 1966. Human adaptability with reference to the IHP proposals for high altitude research. In: Baker PT, Weiner JS, editors. *The biology of human adaptability*. Oxford: Clarendon Press. p 509-520.
- Huang SY, Alexander JK, Grover RF, Maher JT, McCullough RE, McCullough RG, Moore LG, Sampson JB, Weil JV, Reeves JT. 1984. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. *J Appl Physiol* 56:602-606.
- Johnson RL, Cassidy SS, Grover RF, Schutte JE, Epstein RH. 1985. Functional capacities of lungs and thorax in beagles after prolonged residence at 3,100 m. *J Appl Physiol* 59:1773-1782.
- Jones RL, Man SFP, Matheson GO, Parkhouse WS, Allen PS, McKenzie DC, Hochachka PW. 1992. Overall and regional lung function in Andean natives after descent to low altitude. *Respir Physiol* 87:11-24.
- Kashiwazaki H, Dejima Y, Orias-Rivera J, Coward WA. 1995. Energy expenditure determined by the doubly labeled water method in Bolivian Aymara living in a high altitude agropastoral community. *Am J Clin Nutr* 62:901-910.
- Kramer AA. 1992. Heritability estimates of thoracic skeletal dimensions for a high-altitude Peruvian population. In: Eckhardt RB, Melton TW, editors. *Population studies on human adaptation and evolution in the Peruvian Andes. Occasional papers in anthropology no. 14*. University Park, PA: Pennsylvania State University. p 25-49.
- Lasker GW. 1969. Human biological adaptability. *Science* 166:1480-1486.
- Moore GC, Zwillich CW, Battaglia JD, Cotton EK, Weil JV. 1976. Respiratory failure associated with familial depression of ventilatory response to hypoxia and hypercapnia. *N Engl J Med* 295:861-865.
- Moore LG, Curran-Everett L, Droma TS, Groves BM, McCullough RE, McCullough RG, Sun SF, Sutton JR, Zamudio S, Shuan JG. 1992. Are Tibetans better adapted? *Int J Sports Med* 13:86-88.
- Mueller WH, Chakraborty R, Barton SA, Rothhammer F, Schull WJ. 1980. Genes and epidemiology in anthropological adaptation studies: familial correlations in lung function in populations residing at different altitudes in Chile. *Med Anthropol* 4:367-384.
- Niermeyer S, Yang P, Shanmina, Drokler, Zhuang J, Moore LG. 1995. Arterial oxygen saturation in Tibetan and Han infants born in Lhasa, Tibet. *N Engl J Med* 333:1248-1252.
- Remmers JE, Mithoeffer JC. 1969. The carbon monoxide diffusing capacity in permanent residents at high altitudes. *Respir Physiol* 6:233-244.
- Saunders MA, Leeder SR, Rebeck AS. 1976. Ventilatory response to carbon dioxide in young athletes: a family study. *Am Rev Respir Dis* 113:497-502.
- Schoene RB, Roach RC, Labiri S, Peters RM, Hackett PH, Santolaya R. 1990. Increased diffusion capacity maintains arterial saturation during exercise in the Quechua Indians of the Chilean Altiplano. *Am J Hum Biol* 2:663-668.
- Sun SF, Droma TS, Zhang JG, Tao JX, Huang SY, McCullough RG, McCullough RE, Reeves CS, Reeves JT, Moore LG. 1990. Greater maximal O₂ uptakes and vital capacities in Tibetan than Han residents of Lhasa. *Respir Physiol* 79:151-162.
- Vincent J, Hellot MF, Vargas E, Gautier H, Pasquis P, Lefrancois R. 1978. Pulmonary gas exchange, diffusing capacity in natives and newcomers at high altitude. *Respir Physiol* 34:219-231.
- Weiner JS, Lourie JA. 1981. *Practical human biology*. London: Academic Press.
- Williams JH, Powers SK, Kelly-Stuart M. 1986. Hemoglobin desaturation in highly trained athletes during heavy exercise. *Med Sci Sports Exerc* 18:168-173.
- Winslow RM, Monge CM, Statham NJ, Gibson CG, Charache S, Whittembury J, Moran O, Berger RL. 1981. Variability of oxygen affinity of blood: human subjects native to high altitude. *J Appl Physiol* 51:1411-1416.
- Zhuang J, Droma T, Sutton JR, Groves BM, McCullough RE, McCullough RG, Sun S, Moore LG. 1996. Smaller alveolar-arterial O₂ gradients in Tibetan than Han residents of Lhasa (3658 m). *Respir Physiol* 103:75-82.