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Ventilation and Hypoxic Ventilatory Response of Tibetan and Aymara High Altitude Natives

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ABSTRACT Newcomers acclimatizing to high altitude and adult male Tibetan high altitude natives have increased ventilation relative to sea level natives at sea level. However, Andean and Rocky Mountain high altitude natives have an intermediate level of ventilation lower than that of newcomers and Tibetan high altitude natives although generally higher than that of sea level natives at sea level. Because the reason for the relative hypoventilation of some high altitude native populations was unknown, a study was designed to describe ventilation from adolescence through old age in samples of Tibetan and Andean high altitude natives and to estimate the relative genetic and environmental influences. This paper compares resting ventilation and hypoxic ventilatory response (HVR) of 320 Tibetans 9–82 years of age and 542 Bolivian Aymara 13–94 years of age, native residents at 3,800–4,065 m. Tibetan resting ventilation was roughly 1.5 times higher and Tibetan HVR was roughly double that of Aymara. Greater duration of hypoxia (older age) was not an important source of variation in resting ventilation or HVR in either sample. That is, contrary to previous studies, neither sample acquired hypoventilation in the age ranges under study. Within populations, greater severity of hypoxia (lower percent of oxygen saturation of arterial hemoglobin) was associated with slightly higher resting ventilation among Tibetans and lower resting ventilation and HVR among Aymara women, although the associations accounted for just 2–7% of the variation. Between populations, the Tibetan sample was more hypoxic and had higher resting ventilation and HVR. Other systematic environmental contrasts did not appear to elevate Tibetan or depress Aymara ventilation. There was more intrapopulation genetic variation in these traits in the Tibetan than the Aymara sample. Thirty-five percent of the Tibetan, but none of the Aymara, resting ventilation variance was due to genetic differences among individuals. Thirty-one percent of the Tibetan HVR, but just 21% of the Aymara, HVR variance was due to

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genetic differences among individuals. Thus there is greater potential for evolutionary change in these traits in the Tibetans. Presently, there are two different ventilation phenotypes among high altitude natives as compared with sea level populations at sea level: lifelong sustained high resting ventilation and a moderate HVR among Tibetans in contrast with a slightly elevated resting ventilation and a low HVR among Aymara. Am J Phys Anthropol 104:427–447, 1997.

Increased ventilation in response to hypobaric hypoxia is a crucial component of newcomers' acclimatization to high altitude (e.g., Lenfant and Sullivan, 1971; West, 1982). The puzzling findings that adult high altitude residents in the South American Andes and North American Rocky Mountains had relatively low ventilation compared to newcomers led to studies of their ventilatory sensitivity to hypoxia and found small ventilatory response to additional experimentally-induced hypoxia compared with low altitude residents (e.g., Chiodi, 1957; Severinghaus et al., 1966; Weil et al., 1971). Some evidence suggested that the relative hypoventilation and ventilatory insensitivity were gradually acquired after years of exposure to hypoxia during childhood or adulthood. Andean high altitude babies breathed and responded to experimentally-induced hypoxia no differently than sea level babies (Mortola et al., 1990; Mortola et al., 1992). Andean children 12 years of age and living at 3,900 m and Colorado children 9–10 years of age at 3100 m still responded normally to experimentally-induced hypoxia (Lahiri et al., 1976; Byrne-Quinn et al., 1972). Thus the small adult Andean and Colorado ventilatory response to experimentally-induced hypoxic stress, referred to as 'blunting', was apparently acquired between 10 or 12 years of age and young adulthood. Adult migrants in the Andes with periods of 3–42 years of residence at 3,990 and 4,515 m (Chiodi, 1957) also hypoventilated relative to newcomers. Adult migrants to 3,100 m in Colorado developed depressed ventilatory response to experimental hypoxia in proportion to their length of residence at high altitude (Weil et al., 1971). The inference was that prolonged exposure to hypoxia during childhood or adulthood leads to hypoventilation relative to newcomers under everyday conditions and upon exposure to additional experimentally-induced hypoxia. Acquired hypoventilation appeared to be the single pattern of ventilatory response to prolonged exposure to hypobaric hypoxia because it was reported in the Andean high altitude population with a long microevolutionary history of residence, Colorado residents with just 1–3 generations of residence, and long-term migrants with only years of residence at high altitude.

However, it was subsequently demonstrated that the ventilation of adult male Tibetans (including Sherpas[1]) was similar to that of newcomers (Ge et al., 1994a and b; Hackett et al., 1980; Zhuang et al., 1993). Although there were no data on children, childhood acquisition of reduced ventilation seemed unlikely because adult ventilation was high. However, there was some evidence that an increased level of ventilation might not be sustained throughout adulthood. Lower ventilatory response to additional experimentally-induced hypoxia was correlated with greater altitude exposure (Hackett et al., 1980) and age (Curran et al., 1995) among Tibetan men. Similarly, men native to $\geq$ 4,400 m had a lower ventilatory response to additional experimentally-induced hypoxia than residents at 3,658 m (Curran et al., 1995). This was interpreted as due to " . . .increased severity of hypoxic exposure due to their lifelong residence at a higher altitude." (Curran et al., 1995). The authors suggested that future studies distinguish between duration and severity of exposure to hypoxia.

The reasons for the Andean-Tibetan contrasts in level of adult ventilation and re-

[1]Sherpas migrated from Eastern Tibet to Nepal in the mid-1500s (Stevens, 1993) and are therefore considered as Tibetans.

sponse to experimentally-induced hypoxia and apparently different childhood and adult developmental susceptibilities to acquired hypoventilation were unknown. The possibilities included substantive reasons such as differences in genes influencing level of ventilation, susceptibility to blunting or the timing of blunting, differences in other environmental factors influencing ventilation as well as methodological reasons such as differences in sampling, altitudes of residence and ages of individuals in previous studies. None of the high altitude populations had been studied across a broad age range and there were no available data analyzing the genetic and environmental sources of variation in these traits at high altitude.

This paper presents the results of a study designed to provide such information. It compares resting ventilation and ventilatory response to additional experimentally-induced hypoxia (hypoxic ventilatory response or HVR) in 320 Tibetans 9–82 years of age and 542 Bolivian Aymara 13–94 years of age, native residents at 3,800–4,065 m. Tibetan resting ventilation was roughly 1.5 times higher and Tibetan HVR roughly double that of Aymara, confirming previous reports in small samples of men and extending these to females, adolescents, middle-aged and old adults. Neither sample exhibited age differences indicative of acquired hypoventilation in the age ranges studied. More of the variation in both traits could be attributed to genetic factors in the Tibetan than in the Aymara sample.

MATERIALS AND METHODS

Population and sample

The study was conducted in rural sites at 3,800–4,065 m in the Tibet Autonomous Region (TAR), China and Bolivia. The Tibetan study site was Pen-Dri, two rural agropastoral villages with a population of 773 ethnic Tibetans living at 3,800–4,065 m in Lhasa Municipal District, TAR. The average barometric pressure was 479 Torr. Each household was contacted in May, June, October or November 1993 in order to invite household members and their biological relatives nine years of age and older to participate in a study collecting interview, genealogical, anthropometric and physiological data. Ninety-six percent of the households contributed one or more participants and 68% of those eligible by age participated to yield a total sample of 428 people age 9–82. Age was verified with reference to reported animal year of birth which was then translated into the equivalent Western calendar year. Nearly all were residents of the two communities. All were lifelong high altitude native residents at 3,600 m or higher (with the exception of one low altitude native who had lived in the village since 1950).

The Bolivian study site was composed of four dispersed communities in Provincia Murillo, Departamento La Paz, Bolivia with a population of 1,175 ethnic Aymara living at 3,900–4,000 m. The average barometric pressure was 478 Torr. Each household was contacted between May and August 1994 in order to invite household members and their biological relatives 14 years of age and older to participate in the study. Age was verified by birth certificates or identity cards for 64% of the sample and by reference to historical events for a few elderly people. Seventy-seven percent of all households participated and 57% of the residents eligible by age participated to yield a total sample of 608 people age 13–94. Seventy percent of the sample resided in the four communities and the rest were relatives residing elsewhere (one at low altitude). All were Aymara natives (with the exception of one Quechua) of this or nearby high altitude communities.

Measurement

Measurements were conducted in indoor field laboratories established in central locations in the study communities. Demographic, lifestyle and health information were obtained by questionnaire in the native language. Andean highlanders were asked to abstain from coca chewing on the day of the test. Anyone who indicated that he had chewed coca or had fresh coca leaves in his mouth was asked to return another day. Physiological measurements and most anthropometrics were taken by the first author working with a local assistant. After collection of the interview data, anthropometric measurements were taken according to standard protocols (Cameron et al., 1981) and then resting percent of oxygen satura-

tion of arterial hemoglobin (SaO_2) and pulse were measured with a Criticare model 501+ pulse oximeter. The instrument updates and displays SaO_2 and pulse every four to six heartbeats (approximately one to three seconds). The noninvasive sensor was placed on the index finger (occasionally on another finger if a reading were not obtained promptly on the index finger or it was missing), the investigator waited ten to fifteen seconds after a reading appeared on the output screen and then recorded the SaO_2 and pulse readings every ten seconds for a total of six measurements each. The average of the six measurements is reported for SaO_2 (Beall and Goldstein, 1990; Beall et al., 1994; Beall et al., 1997) and pulse. The repeatability of this measure of SaO_2, assessed by the mean and standard deviation of the difference between measurements of the same individuals on two different days (Bland and Altman, 1986) was +1.3 ± 2.7%, n = 22 in the Tibetan and +0.3 ± 2.9%, n = 22 in the Aymara sample. The repeatability of this measure of pulse was +2 ± 12 f/min (frequency per minute), n = 22 in the Tibetan and +4 ± 9 f/min, n = 22 in the Aymara sample. The pulse oximeter read to the nearest percent of SaO_2 and integer of heart rate.

Individuals who reported that they were not pregnant and were free of symptoms of respiratory disease then provided ventilation measurements consisting of a three-minute resting ventilation determination followed by a three to five minute rest and then three HVR determinations separated by ten minute rests. At least an hour had elapsed since the last meal and the study participant had been seated for ten to fifteen minutes before the beginning of the ventilation measurements. A complete set of measurements took place in the following order: interview, anthropometry, resting pulse and SaO_2 (unattached to the ventilation testing apparatus), resting ventilation, and three HVR determinations.

The following instrumention and physiological measurement recordings were used for the ventilation determinations. Inspiratory and expiratory carbon dioxide (CO_2) were measured in real time at the mouthpiece by a Biochem Lifespan CO_2 monitor validated with a two point calibration (room air and a gas of known concentration) every two to three study participants or, for part of the Aymara sample, a Biochem Capnograph validated with a one point calibration (room air) prior to testing each person. SaO_2 and pulse were measured continuously with a Criticare 501+ pulse oximeter whose analog output was validated by a self-calibration routine. Inspiratory and expiratory airflow velocity and volume and ventilatory frequency were measured by a Fleisch pneumotachograph connected to a +3.0 cm H_2O Validyne pressure transducer that was electronically balanced daily. The voltage output of the pressure transducer was amplified by a Validyne carrier demodulator and amplifier.

The Biochem Lifespan CO_2 monitor failed part way through the Aymara data collection and the Biochem Capnograph was substituted. The latter had only a one point calibration capability and therefore the end-tidal CO_2 values of the two machines are not comparable. Only the values obtained with the Biochem Lifespan are reported here. However, the Biochem Capnograph voltage output was used to directly monitor end-tidal CO_2 during the ventilation tests.

The ventilation measurements were administered carefully to seated study participants whose noses were occluded with noseclips as they breathed through a rubber mouthpiece attached to a large bore, low-resistance Collins valve attached to the Fleisch pneumotachograph. The Collins valve was open to room air during the resting ventilation determinations and open to the rebreathing circuit during the HVR determinations. Large bore, low resistance one-way valves directed exhaled gas through the rebreathing circuit which had a T-piece connector at the mid-point. A variable speed blower drew a portion of the exhaled gas from the T-piece through a cannister containing CO_2 absorbing crystals. The blower was adjusted as needed in order to maintain constant end-tidal CO_2. The exhaled gas (partially cleansed of CO_2) was directed into a seven-liter weather balloon which was inflated with three liters of room air prior to each rebreathing trial and emptied between trials. As the study participant inspired, gas

was drawn from the balloon, directed through one-way valves through the pneumotachograph and to the mouthpiece. Thus, the individual rebreathed previously exhaled gas, some of which had been scrubbed of some CO_2, that became increasingly hypoxic as the oxygen was consumed in the closed circuit. An external pump infused supplemental room air into the rebreathing circuit to regulate the rate of arterial hemoglobin oxygen desaturation to approximately 1 to 2% every 15 seconds.

Isocapnic HVR was measured by a modified Rebuck and Campbell (1974) rebreathing technique. The modifications were a) initiation of the rebreathing trial from a three-liter mixture of 5% CO_2 and 20–21% O_2 (rather than 5–6% CO_2 and 24% O_2), b) termination of rebreathing trials at 75% SaO_2 (rather than 65%) and c) slowing the rate of descent of SaO_2 by adding supplemental room air. Isocapnia was maintained during the HVR determinations at or near the individual's average end-tidal CO_2 during the resting ventilation determination. The average and standard deviation of the difference between end-tidal CO_2 measured during the resting ventilation determination. The average and standard deviation of the difference between end-tidal CO_2 measured during the resting ventilation and that measured during the HVR determination was -0.3 ± 2.2 Torr, $n = 303$ in the Tibetan sample and $+0.3 \pm 2.8$ Torr, $n = 149$ in the Aymara sample. The repeatability of this difference was -0.10 ± 4.1 Torr, $n = 21$ in the Tibetan sample. The repeatability could not be calculated for the Aymara sample because the repeat determinations were conducted after the change of capnometers. The CO_2 monitors read to the nearest integer Torr.

HVR was calculated on a breath-by-breath basis as the change in ventilation divided by the change in SaO_2 determined by the regression of ventilation on SaO_2 (ΔL/min/Δ%SaO_2). HVR is usually a negative value because SaO_2 falls during the test and ventilation usually rises. In the present paper HVR values were multiplied by -1 so that stronger responses have higher values.

A resting ventilation or HVR determination was judged to be technically unacceptable for inclusion in the analyses if one or more of the following occurred: a) less than 90 seconds of data were collected for a resting ventilation determination, b) breath-by-breath end-tidal CO_2 fluctuated more than 4 Torr from the baseline, c) the amplitude of the airflow signal decreased more than 40% from one breath to the next (indicating pneumotachograph failure), d) SaO_2 fell abruptly to less than 80% after the mouthpiece was in place, e) if breathing were erratic or f) the investigator stopped the measurement due to observed discomfort of the study participant. Ninety-one percent of all Tibetan HVR determinations and 95% of all Aymara determinations were technically acceptable. An individual's HVR was the average of all his or her technically acceptable determinations. Eighty percent of the Tibetan and 91% of the Aymara HVR values analyzed were the average of three determinations.

The repeatability of the resting ventilation determinations was 3.5 ± 1.6 L/min, $n = 25$ in the Tibetan sample and -0.83 ± 0.43 L/min, $n = 20$ in the Aymara sample. The repeatability of the HVR determinations was -0.05 ± 0.19 ΔL/min/%SaO_2, $n = 25$ in the Tibetan sample and $+0.12 \pm 0.09$ ΔL/min/%SaO_2, $n = 20$ in the Aymara sample. These small differences indicate that the measurement techniques had good reliability in both sites.

Steps were taken to ensure that study participants were at ease during the ventilation testing. The investigators carefully explained and demonstrated the instruments and procedures in the native language. Each study participant practiced wearing noseclips and breathing through a mouthpiece unattached to the Fleisch pneumotachograph before practicing on the rebreathing circuit itself. If he or she did not appear to breathe comfortably and naturally on the rebreathing circuit then the explanations, demonstration, and practice were repeated. Evidence suggesting that the study participants were equally at rest before and during the ventilation determinations is provided by pulse and SaO_2 measurements taken at the two times. Resting pulse and SaO_2 measured while resting and unattached to the

rebreathing circuit, as described above, differed little from pulse and SaO_2 measured while breathing room air with the mouthpiece and noseclips in place during the resting ventilation determination. The average difference between pulse measured while quietly resting and unattached to the rebreathing circuit and pulse measured during the resting ventilation determinations was 3.4 ± 5.0 f/min, n = 18 in the Tibetan and 4.2 ± 11.9 f/min, n = 17 in the Aymara sample. The average and standard deviation of the difference between SaO_2 measured while resting and unattached to the rebreathing circuit and that maintained while breathing with the noseclips and mouthpiece during the three-minute determination of resting ventilation was +0.8% ± 3.4, n = 298 in the Tibetan sample and +1.2% ± 2.6, n = 383 in the Aymara sample.

Additional evidence that the study participants were not particularly anxious about the testing procedure was provided by the good repeatability of pulse, SaO_2, and end-tidal CO_2 measured during resting ventilation and the repeatability of the resting ventilation and HVR measurements. Familiarity with the tests gained during the first measurement would have lessened any test associated anxiety and could have resulted in recording different values during the second test; however, the readings were stable. The average repeatability of pulse during the resting ventilation determination was −4.3 ± 15.9 f/min, n = 16 in the Tibetan and +6.2 ± 10.2 f/min, n = 13 in the Aymara sample. The average repeatability of the SaO_2 maintained during the resting ventilation determination was −0.5 ± 3.7%, n = 28 in the Tibetan and −0.7 ± 4.0, n = 20 in the Aymara sample. The average repeatability of the resting ventilation end-tidal CO_2 was −0.4 ± 1.9 Torr, n = 20 and that during HVR determination was +0.7 ± 7.2 Torr, n = 20 in the Tibetan sample. Thus we did not detect physiological variability that could be attributed to anxiety or learning (alternatively, the study participants learned nothing during the first ventilation determinations and were equally anxious during the second).

Analysis

The analyses were conducted with samples of 320 Tibetans and 542 Aymara males and females 9–94 years of age who reported that they were healthy and not pregnant and who had a technically acceptable resting ventilation measurement and/or one or more technically acceptable HVR measurements within three standard deviations of the respective sample mean. Individuals 20 years of age and older are considered adults because height growth is completed by then in both sexes in both populations. Table 1 describes the characteristics of Tibetan children 9–12 years of age, Tibetan and Aymara adolescents 13–19 years of age and adults 20 years of age and older. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

Means and standard deviations are reported. Bivariate correlations, multiple regression analyses, analyses of variance and covariance, and *t*-tests address various hypotheses about resting ventilation and HVR. A significance level of 0.05 is used.

Quantitative genetic analyses tested a series of hypotheses regarding sources of variation in resting ventilation and HVR using maximum likelihood variance decomposition methods (Hopper and Mathews, 1982; Lange and Boehnke, 1983) available in the computer programs FISHER (Lange et al., 1988). These analyses provided information regarding the relative importance of genetic, shared environmental, and random environmental effects for resting ventilation and HVR variation.

Quantitative resting ventilation HVR variation was modeled based on the following linear function for the vector of phenotypes in a pedigree of size *n* (bold lower case letters denote vectors and bold upper case letters denote matrices):

$$\mathbf{y} = \mu\mathbf{l}_n + (\mathbf{X} - \mathbf{l}_n\mathbf{s}')\boldsymbol{\beta} + \mathbf{g} + \mathbf{h} + \mathbf{e} \quad (1)$$

where $\mathbf{y}$ is the $n \times \mathbf{1}$ vector of phenotypes, μ is the grand mean of the trait, $\mathbf{X}$ is an $n \times k$ matrix containing k covariates, $\mathbf{l}_n$ is a vector of n ones, $\mathbf{s}$ represents a vector of baseline covariates (e.g. 0 for qualitative covariates and x for continuous covariates), $\boldsymbol{\beta}$ is a $k \times 1$ vector of regression coefficients, $\mathbf{g}$ is the

TABLE 1. Characteristics of Tibetan and Aymara samples[1]

	Tibetan			Aymara		
	Mean	S.D.	n	Mean	S.D.	n
Males						
Children, 9–12 yrs						
Age	11	1	22	—	—	—
Height, cm	131	8	22	—	—	—
Weight, kg	24.5	36	22	—	—	—
BMI, kg/m^2	14.2	0.8	22	—	—	—
Chest width, cm	21.4	1.2	22	—	—	—
Chest depth, cm	15.7	0.9	21	—	—	—
SaO_2	91.1	2.3	22	—	—	—
Pulse, f/min	92	14	22	—	—	—
Adolescents, 13–19 yrs						
Age	16	2	34	16	2	55
Height, cm	154	11	34	153	9	55
Weight, kg	39.2	8.5	34	45.4	8.8	54
BMI, kg/m^2	16.4	1.6	34	19.2	2.2	54
Chest width, cm	25.0	1.9	34	26.5	2.1	55
Chest depth, cm	18.0	1.3	33	18.2	1.8	55
SaO_2%	89.7	2.6	34	93.3	2.2	39
Pulse, f/min	81	14	33	74	12	55
Adults, 20+ yrs						
Age	38	14	88	41	16	232
Height, cm	165	7	87	160	5	229
Weight, kg	51.9	6.1	87	59.2	8.5	229
BMI, kg/m^2	19.1	1.4	87	23.0	2.8	228
Chest width, cm	28.0	1.5	86	29.1	1.8	228
Chest depth, cm	20.7	1.3	87	21.1	2.0	230
SaO_2%	88.5	3.3	87	92.2	2.8	167
Pulse, f/min	73	13	88	67	11	231
Females						
Children, 9–12 yrs						
Age	11	1	15	—	—	—
Height, cm	128	10	15	—	—	—
Weight, kg	23.1	3.7	15	—	—	—
BMI, kg/m^2	14.1	0.7	15	—	—	—
Chest width, cm	20.5	1.1	15	—	—	—
Chest depth, cm	15.1	0.9	15	—	—	—
SaO_2%	91.8	3.0	15	—	—	—
Pulse, f/min	93	14	15	—	—	—
Adolescents, 13–19 yrs						
Age	16	2	39	16	2	52
Height, cm	148	10	39	149	5	52
Weight, kg	36.4	8.6	38	47.6	8.8	50
BMI, kg/m^2	16.4	2.2	38	21.3	3.3	50
Chest width, cm	23.8	1.9	39	26.8	1.9	50
Chest depth, cm	17.1	1.8	39	17.9	1.7	51
SaO_2%	89.8	2.5	38	92.9	2.1	36
Pulse, f/min	84	12	39	80	11	52
Adults, 20+ yrs						
Age	38	14	122	40	15	212
Height, cm	153	5	122	149	5	210
Weight, kg	44.9	5.6	115	52.2	8.6	200
BMI, kg/m^2	19.2	1.8	115	23.6	3.5	198
Chest width, cm	25.6	1.6	121	28.1	1.8	208
Chest depth, cm	19.3	1.4	120	19.0	1.7	208
SaO_2%	89.3	3.2	87	91.2	2.9	100
Pulse, f/min	77	12	122	73	10	212

[1] BMI = body mass index, SaO_2% = percent of oxygen saturation of arterial hemoglobin.

vector of additive genetic values, **h** is a vector of shared household effects, and **e** is a vector of random environmental deviations. Given this model, the expected variance/covariance matrix for **y** is written:

$$\mathrm{Var}(\mathbf{y}) = \mathbf{\Omega} = 2\mathbf{\Phi}\sigma_g^2 + \mathbf{Z}\sigma_d^2 + \mathbf{I}_n\sigma_e^2 \quad (2)$$

where $\mathbf{\Phi}$ is the $n \times n$ matrix of kinship coefficients, **Z** is an indicator matrix whose ij-th element is 1 if the i-th and j-th individuals live in the same household and is 0 otherwise, and $\mathbf{I}_n$ is an identity matrix of order n. The variance terms in Eq. (2) include the additive genetic variance (σ_g^2), the variance due to shared household effects (σ_h^2), and the random environmental variance (σ_e^2). Assuming multivariate normality of **y**, the likelihood of the pedigree is easily calculated and optimization methods can be used for parameter estimation. Subsequent hypothesis testing is performed using likelihood ratio tests. As implied in Eq. (1), the effects of potential covariates (such as age, sex, BMI) were simultaneously estimated in all analyses. The effects of covariates were tested using likelihood ratio tests.

Residual heritability (h^2) was calculated as the additive genetic variance/(1-covariate variance). Residual household variance (c^2) was calculated as the shared household effects variance/(1-covariate variance). The variance component analyses of resting ventilation used 295 individuals in nine pedigrees (groups of individuals with a common ancestor) from the Tibetan sample and 537 individuals in 59 pedigrees from the Aymara sample. The variance component analyses of HVR used 319 individuals in nine pedigrees from the Tibetan sample and 522 individuals in 58 pedigrees from the Aymara sample.

RESULTS

Figures 1 and 2 illustrate the higher Tibetan resting ventilation and HVR values and wider Tibetan variation throughout the age range. There were no notable age trends from childhood to old age in either sample. Tibetan resting ventilations were about 1.4 to 1.7 times higher than the Aymara and HVR were about double the Aymara, depending upon age and sex (Table 2). The higher Tibetan resting ventilation was associated with tidal volumes roughly 1.4 to 1.7 times higher than Aymara. Tibetan end-tidal CO_2 during rest breathing ambient air and during HVR determinations were 2–6 Torr lower than Aymara. End-tidal CO_2 during resting

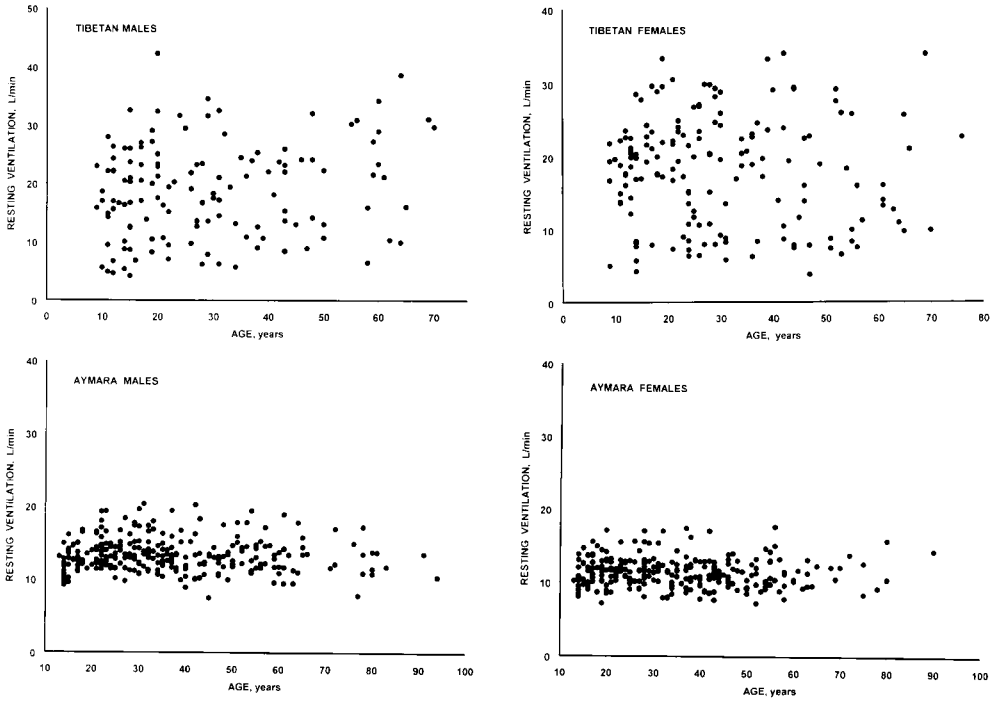

Fig. 1. Resting ventilation (L/min) of Tibetan and Aymara males and females 9–94 years of age.

ventilation averaged within one Torr of that during HVR determination in both sites. HVR determinations took less time among the Tibetans, consistent with starting at a lower resting SaO_2.

There was no evidence for adolescent acquisition of hypoventilation (i.e., no negative association between age and ventilation) in either sample. Adolescent development of ventilation was analyzed in those 13–19 years of age (Table 3). There was a significant, moderate, positive correlation between age and resting ventilation among Tibetan females and Aymara males. There was no consistent pattern of association between body size measured as height, weight, BMI, or chest depth and resting ventilation or HVR among the Tibetan adolescents. Tibetan males had a significant, moderate, positive association between chest depth and resting ventilation and a significant, small, positive association between chest depth and HVR. In contrast, there was a consistent significant, moderate, positive association between body size measures and resting ventilation and HVR among the Aymara adolescent males and females.

Tibetan adolescents exhibited significant, moderate, negative associations between SaO_2 and resting ventilation and between end-tidal CO_2 and resting ventilation, but not HVR. Aymara adolescents exhibited insignificant associations between the SaO_2 and resting ventilation in the opposite, positive, direction. There were no significant associations between end-tidal CO_2 and ventilation in the Aymara sample, perhaps due to the small sample size. There was a significant, moderate, positive correlation between resting ventilation and HVR in the Aymara sample.

There was scant evidence for adult acquisition of hypoventilation. The only negative association between age and ventilation among adults was a trend ($P = 0.05$) toward lower resting ventilation with age among Aymara men that explained less than 2% of the variation and a slight, significant, negative correlation of HVR with age that explained just 3% of the variation (Table 4).

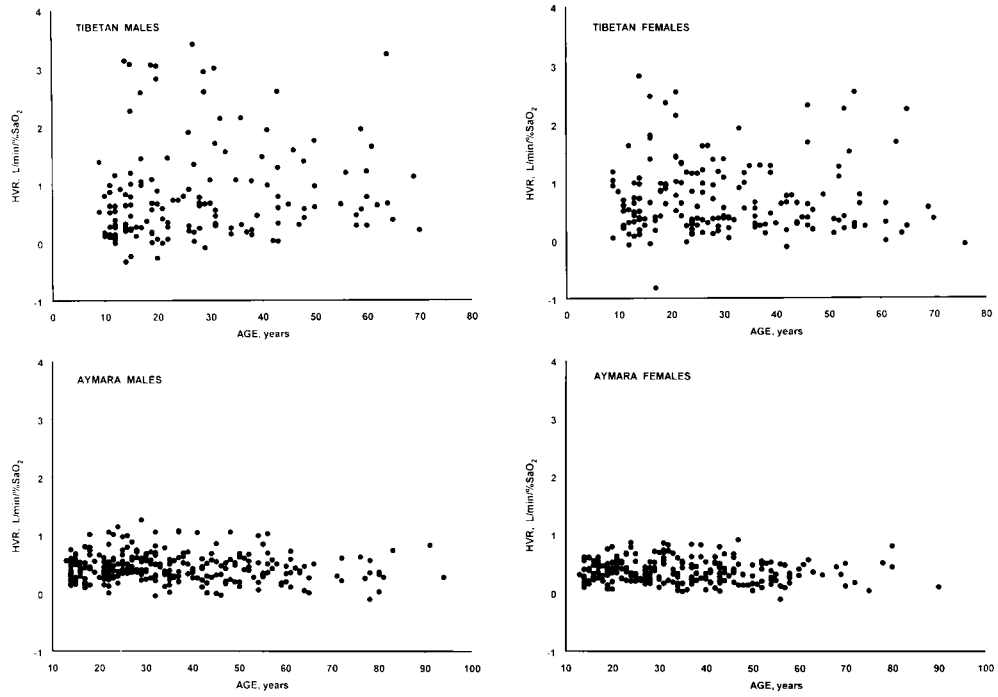

Fig. 2. HVR (ΔL/min/Δ%SaO_2) of Tibetan and Aymara males and females 9–94 years of age.

There was no association between body size and ventilation in Tibetan adults. Height, weight and chest width had small, significant, positive correlations with resting ventilation and HVR among the Aymara adults.

Resting ventilation had a small, significant, negative correlation with SaO_2 among the Tibetan adults and a small, significant, positive correlation with SaO_2 among Aymara women. The associations with SaO_2 account for just 4–7% of the variation in resting ventilation. HVR had a small, significant, positive association with SaO_2 only among Aymara women that explained less than 2% of the variation (Table 4).

In both samples, adults with higher HVR had higher resting ventilation. There was a significant, moderate, positive correlation among Tibetans and a significant small positive correlation among Aymara. Individuals with both higher HVR and lower SaO_2 would be expected to have higher resting ventilation. This hypothesis was explored with multiple regression analyses. The multiple R^2 of age, SaO_2 and HVR with resting ventilation was significant for Tibetan men and women, but not Aymara (Table 5). The additional contribution of body size variables was assessed because they were associated with ventilation among the Aymara. Height added significantly to the explained variation only among Aymara men. Chest width added significantly to the explained variation among Aymara women and chest depth did so among Tibetan women. The multiple R^2 for the six variable model accounted for more of the Tibetan than the Aymara variation, yet these traits explained just 10–36% of the resting ventilation variation.

The contribution of genetic factors to resting ventilation and HVR variation in each sample was evaluated by estimating the relative importance of genetic effects, shared household environment and random environment effects using maximum likelihood variance decomposition methods to analyze the familial patterning of these traits. The residual heritability (h^2) of Tibetan resting ventilation was 0.317 and of Tibetan HVR was 0.345 (Table 6). That is, about 1/3 of the variance in both traits in the Tibetan sample was attributable to additive genetic factors.

TABLE 2. Ventilatory characteristics of Tibetan and Aymara high altitude natives[1]

	Tibetan			Aymara			t, site differences
	Mean	S.D.	n	Mean	S.D.	n	
Males							
Children, 9–12 yrs							
Resting ventilation, L/min	16.4	7.2	20	—	—	—	—
Tidal volume, L/min	1.1	0.5	22	—	—	—	—
Breathing frequency, f/min	17.9	4.2	22	—	—	—	—
HVR, $\Delta L/min/\Delta\%SaO_2$	0.46	0.39	22	—	—	—	—
Length of HVR determination, sec	82	32	22	—	—	—	—
Resting end-tidal CO_2, Torr	32.8	5.2	20	—	—	—	—
HVR end-tidal CO_2, Torr	32.7	6.1	22	—	—	—	—
Resting-HVR difference in end-tidal CO_2, Torr	−0.03	2.1	20	—	—	—	—
Adolescents, 13–19 yrs							
Resting ventilation, L/min	17.3	8.0	30	12.2	1.8	54	3.5[2]
Tidal volume, L/min	1.1	0.6	30	0.7	0.1	54	3.3[2]
Breathing frequency, f/min	17.8	4.5	31	17.1	2.0	54	0.8
HVR, $\Delta L/min/\Delta\%SaO_2$	0.84	0.94	34	0.42	0.20	53	2.6[2]
Length of HVR determination, sec	110	47	34	143	37	53	−3.7[2]
Resting end-tidal CO_2, Torr	29.5	5.2	31	35.2	2.8	13	−3.8[2]
HVR end-tidal CO_2, Torr	29.2	5.9	34	34.3	2.7	13	−4.1[2]
Resting-HVR difference in end-tidal CO_2, Torr	−0.3	2.1	30	1.0	1.5	13	−2.0
Adults, 20+ yrs							
Resting ventilation, L/min	19.7	8.4	84	13.4	2.4	230	6.8[2]
Tidal volume, L/min	1.4	0.6	85	0.9	0.2	222	8.6[2]
Breathing frequency, f/min	14.8	3.4	86	15.5	2.8	225	−1.8
HVR, $\Delta L/min/\Delta\%SaO_2$	0.93	0.85	87	0.45	0.25	222	5.2[2]
Length of HVR determination, sec	136	50	88	194	50	225	−9.1[2]
Resting end-tidal CO_2, Torr	29.7	4.6	86	33.8	4.1	66	−5.8[2]
HVR end-tidal CO_2, Torr	30.4	4.7	87	33.3	5.1	67	−3.6[2]
Resting-HVR difference in end-tidal CO_2 Torr	−0.6	2.0	85	0.3	2.4	65	−2.6[2]
Females							
Children, 9–12 yrs							
Resting ventilation, L/min	17.5	4.7	15	—	—	—	—
Tidal volume, L/min	1.1	0.3	15	—	—	—	—
Breathing frequency, f/min	18.5	5.2	15	—	—	—	—
HVR, $\Delta L/min/\Delta\%SaO_2$	0.60	0.5	15	—	—	—	—
Length of HVR determination, sec	79	24	15	—	—	—	—
Resting end-tidal CO_2, Torr	28.8	8.9	15	—	—	—	—
HVR end-tidal CO_2, Torr	28.5	8.1	15	—	—	—	—
Resting-HVR difference in end-tidal CO_2, Torr	+0.2	2.6	15	—	—	—	—
Adolescents, 13–19 yrs							
Resting ventilation, L/min	19.2	7.1	36	11.4	1.9	51	6.4[2]
Tidal volume, L/min	1.0	0.5	36	0.7	0.1	51	5.0[2]
Breathing frequency, f/min	19.7	4.1	36	17.9	2.2	50	2.5[2]
HVR, $\Delta L/min/\Delta\%SaO_2$	0.76	0.72	38	0.36	.16	49	3.4[2]
Length of HVR determination, sec	105	42	39	146	47	50	−4.3[2]
Resting end-tidal CO_2, Torr	29.7	5.2	36	32.9	3.6	18	−2.4[2]
HVR end-tidal CO_2, Torr	29.6	5.3	39	31.6	5.2	19	−1.4
Resting-HVR difference in end-tidal CO_2, Torr	−0.3	1.8	36	0.3	0.9	17	−1.6
Adults, 20+ yrs							
Resting ventilation, L/min	17.7	7.8	111	11.5	2.1	207	8.3[2]
Tidal volume, L/min	1.2	0.5	114	0.7	0.1	203	9.3[2]
Breathing frequency, f/min	16.4	3.1	112	17.0	2.8	204	−1.6
HVR, $\Delta L/min/\Delta\%SaO_2$	0.70	0.59	121	0.37	0.20	197	6.0[2]
Length of HVR determination, sec	131	58	122	156	48	200	−3.9[2]
Resting end-tidal CO_2, Torr	29.2	5.5	113	34.0	4.5	49	−5.5[2]
HVR end-tidal CO_2, Torr	29.4	4.9	119	34.0	4.6	51	−5.7[2]
Resting-HVR difference in end-tidal CO_2, Torr	−0.3	2.1	114	0.0	2.0	49	−0.8

[1] HVR = hypoxic ventilatory response.
[2] $P < 0.05$.

There was a significant high genetic correlation of 0.67 between Tibetan resting ventilation and HVR indicating that some pleiotropic genes influence both traits. The residual heritability of Tibetan end-tidal CO_2 was 0.218. The residual variance due to shared household effects (c^2) was 0.303 for resting ventilation and 0.153 for HVR and 0 for end-tidal CO_2. Random environmental differences accounted for roughly ⅓ of the Tibetan

TABLE 3. Bivariate correlations with resting ventilation and HVR in samples of 13–19 year olds[1]

	Tibetan		Aymara	
	Males	Females	Males	Females
Resting ventilation with:				
Age	+0.18	+0.39[2]	+0.42[2]	+0.17
Height	+0.27	+0.23	+0.67[2]	+0.59[2]
Weight	+0.34	+0.16	+0.68[2]	+0.41[2]
BMI	+0.36	+0.13	+0.53[2]	+0.20
Chest width	+0.13	+0.10	+0.55[2]	+0.30[2]
Chest depth	+0.38[2]	+0.13	+0.33[2]	+0.19
HVR	+0.33	+0.20	+0.43[2]	+0.39[2]
SaO_2	−0.52[2]	−0.36[2]	+0.24	+0.19
End-tidal CO_2	−0.51[2]	−0.37[2]	0.50	−0.16
			(n = 13)	(n = 18)
HVR with:				
Age	+0.03	+0.17	+0.20	+0.11
Height	+0.03	+0.15	+0.25	+0.46[2]
Weight	−0.01	+0.09	+0.37[2]	+0.43[2]
BMI	0.00	+0.02	+0.42[2]	+0.31[2]
Chest width	−0.04	+0.14	+0.43[2]	+0.19
Chest depth	+0.13[2]	−0.13	+0.04	+0.26
SaO_2	−0.13	−0.27	+0.09	+0.11
End-Tidal CO_2	−0.15	−0.06	−0.18	−0.25
			(n = 13)	(n = 18)
Age with height	+0.72[2]	+0.74[2]	+0.62[2]	+0.38[2]

[1] BMI = body mass index, HVR = hypoxic ventilatory response, SaO_2 = percent of oxygen saturation of arterial hemoglobin.
[2] $P < 0.05$.

TABLE 4. Bivariate correlations with resting ventilation and HVR in samples of adults 20 years of age and older[1]

	Tibetan		Aymara	
	Males	Females	Males	Females
Resting ventilation with:				
Age	+0.13	−0.05	−0.13[3]	−0.05
Height	−0.02	−0.10	+0.20[2]	+0.13
Weight	−0.01	+0.08	+0.15[2]	+0.16[2]
BMI	+0.00	+0.18	+0.08	+0.11
Chest width	−0.08	−0.09	+0.17[2]	+0.26[2]
Chest depth	−0.01	+0.14	+0.05	+0.19[2]
HVR	+0.53[2]	+0.43[2]	+0.14[2]	+0.18[2]
SaO_2	−0.22[2]	−0.27[2]	+0.11	+0.13[2]
End-tidal CO_2	−0.08	−0.33[2]	−0.38[2]	+0.57[2]
			(n = 65)	(n = 48)
HVR with:				
Age	+0.02	−0.05	−0.18[2]	−0.14[3]
Height	0.00	−0.09	+0.15[2]	+0.14
Weight	+0.02	0.00	+0.15[3]	+0.10
BMI	+0.01	+0.06	+0.10	+0.04
Chest width	+0.16	+0.09	+0.19[2]	+0.17[2]
Chest depth	−0.06	−0.02	−0.05	+0.01
SaO_2	−0.11	−0.14	+0.02	+0.25[2]
End-Tidal CO_2	−0.08	−0.12	−0.15	−0.08
Age and height	−0.12[2]	−0.37[2]	−0.34[2]	−0.27[2]

* $p < .05$, †$p = .05$
[1] BMI = body mass index, HVR = hypoxic ventilatory response, SaO_2 = percent of oxygen saturation of arterial hemoglobin.
[2] $P < 0.05$.
[3] $P = 0.05$.

resting ventilation variance and ½ of the HVR variance and ¾ of the end-tidal CO_2 variance.

In contrast, the Aymara sample had no significant residual h^2 of resting ventilation, just 22% residual h^2 of HVR and no significant variance in either trait due to shared household effects. Random environmental differences accounted for roughly 7/10 of Aymara resting ventilation and HVR variation.

Lifestyle factors such as drinking salted butter tea among Tibetans, coca chewing among Andean highlanders, and cigarette smoking were considered for their potential to account for some of the random environmental variation. Nearly all Tibetan adults drank salted butter tea, however, the volume consumed (categorized as < 1 L/day, 1–2 L/day or 2+ L/day) was not associated with resting ventilation or HVR variation (F of two way ANOVA by amount of tea and sex on resting ventilation = 0.9, on HVR = 0.1, both $P > 0.05$). Among Aymara adults there was no effect on resting ventilation or HVR of chewing coca leaves (F of two way ANOVA comparing male and female, chewers and non-chewers, controlling for age on resting ventilation = 0.2, on HVR without controlling for age = 0.1, both $P > 0.05$). Non-smoking Tibetan men (Tibetan women do not smoke) had a mean resting ventilation of 21.4 L/min compared with smokers' mean of 17.8 L/min (t = 2.0, p=0.5). There was no smoking-related difference in Tibetan HVR (t = 1.5, $P > 0.05$). There was no influence of smoking on Aymara resting ventilation or HVR (F of two way ANOVA of male and female smokers and non-smokers, controlling for age on resting ventilation = 0.1, on HVR without controlling for age = 0.04, both $P > 0.05$).

DISCUSSION

Healthy Tibetan males and females had markedly higher ventilation than Aymara under normal conditions of ambient hypoxia and under conditions of additional experimentally-induced hypoxia at 3,800–4,065 m. Tibetan adults at rest breathed about 1.5 times more air per minute than Aymara. When exposed to additional experimentally-induced hypoxia, Tibetan breathing in-

TABLE 5. Multiple regression analysis of adult resting ventilation: R^2 and F of R^2 differences with the addition of predictor variables[1,2]

	Multiple R^2 of age, SaO_2 and HVR	R^2 change with height added	R^2 change with chest width added	R^2 change with chest depth added	Multiple R^2 with age, SaO_2, height, chest width and chest depth
Tibetan men	0.324[3]	0.001	0.012	0.005	0.360[3]
Tibetan women	0.247[3]	0.000	0.005	0.038[3]	0.290[3]
Aymara men	0.047	0.036[3]	0.018	0.001	0.101[3]
Aymara women	0.068	0.032	0.072[3]	0.019	0.193[3]

[1] SaO_2 = percent of oxygen saturation of arterial hemoglobin, HVR = hypoxic ventilatory response.
[2] The statistical test was an F test of the increase in the amount of explained variance with the addition of each predictor variable. The multiple correlation coefficient for the three variable model was 0.59 for Tibetan men, 0.50 for Tibetan women (both $P < 0.05$), and 0.21 for Aymara men and 0.22 for Aymara women (both $P > 0.05$). The multiple correlation coefficient for the six variable model was also 0.60 for Tibetan men, 0.54 for Tibetan women, and 0.32 for Aymara men and 0.44 for Aymara women (all $P < 0.05$).
[3] Significance of $F < 0.05$.

creased roughly twice as much as the Aymara. For example, a 10% fall in SaO_2 produced an average 9.3 L/min increase among Tibetan men compared to a 4.5 L/min increase among Aymara men. The population difference occurred from the second through the ninth decade of life.

The study was designed and implemented to exclude differences in recruitment and measurement as sources of error. With respect to recruitment, the method of identifying and contacting study participants was the same and the rate of family and individual participation was high in both study sites. Sample selection in the present study began with a complete census of the local community and eventually included 96% of the Tibetan and 77% of the Aymara households; 68% of the Tibetans eligible by age and 57% of the Aymara eligible by age. The large proportion of households and individuals participating makes it unlikely that the results are influenced by selection bias for ventilatory traits.

With respect to measurement, several lines of evidence indicate that the sample differences are substantive rather than an artifact of methodology. First, the same investigator used the same equipment (with the noted exception of the capnometer) and carefully administered the same testing protocol in both study sites. The same criteria for excluding determinations from analyses were applied in both sites. (We found no other published criteria or rate of exclusion.) Second, the repeatability of the resting ventilation and HVR determinations was good and was similar in the two study sites. A review of 33 published studies of resting ventilation found no reports of repeatability with which to compare these findings. A review of 23 published studies of HVR found three mentions of HVR repeatability. Those three reported the average of two trials as the HVR and reported that the two trials were "not different" in a US sample (Chapman and Cherniack, 1987), and differed by an average of -0.03 ΔL BTPS/min/Δ%SaO_2

TABLE 6. Relative variance components of ventilation in Tibetan and Aymara high altitude native samples[1]

	Proportion of total phenotype variance					
Variables	Covariates[2]	Genes	Household	Environment	Total phenotypic S.D.	Residual h^2
Tibetan						
Resting ventilation	0.014[4]	0.313[4]	0.303[5]	0.370	7.556	0.317
HVR	0.000	0.345[3]	0.153[3]	0.502	0.734	0.345
End tidal CO_2	0.029[3]	0.218[3]	0.000	0.753	5.538	0.225
Aymara						
Resting ventilation	0.203[6]	0.044	0.073	0.680	2.378	0.055
HVR	0.051[6]	0.209[4]	0.025	0.715	0.252	0.220

[1] h^2 = heritability, HVR = hypoxic ventilatory response.
[2] Covariates for Tibetan resting ventilation are height and male age, for Tibetan end-tidal CO_2 they are female age and age^2, for Aymara resting ventilation they are sex and height, for Aymara HVR it is height.
[3] $P < 0.05$.
[4] $P < 0.01$.
[5] $P < 0.001$.
[6] $P < 0.0001$.

(Curran et al., 1995) and an average of +0.02 ΔL BTPS/min/Δ%SaO_2 (Zhuang et al., 1993) in two samples of Tibetan males. Those calculations differ from the present repeatability measures (the average difference between two days of HVR calculated as the average of three determinations each day). Yet, they accord well with the repeatability of −0.05 and +0.12 ΔL/min/Δ%SaO_2 found in the present study and indicate some consistency of HVR repeatability across studies. Third, the possibility that responses to testing might account for the sample differences can be discounted. If the Tibetans, but not the Aymara, were anxious during the ventilation determinations, then this could result in a systematic elevation of pulse and oxygen saturation in the ventilation testing situation compared with a non-ventilation testing situation in the Tibetan, but, not the Aymara sample. This was not observed. Instead, the differences between pulse measured during quiet rest and that measured during the resting ventilation determination was 3–4 f/minute in both sites and the difference between SaO_2 measured during quiet rest and that measured during the resting ventilation determination was about 1% in both sites. The two study samples appear to have responded similarly to ventilatory testing (alternatively, they were equally anxious).

Fourth, the possibility that the Tibetans participating in this study were unique can be discounted by comparing the results of the present study with those of previously published studies of Tibetan men (we are not aware of any on Tibetan children or women). The differences of 0.8% (Tibetan) and 1.2% (Aymara) between resting and testing SaO_2 found in the present study were very similar to the 0.7% and 2.1% reported for Tibetan men measured with and without mouthpieces (Zhuang et al., 1993; Curran et al., 1995). The resting heart rates of Tibetan men in the present study are 73 f/min which is in the range of 71–87 f/min reported for young adult Tibetan men measured at their habitual altitudes of residence (Ge et al., 1994 a; Zhuang et al, 1993; Sun et al., 1990); as well as the range of 56–92 f/min reported for Tibetan men measured while visiting at altitudes below their habitual altitudes of residence (Curran et al., 1995; Ge et al., 1994b). The standard errors of the mean (SEM) of resting heart rates were similar also (ranging from 1.4 in the present study to 3 in Curran et al. 1995). The breathing frequency of the present sample of Tibetan men was 15 f/min which is slightly lower than the 17–21 f/min reported for Tibetan and Sherpa men measured at or near their habitual altitudes of residence (Sun et al., 1990; Ge et al., 1994 a and b; Hackett et al., 1980; Zhuang et al., 1993) and the 21 f/min reported for Tibetan men measured while visiting at lower altitudes (Curran et al, 1995; Ge et al, 1994b). The SEM of breathing frequencies were similar in the various studies (ranging from 0.4 in the present study to 1.1 in Hackett et al. 1980). The adult male resting end-tidal CO_2 of the present sample of Tibetan men is 30.1 Torr which is a bit higher than the 29 Torr reported for Sherpas at 1,700 m who live and work at a variety of altitudes and lower than the 32 Torr reported for men at their habitual altitude of residence (Zhuang et al., 1993) and 33 Torr reported for Tibetan men visiting at lower altitude (Curran et al., 1995). The SEM of end-tidal CO_2 were also similar in the various studies (ranging from 0.5 in Sun et al., 1990 and Zhuang et al., 1993, to 0.9 in the present study, to 1.1 in Ge et al., 1994a). The similarity of the means and standard errors indicates that the study subjects were equally at rest during the present and published studies (or that all Tibetans are anxious).

In summary, small physiologic differences between resting and testing situations are evidence that the testing apparatus did not induce anxiety. The good repeatability indicates that study participants were not anxious during their first ventilation tests and that the measurement techniques were precise. The similar size of these differences in the two sites suggests that the Tibetan and Aymara study participants were equally comfortable during ventilation testing and that the measurement techniques did not differ. The repeatability findings and resting physiological data accord with other published studies of Tibetans and indicate similar repeatability of measurement technique and similar relaxed state of the study partici-

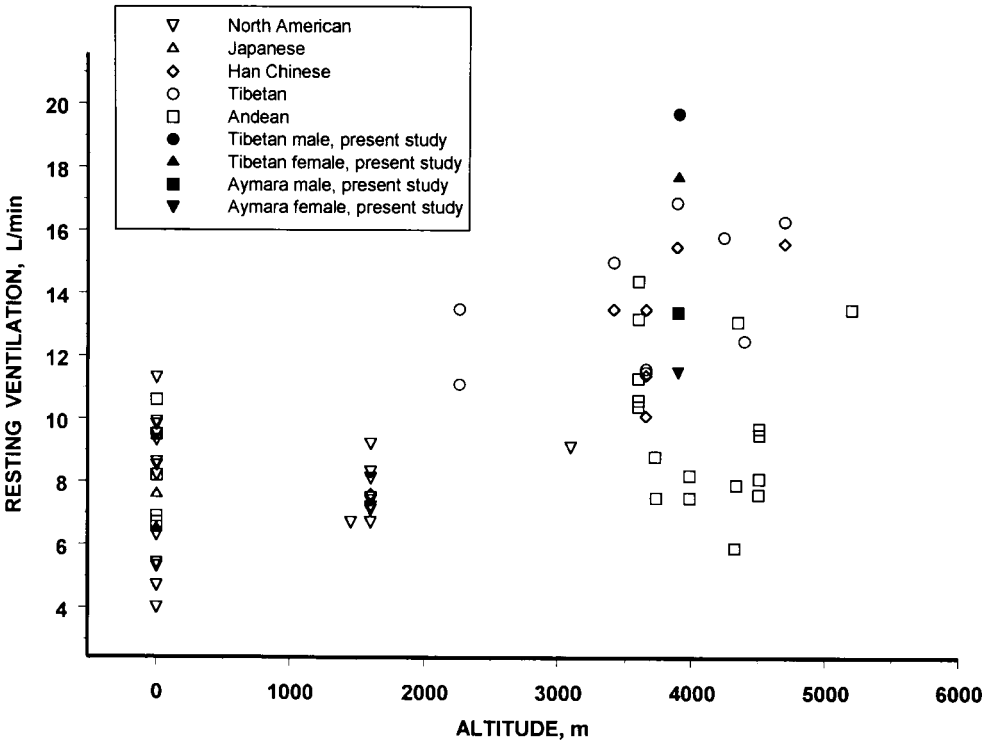

Fig. 3. Summary of studies of resting ventilation at various altitudes.

pants. These diverse lines of evidence argue strongly that the findings of the present study are substantive, rather than methodological.

The adult findings of the present study are quantitatively consistent with previous reports of resting ventilation and HVR on smaller and less representative samples of Tibetans and Andean highlanders. Figure 3 summarizes reports of mean values of resting ventilation of 1,116 natives and long-term residents above 2,000 m, including 632 from the present study, and contrasts these with reports from low altitude.[2] There is a wide range of variation at all altitudes. There is a 7.3 L/min difference between the lowest and highest North American mean resting ventilation and there is an 8.5–8.6 L/min difference between the lowest and highest Tibetan and Andean resting ventilations. The wider span of values at high altitudes probably reflects the range of altitudes of the studies. The lowest Tibetan resting ventilations overlap only with the highest sea level values. In contrast, the means of eleven of the fifteen Andean samples lie in the sea level range and just four are above. That is, Andean high altitude natives generally breathe at rest about

[2]Studies reported values in L if a flow measurement (e.g. pneumotachograph) were used and in L BTPS if a volume measurement (e.g. weather balloon) were used. To determine whether the two types of measurements gave similar results, we conducted analyses of variance comparing the published means of low altitude samples reporting resting ventilation in L measured by pneumotachograph, ventilation in L measured by other flow devices (hot-wire flowmeter or bidirectional turbine) and ventilation in L BTPS measured from a volume. There was no significant effect of measurement technique on resting ventilation or HVR. Therefore we report the published means on the same figures. Reports of studies employing pneumotachographs include those by Filuk et al., 1988; Georgopoulos et al., 1989 a and b; Holtby et al., 1988; Littner et al., 1984; Peterson et al., 1981; Sato et al., 1992. The studies by Schoene, 1982 and Schoene et al., 1990 using pneumotachographs were corrected to BTPS. Studies employing other flow devices include Nishimura et al., 1987; Nishimura et al., 1989; Poulin et al., 1993; and Suzuki et al., 1989. Studies reporting volume measure in L BTPS include Altman and Dittmer, 1971; Beall et al., 1992; Chapman et al., 1987; Chiodi, 1957; Cruz, 1973; Cudkowicz et al., 1972; Curran et al., 1995 ; Ge et al., 1994 a and b; Ge et al. , 1995; Hackett et al., 1980; Huang et al., 1984; Hultgren et al., 1965; Hurtado et al., 1964; Kryger et al., 1978; Levine et al., 1992; Moore et al., 1986. The Huang et al., 1981 study did not specify measurement technique and it is assumed to be BTPS.

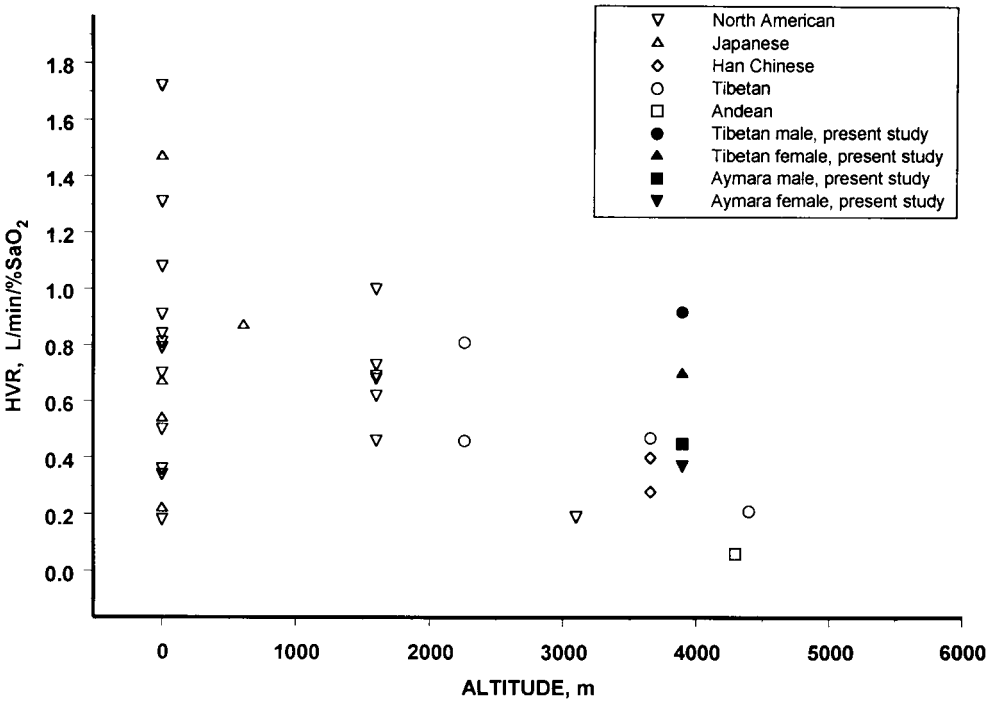

Fig. 4. Summary of studies of HVR at various altitudes.

the same as or slightly more than low altitude natives at low altitude despite the difference in hypoxic stimulus to breathe.

Figure 4 summarizes reports of mean HVR in 788 adult natives and long term residents above 2,000 m, including 639 from the present study, and contrasts these with reports from low altitude. Again, there is a wide range of variation among low altitude sample means. All but one of the high altitude samples lie within that range. Five of the six Tibetan sample means lie in the middle of the sea level range of variation while one is in the low end. The present Andean sample lies in the lower end of the sea level range and the one other study of Andean highlanders reporting HVR in this form reported a mean below the sea level normal range.

Figures 3 and 4 illustrate that, compared with samples at sea level, adult Tibetan high altitude natives have generally elevated resting ventilation and mid-range HVR while Andean high altitude natives have mid-range resting ventilation and low-range HVR. However, the wide range of variation at any one altitude limits confidence in comparisons between altitudes and populations. For example, the mean HVR of samples reported from the same North American laboratory at 1,600 m ranges from 1.0 to 0.46 ΔL BTPS/min/Δ %SaO_2 which is roughly the same as the contrast of 0.93 and 0.37 ΔL/min/Δ%SaO_2 between Tibetan men and Aymara women in the present study.

The traditional explanation has been that the Aymara acquired blunting due to prolonged exposure to high altitude hypoxia. In the present study, ambient hypoxia inferred from barometric pressure was similar in the two sites (478 and 479 Torr). Physiological hypoxia was different in the two sites as Tibetans had lower mean SaO_2. Duration of hypoxia (older age) was not an important determinant of resting ventilation and HVR in either of the present samples. The only negative association of HVR and age was small and could be due to the smaller number of older men. Otherwise no associations between either measure of ventilation and

age were found during adulthood. Thus the population difference was not due to acquired blunting during adulthood in the present study.

This finding contrasts with some but, not all, investigations of acquired blunting. One Andean study compared five long term male residents at 3,990 and 20 at 4,515 m with newcomers and found a low resting ventilation (Chiodi, 1957). However, another Andean study of sea level natives at high altitude failed to find any longer term migrants with low HVR (Sorenson and Severinghaus, 1968). One study of Tibetans reported no change in HVR with age across the span from 21 to 31 years of age (Zhuang et al., 1993). Another noted a significant moderate decrease in HVR from 20 to 30 years of age in a sample of 20 Tibetan males native to ≥4,400 m measured while visiting at 3,658 m (Curran et al., 1995). That finding may be due to the small sample sizes at the ends of the age range that captured a restricted portion of the range of variation rather than to a biological phenomenon in the population. Another noted a decrease in HVR with increasing altitude exposure assessed as a multiple of altitude of birth and years of residence at that altitude (Hackett et al., 1980). That sample of elite Sherpa male climbers was native to a range of altitudes and had a variety of exposures to altitude including the summit of Everest and was measured while visiting at 1,377 m. Inspection of the published figure reveals that the impression of an association is mainly due to two Sherpas who were outliers on the altitude exposure variable and who had negative HVRs. Three of 25 Sherpas (12%) measured had negative HVRs, yet, just ten of the 418 men (2%) in the present study had negative HVRs. These observations suggest that the sample may not have been representative of high altitude native Sherpa and that the conclusion that the reported results are due to duration of altitude exposure may be confounded by self-selection for the occupation of high-altitude climber. These differences in sample size and/or sample characteristics may account for the different conclusions of published studies suggesting an association between blunting and longer duration of high altitude exposure and the present study which finds no such association.

Nor is severity of hypoxia an important determinant of resting ventilation and HVR in the present sample. Within populations there was a small negative Tibetan association between SaO_2 and resting ventilation, but not HVR, that accounted for very little variation. Apart from the small positive association of SaO_2 and resting ventilation in Aymara females, associations of SaO_2 with ventilation were not found in the Aymara sample. Between populations, the more hypoxic Tibetans had higher ventilations. This also contrasts with a previous study. One previous report measured a sample of Tibetan men native to ≥4,400 m measured while visiting at 3,658 m and compared it with a sample of residents at 3,658 m (Curran et al., 1995). It found a lower HVR, but not resting ventilation, in the sample visiting from high altitude and concluded that it was due to the more severe lifelong hypoxia at ≥4,400 m compared with 3,658 m. The present study found the opposite: Tibetans with more severe hypoxia had slightly higher resting ventilation, but not HVR, and between samples, the more hypoxic Tibetans had higher ventilations and HVR. Possible reasons for the different findings include the following. The sample from ≥4400m in that study was selected to match a sample from a previous study by many of the same authors and thus may not be representative of its population of origin. Furthermore, information on lifelong physiological hypoxia was not provided for those from ≥4,400 m. There is a wide range of physiological hypoxia at any altitude, partly genetically determined in Tibetans (Beall et al., 1994; Beall et al., 1997). For example, some individuals at 4,850–5,450 m have SaO_2 no different from some individuals at 3,800–4,065 m (Beall et al., 1994a; Beall et al., 1997). These considerations make it difficult to evaluate the inference that the lower mean HVR in the sample from ≥4,400 m was due to greater hypoxia at the higher altitude of residence.

The adolescent findings from the present study do not confirm previous studies suggesting that Andean hypoventilation is acquired during adolescence (Lahiri et al.,

1976). The published data on 58 Andean high altitude natives between 13 and 20 years of age were reported categorically as normal, intermediate and blunted, rather than numerically, in the single study available (Lahiri et al., 1976). Therefore it is not possible to examine these data and to suggest a reason for the contrast with the results of the present study of 105 Aymara between 13 and 19 years of age. Generally, a functional ventilatory decrease seems unlikely to develop during adolescence. Circulating levels of estrogen, progesterone and testosterone, all associated with greater resting ventilation and HVR (e.g. Regensteiner et al., 1989; Tatsumi et al., 1991; Tatsumi et al., 1994), increase during adolescence generally (Tanner, 1978). Plasma testosterone concentration increased as expected during adolescence in the present two samples (Beall and Worthman, unpublished observations). Aymara and European adolescents exhibit functional increase in cardiorespiratory characteristics during adolescence at high altitude including an age related increase in ventilation during maximal exercise (Greksa et al., 1985). If hypoxia were the causal agent for the Aymara hypoventilation relative to Tibetans in the present study sample, it would have to have exerted its influence entirely before thirteen years of age. A definitive test of the absence of blunting would require longitudinal studies and studies of younger age groups.

If blunting during adolescence in the Aymara sample does not explain the population differences in ventilation found in the present study, then other factors must be considered. Larger body size could possibly explain the greater ventilation among the taller Tibetans. However, Tibetans also had significantly greater ventilation relative to stature. Among men, the average resting ventilation relative to stature was 12.0 ± 5.1 L/meter among Tibetans compared with 8.4 ± 1.5 L/meter among Aymara ($t = 6.2$, $P < 0.05$). The average HVR relative to stature was 0.58 ± 0.55 ΔL/min/Δ%SaO_2/meter among Tibetans compared with 0.29 ± 0.18 ΔL/min/Δ%SaO_2/meter among Aymara ($t = 8.8$, $P < 0.05$). The same magnitude contrast was found among women. The average resting ventilation relative to stature was 11.6 ± 5.2 L/min/meter among Tibetan women compared with 7.8 ± 1.5 L/min/meter among Aymara ($t = 7.7$, $P < 0.05$). The HVR relative to stature was 0.48 ± 0.42 ΔL/min/Δ%SaO_2/meter among Tibetan women compared with 0.26 ± 0.15 ΔL/min/Δ%SaO_2/meter among Aymara ($t = 5.6$, $P < 0.05$). Comparisons using BMI rather than stature yielded (data not shown) even greater population contrast because the Tibetans have lower BMI. Thus, the shorter stature of the Aymara does not account for their low ventilation compared to Tibetans.

Other factors that might cause Aymara hypoventilation include endurance training and a family history of chronic obstructive pulmonary disease (Saunders et al., 1976; Kawakami et al., 1981). It seems unlikely that either occurs on a population-wide basis from adolescence through old-age in both sexes. Because testosterone raises HVR (Tatsumi et al., 1994), lower testosterone concentrations could hypothetically account for the lower Aymara HVR, but this is also unlikely because the population difference was found among males and females. Furthermore, the Aymara and Tibetan adult male mean plasma testosterone concentrations do not differ (Worthman et al., 1977). There is evidence that intrauterine cocaine exposure is associated with blunted HVR in infant humans and rabbits (Ward et al., 1992; Weese-Mayer et al., 1992). However, the normal Andean newborn resting ventilation and HVR (Mortola et al., 1990; Mortola et al., 1992) argue against any influence of maternal coca chewing. Overall, there was no evidence to suggest that known systematic environmental factors account for the low Aymara mean and variance of resting ventilation and HVR.

On the other hand, the population difference could be due to elevation of Tibetan, rather than depression of Aymara, ventilation. Factors that might cause Tibetan hyperventilation include systematically elevated metabolic rate (Huang et al., 1984; Regensteiner et al., 1990). Because both Tibetan and Andean highlanders have basal metabolic rate similar to those predicted by sea level equations (Beall et al., 1996), this is an unlikely explanation. Early hypertension, reported to increase resting ventilation

(Tafil-Klawe et al., 1989), is common among Tibetans simply because there is a high prevalence of hypertension (Beall et al., under submission a). Reasoning that hypertensives under 25 years of age are likely to be in the early phases of hypertension, an analysis of variance compared the ventilation of Tibetan normo-and hypertensives. Seven of 43 males and eight of 54 females in the 13-24 year age range were hypertensive but did not differ from the normotensives in resting ventilation or HVR. Just one of 177 Aymara in that age range was hypertensive. Caffeine and xanthines are respiratory stimulants in tea (Howell, 1992; Larrick, 1991). Daily intake of a liter or more of black tea flavored with salt and butter was nearly universal among Tibetan adults. Tea consumption was much lower in the Aymara sample where individuals drank just 1–3 cups of black or herbal tea/day. Because Tibetan children and teenagers drink less tea than adults and the population difference was found throughout the age range, tea drinking probably does not account for the Tibetan hyperventilation.

Thus there was little evidence to indicate that sustained lifelong Tibetan hyperventilation and relative Aymara hypoventilation were due to the systematic influence of environmental factors. Population differences in the frequencies of alleles influencing the level of ventilation could account for some of the differences according to the following logic. Quantitative genetic analyses revealed evidence of significant genetic variation in resting ventilation only in the Tibetan sample and more genetic variation in HVR in the Tibetan than the Aymara sample. Because the potential for natural selection is a function of the amount of genetic variance, this means that only the Tibetan population has the potential for natural selection on resting ventilation and it also has more potential for natural selection on HVR. The present data suggest a hypothesis explaining how this came about. With respect to resting ventilation, the combination of high Tibetan values compared to sea level and the existence of intrapopulation genetic variation suggest the hypothesis that natural selection and/or random genetic drift has acted to increase the frequency of alleles for high ventilation. The similarity of Aymara resting ventilation compared to sea level values, the absence of Aymara genetic variation, and the absence of evidence for environmental blunting of Aymara ventilation suggest the hypothesis that natural selection has not acted on resting ventilation in Andean populations because there was no heritable variation upon which to act. With respect to HVR, the combination of normal Tibetan values compared to sea level, the existence of Tibetan genetic variation, and of genetic variation in HVR of sea level populations (Collins et al., 1978; Kawakami et al., 1984; Kawakami et al., 1981; Moore et al., 1976; Saunders et al., 1976) suggest the hypothesis that natural selection has acted to maintain existing genetic variation in the Tibetan sample. The low normal to below sea level Aymara HVR and the relatively low genetic variance suggest the hypothesis that genetic variation has been lost in the Andean population due to natural selection and/or random genetic drift and that alleles for high values have been lost. Current knowledge of the genetics of these traits does not permit direct evaluation of these models positing different microevolutionary histories leading to different ventilation patterns in these two populations with long histories of high altitude exposure.

The conclusion of this paper differs fundamentally from previous studies emphasizing the importance of acquired hypoventilation and blunting of HVR. One methodological reason for this may be the combination of the small samples often reported, sometimes of specialized occupational groups, sometimes not measured at their habitual altitudes of residence, and usually of unspecified representativeness. Another methodological reason for the different conclusion may be the broad age range sampled in the present study which provided the opportunity to observe trends or, more importantly as it turned out, their absence. Another reason may be the extraordinarily wide range of normal variation in these two traits. The coefficient of variation of HVR was 0.56 among the Aymara and 0.90 among Tibetan adults in the present study while the coefficient of variation in height was 0.05 in both

samples. Others have noted that normal HVR varies eight-fold (e.g. Reeves et al., 1993). That much variation in a trait such as height would be unimaginable. With such a variable trait, there is great potential for misleading findings from small samples that inadvertently capture just a fraction of the normal range.

It is not clear whether the ventilation differences are relevant to successful high-altitude adaptation. Lower ventilation would seem likely to increase the chances of poorer SaO_2 and oxygen delivery, but, the Aymara sample had the higher mean SaO_2. Both populations deliver adequate oxygen to tissues under a range of conditions as demonstrated by normal basal metabolic rates and maximal physical work capacities, (Baker, 1976; Beall, et al., 1996; Lahiri et al., 1976; Mazess et al., 1969; Sun et al., 1990; Tufts et al., 1985). Both populations are successful by a number of criteria generally used for evolutionary analyses. Both are growing populations. The Tibetan population had a 15.2/1,000 rate of natural increase in 1990 (Xi Zang Tong Ji Jian Jian, 1993) and the Andean region had a 20.5/1,000 rate of natural increase in 1990–1995 (Pan-American Health Organization, 1994). Both have persisted for millennia in their high altitude environments. The earliest chronometrically dated evidence for occupation of the Tibetan Plateau above 2,500 m is a farming site that dates to 4,000–5,500 years ago (Chang, 1992). The earliest evidence for occupation of the Andean Plateau above 2,500 m dates to 11,000 years ago (Aldenderfer, in press 1997). These functional and demographic lines of evidence suggest that both populations are well-adapted.

Thus the relatively low ventilation does not appear to have particularly adverse consequences for the Aymara and the hyperventilation does not appear to be particularly advantageous for the Tibetans. However, these traits must be viewed in a broader context. The Tibetan and Aymara samples differ on more than ventilation. The Tibetans also have significantly lower hemoglobin concentration and SaO_2 than the Aymara (Beall et al., 1997, submitted). There is evidence for significant genetic variation in Tibetan resting ventilation, HVR, SaO_2 (for which there is a major gene) and hemoglobin concentration. There is evidence for an absence of genetic variance in Aymara resting ventilation and SaO_2, small genetic variance in HVR, and substantial genetic variance in hemoglobin concentration (Beall et al., 1994; Beall et al., under submission). The results of the present paper add evidence to the hypothesis that natural selection has acted on a suite of traits to produce quantitatively different, well-adapted phenotypes in these two populations with long, successful histories of high altitude residence.

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