HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 1, Number 1, 2000, 25–32
Mary Ann Liebert, Inc.

Oxygen Saturation Increases During Childhood and Decreases During Adulthood Among High Altitude Native Tibetans Residing at 3800–4200 m

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ABSTRACT

This report describes age differences in oxygen saturation throughout the life cycle in a sample of high altitude native Tibetans residing in villages at 3800–4200 m altitude in the Tibet Autonomous Region, China. Oxygen saturation of 3812 Tibetans was measured by pulse oximetry and a subsample of 1582 healthy, nonpregnant, nonsmokers from 1 week to 80 years of age was selected for analyses. Infants under 1 year of age had 5–6% lower oxygen saturation than the peak of 89.8% attained at 11 years of age. There was a steady increase in mean oxygen saturation-for-age during the first decade of life, but not during the second decade. Adult males exhibited a slight decrease starting in the 20–29 year age range. Adult females maintained the peak oxygen saturation through the 40–49 year age range, exhibiting a decrease in oxygen saturation beginning in the 50–59 year age range and as a result had higher oxygen saturation than males during the female reproductive span. Thus, developmental factors during infancy and childhood, but not adolescence, enhanced oxygen transfer in this high altitude native resident Tibetan sample. The age of onset of aging processes detrimental to oxygen transfer differed for females and males.

Key Words: oxygen saturation; high altitude; Tibetans; age differences

INTRODUCTION

VARIATION IN THE PERCENT OF OXYGEN saturation of arterial hemoglobin (oxygen saturation, SaO_2) of healthy people at high altitude is evidence of variation in ventilation and in the transfer of oxygen from the air to the blood. Identifying factors associated with such variation may lead to recognizing characteristics associated with differences in the effectiveness of the initial steps of the homeostatic response to high altitude hypoxia. Age may be a relevant factor for oxygen transfer. Age is also relevant to understanding the potential for natural selection to increase the frequency of alleles enhancing oxygen transfer because natural selection is strongest early in life and decreases in strength with age (Finch, 1990). A trend toward lower SaO_2 at older adult ages identified among Tibetan and Andean high altitude natives (Beall et al., 1997b, 1999) suggests that biological aging processes in one or more systems underlie poorer homeostasis similar to that observed at sea level (Cotes, 1979). At the other end of the life-cycle, infants have 2–3% lower SaO_2 during the first few months of life than adults at 1600 and 3100 m in Colorado (Kryger et al., 1978; Huang et al., 1984; Thilo et al., 1991;

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Niermeyer et al., 1993). Similar findings were reported for Han Chinese infants at 3658 m in the Tibet Autonomous Region. However, Tibetan infants already had SaO_2 similar to that reported in another study of Tibetan adults at that altitude (Zhuang et al., 1993; Niermeyer et al., 1995). Those findings suggested that developmental phenomena underlie early increases in SaO_2 in some high altitude populations, but, not Tibetans. A possible reason for the difference is the long history of Tibetan residence at high altitude and the opportunity for natural selection to have acted to increase traits that enhance oxygen transfer early in life. In contrast, the Colorado and Han Chinese populations have migrated to high altitudes only in recent decades and natural selection has had little opportunity to act. However, those infant–adult comparisons are based on separate studies of infant and adults made by different investigators using different protocols for infants and adults. Information obtained using the same measurement technique over a wide age range would be required to address the hypothesis that Tibetan high altitude natives attain adult levels of SaO_2 in the first few months after birth.

This report provides cross-sectional information on oxygen saturation in a sample of 1582 Tibetan high altitude natives between one week and 80 years of age residing in villages between 3800 and 4200 m altitude in the Tibet Autonomous Region, China. Infants at this altitude had 5–6% lower SaO_2 than young adults and SaO_2 increased with age during the first 10 years of life. Among adults, a trend toward lower SaO_2 began in their twenties among males and in their fifties among females.

MATERIALS AND METHODS

Oxygen saturation of 3812 high altitude native resident Tibetans was measured with pulse oximetry from December 1997 through June 1998. The study participants ranged from one week to 95 years of age and lived in 14 rural villages at altitudes ranging from 3800–4200 m in Medrogungar, Lhundrup, and Benam counties, Tibet Autonomous Region, China. Tibetan research assistants collected data during visits to 905 households, 95% of those identified by local officials. Everyone encountered in each household was invited to participate in a survey that involved providing information on age, sex, pregnancy status, self-reported health status, self-reported symptoms of chronic obstructive lung disease, medications, and smoking behavior as well as measurement of oxygen saturation. About 63% of the household residents were contacted and 95% of those contacted agreed to participate (3812 of 4024). Sixty-eight percent of those who declined to participate were under 10 years of age.

Six villages were located at 3800 m, three villages at 3850 m, two villages at 4065 m, and three villages at 4200 m altitude. The proportion of people in four broad age ranges (under 10 years, 10–19 years, 20–49 years, and over 50 years of age) did not vary across the altitudes ($\chi^2 = 13.3$, $df = 9$, $p > 0.05$). The proportion of males and females did not vary across the altitudes ($\chi^2 = 7.8$, $df = 3$, $0.10 > p > 0.05$).

Age was reported in years. An individual is 1 year of age at birth in the Tibetan system, turns 2 years of age at the next Tibetan New Year, turns 3 years of age at the subsequent Tibetan New Year and so on. Thus Tibetan ages average 18 months higher than Western ages. One year was subtracted from an individual's reported age to obtain Western age in elapsed years since birth. Age was confirmed using the reported animal year of birth translated into the corresponding Western calendar year. In rural Tibet, an individual's animal year has more cultural meaning than his chronological age and is an important datum to remember. Therefore, animal year took precedence when there was a discrepancy between the two forms of age estimation. Parents were asked to recall the month of birth of infants under 2 years of age and the week of birth of infants under 2 months of age.

A Criticare model 503 pulse oximeter (Waukesha, WI) was used to measure pulse oximetry on the right forefinger of individuals 8 years of age and older using a finger sensor and on the right big toe of children under 8 years of age using a multisite sensor. Adequate perfusion to the hand or foot was ensured by placing it on a hand warmer for a few minutes while the questionnaire was administered prior to the measurement and allowing it to remain there throughout the measurement. Individuals sat quietly for about 5 min before the measurements began and sat silently during the measurements. After placing the sensor on the finger or toe, the research assistant waited until a reading registered on the oximeter display, waited another 10–15 sec to verify a steady signal, and then began recording SaO_2 and pulse using the Criticare model 550 printer module programmed to record every 10 sec. Six observations were recorded and their average was used as the individual's SaO_2 as in previous studies (Beall et al., 1992, 1994, 1997a, 1999; Beall and Goldstein, 1990). The repeatability of the SaO_2 measurements was evaluated by remeasuring 65 people and calculating the average difference between the two measurements on different days (Bland and Altman, 1986). The average difference was $0.33 \pm 3.7\%$ SD ($n = 65$). This value is slightly lower than the value of $1.0 \pm 0.6\%$ obtained in another study of high altitude native Tibetans that reported familial patterning of SaO_2 consistent with a Mendelian pattern of inheritance (Beall et al., 1997b).

Health status was evaluated by the individual's own report. Interviewers asked two general questions about the study paticipant's health and current medications. They subsequently asked specific questions about cough, phlegm production, and breathlessness. Individuals reporting any of those symptoms were asked about the time of day, occurrence throughout the day, seasonality, and persistence of the symptoms. Adult household members answered on behalf of young children and infants. Smoking status was established by asking if the individual smoked and if so, how many cigarettes per day. Pregnancy status was established by asking each woman if she was pregnant.

Table 1 summarizes the criteria involved in selecting a healthy subsample of individuals from the sample of 3812 with SaO_2 measurements. Nine individuals with oxygen saturation more than three standard deviations below the mean were excluded. 1068 people reporting poor health or a chronic illness that might impair oxygen saturation (such as lung or heart disease, tuberculosis) were excluded as were 1168 who reported themselves as healthy yet also reported temporary (<3 months' duration) symptoms of chronic obstructive pulmonary disease such as cough or breathlessness. Seven pregnant women who remained in the healthy subsample were also excluded along with two women for whom pregnancy status was not determined. Seventy-eight cigarette smokers were excluded. The sample of healthy people remaining for analyses was 1582. There were 675 males and 907 females with an average age of 18 years ranging from a low of 1 week to a high of 80 years.

Means and standard errors of the mean (SEM) are reported. The effects of age and sex on SaO_2 are evaluated using a general linear model.

TABLE 1. SELECTION CRITERIA APPLIED TO IDENTIFY THE HEALTHY SUBSAMPLE FOR ANALYSIS

Characteristic	*Number of people excluded on the basis of this criterion*	*Mean ± SEM of SaO_2 of remaining sample*	*Number of people remaining in sample*
Total sample		88.2 ± 0.03	3,812
$SaO_2 > 3$ SD from mean	9	88.3 ± 0.03	3,803
Self-reported illness	1068	88.5 ± 0.02	2,835
Self-reported COPD symptoms, not excluded by above criteria	1168	88.8 ± 0.04	1,667
Pregnant, not excluded by above criteria	7	88.8 ± 0.04	1,660
No information on pregnancy status, not excluded by above criteria	2	88.8 ± 0.04	1,658
Cigarette smoker, not excluded by above criteria	78	88.8 ± 0.05	1,582

RESULTS

Figure 1 is a scatterplot of SaO_2 with age for the total sample of 1582 healthy, nonpregnant, nonsmokers. The superimposed curve is a locally weighted linear regression. A trend toward higher values in the first decade of life is followed by a trend toward lower values in subsequent decades. There are scattered low values in the 70s and scattered high values in the high 90s throughout the age range. The average saturation for the total sample was 88.8 ± 0.05% with a range from 66.8 to 99.0%.

Figure 2 presents the mean ± SEM of SaO_2 in 1-year increments for the 1063 study participants under 20 years of age. The standard error decreased markedly after 2 years of age. The mean SaO_2 of the 43 infants under 1 year of age was 83.6 ± 0.14% with a range from 68.3 to 96.3%. A mean SaO_2 of 89.3 ± 0.38% with a range from 83.2 to 96% was achieved at 11 years of age. From 11 through 19 years of age there were minor fluctuations of less than 0.6% in the mean values, but, no trend toward higher means at older ages. The average SaO_2 of males in this age range was 88.5 ± 0.09% (n = 503). The average SaO_2 of females in this age range was 88.6 ± 0.09% (n = 560).

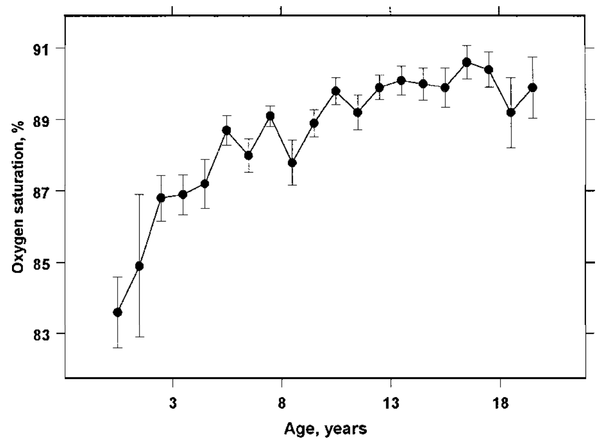

FIG. 2. Mean ± SEM SaO_2 for 1-year age groups from 1 to 19 years of age.

Figure 3 presents the mean SaO_2 for 10 year age groups throughout the age range and illustrates a slight decrease in mean saturation starting in the 20–29 year age group. The mean SaO_2 difference between decades was small in the 10–49 year age range. The difference between the means of the 10–19 year age range and the 40–49 year range was just 0.6%. The age differences increase with age. The mean SaO_2 of those in their fifties was 1.2% lower than the preceding decade and, in turn, the mean of those in their sixties was 1.5% lower than during the preceding decade. The reversal of this trend in the form of the 2.6% higher mean SaO_2 among the 11 people 70–80 years of age suggests that individuals with higher SaO_2 may have substantially higher survival rates. Males had lower SaO_2 than females in the age range above 20 years. The average SaO_2 of males in this age range was 88.2 ± 0.15% (n = 171). The

FIG. 1. Scatterplot of SaO_2 with age for the total sample.

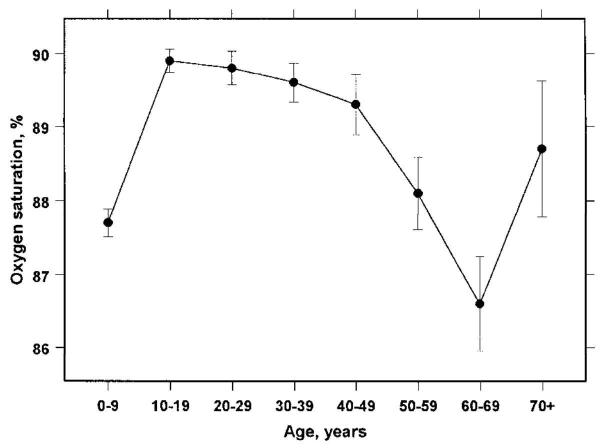

FIG. 3. Mean ± SEM SaO_2 for 10-year age groups from 0–9 to 70+ years of age.

TABLE 2. RESULTS OF THE GENERAL LINEAR MODEL PROCEDURE TESTING FOR THE EFFECTS OF SEX AND AGE ON SaO_2

Source	*Sum of squares*	df	*Mean square*	F	*Sig.*
Corrected model	2885.026	7	412.147	27.256	.000
Intercept	1389709.009	1	1389709.009	91904.357	.000
Sex	133.201	1	133.201	8.809	.003
Age	1616.305	1	1616.305	106.890	.000
Age^2	1096.946	1	1096.946	72.543	.000
Age^3	703.736	1	703.736	46.540	.000
Sex * Age	77.076	1	77.076	5.097	.024
Sex * Age^2	11.526	1	11.526	.762	.383
Sex * Age^3	5.717E-02	1	5.717E-02	.004	.951
Error	23785.731	1573	15.121		
Total	12479323.778	1581			
Corrected total	26670.756	1580			

average SaO_2 of females in this age range was 89.6 ± 0.10% ($n = 347$).

Table 2 presents the results of an analysis testing for the effects of sex while controlling for age, age,^{2} and age^3 and their interactions with sex. Those factors accounted for about 11% of the total variance and there was a significant interaction between age and sex. Figure 4 illustrates that females had higher SaO_2 from the age of 10–19 years through 40–49 years. The mean SaO_2 of females varied little in that age range coinciding with the female reproductive span. SaO_2 of females began to decline in the 50–59 year age range. In contrast, males exhibited no plateau and small age decrements in mean SaO_2 began in the 20–29 year age range.

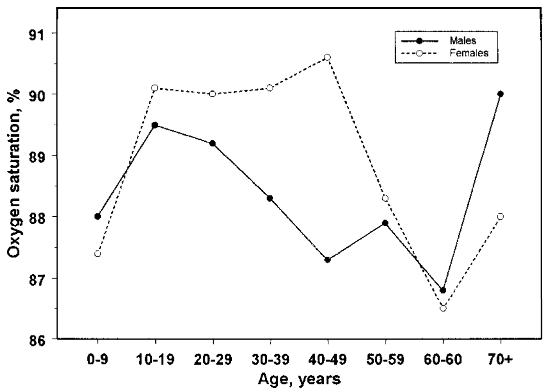

FIG. 4. Sex differences in mean SaO_2 for 10-year age groups from 0–9 to 70+ years of age.

The 14 villages were located at 4 altitudes and there was a trend toward lower SaO_2 at high altitude. The age and sex differences just described for the total sample were observed in the subsamples at the various altitudes. Table 3 reports that the average in the 0–9 year age range at 3800 m was 89.3% as compared with 85.5% at 4200 m. The increase in SaO_2 during the first decade of life occurred at all the altitudes. The average SaO_2 for the 10–19 year age range as compared with the 0–9 year range was 1.6% higher at 3800 m and 3.2% higher at 4200 m. Adult females in the 20–49 year age range had higher SaO_2 than adult males at all the altitudes.

DISCUSSION

Peak SaO_2 values were attained at 11 years of age after increasing from the first year of life. The peak value was essentially maintained through their forties and then declined markedly through their fifties and sixties. Adult females maintained a higher SaO_2 and started to exhibit age differences at a later age than males. The result was higher SaO_2 of adult females.

Pulse oximetry is a noninvasive measure of SaO_2 that substitutes for direct, invasive analyses of arterial blood gases. The pulse oximeter used in this study has been validated against invasive measures and found to be accurate and precise across the range of values reported (Severinghaus and Naifeh, 1987; Nickerson et al., 1988; Hannhart et al., 1991). Several poten-

TABLE 3. AGE AND SEX EFFECTS ON MEAN SaO_2 AT DIFFERENT ALTITUDES

Altitude (m)	N	*Mean SaO_2 in the 0–9 year age range (%)*	*Mean SaO_2 elevation in the 10–19 year age range compared with the 0–9 year age range (%)*	*Mean SaO_2 in the 20–49 year age range (%)*	*Mean SaO_2 elevation among females compared with males in the 20–49 year age range (%)*
3800	735	89.3	1.6	90.2	1.5
3850	422	86.7	2.2	89.2	1.7
4065	126	86.9	3.4	88.7	3.3
4200	294	85.5	3.2	88.9	1.0

tial sources of confounding were controlled by excluding some types of individuals from analyses. Pulmonary or cardiovascular disease might decrease oxygen saturation. Therefore, the sample for analysis was limited to people who reported themselves to be healthy, did not report illnesses that might impair oxygen transfer, and did not report symptoms of chronic obstructive pulmonary disease. Individuals who reported generally poor health or an oxygen-transfer impairing disease had an average SaO_2 of 87.6 ± 0.06% (n = 970) that was lower than the averages of 89.9 and 89.8% in the 10–19 and 20–29 year age groups. Individuals who reported temporary (less than 3 months in duration) symptoms of chronic obstructive pulmonary disease such as cough or phlegm had an average SaO_2 of 88.2 ± 0.05% (n = 1,168). Thus, poor health was associated with lower SaO_2 in this sample. high altitude pregnancy is associated with higher SaO_2 caused by progesterone mediated increase in ventilation (Moore et al., 1987). The 29 pregnant women who were excluded from analyses had an average SaO_2 of 90.7 ± 0.6%. Cigarette smoking might impair lung function and decrease SaO_2. However, smoking also increases carboxyhemoglobin concentration, which the pulse oximeter does not distinguish from oxyhemoglobin. Thus, smokers may have falsely elevated SaO_2 readings. The 78 cigarette smokers had an average SaO_2 of 89.0 ± 0.2%.

The age differences found in this study were not consistent with the age difference found when comparing a study of a small sample of Tibetan infants with a study of a sample of Tibetan adults measured at 3658 m (Zhuang et al., 1993; Niermeyer et al., 1995). From the first week to the fourth month of life, those infants had SaO_2 values no different from adult males at the same altitude of 3658 m. The contrast between the findings of the present study and the previous study could be methodological. The earlier studies used different protocols to obtain the SaO_2 measurements of infants and those of adults. However, the contrast between the two sets of finding may be substantive. For example, the higher altitudes of the present study were more stressful and may have elicited a different response from infants and children. A larger sample including a wide age range at 3658 m would be required to evaluate that hypothesis.

The findings of the present study identify two age-related phenomena during the first decade of life that point to the influence of developmental events on SaO_2. One was the sharp decrease in variance after 2 years of age. It was not due to deaths of infants with low SaO_2. All 15 infants under 2 years of age with SaO_2 below 80% remained alive in the summer of 1999, 1 year after the survey. Instead, the smaller variance suggests that all surviving infants had finally passed through some developmental stage that results in higher SaO_2. The high early variance may be due to differences in the age at attaining that developmental stage and thus a heterogeneous group of infants at the younger ages. There are no relevant data on this age range to suggest what the developmental stage might be. The other age-related phenomenon was the steady increase in SaO_2 from year to year until around the age of eleven. That suggests that some progressive childhood developmental phenomenon influence SaO_2, although again there are no data on factors such as ventilation for most of this age range. The stability of SaO_2 through adolescence is consistent with previous studies of Tibetan and Andean samples (Beall et al., 1997b, 1999).

A plateau of SaO_2 was maintained throughout the adult reproductive period in this sample and was more steadily maintained among females than males. The finding of higher female SaO_2 and sex differences in the age-related changes are distinctive of the present study. Females in another Tibetan sample had very slightly but not significantly higher SaO_2 (Beall et al., 1997b). The larger sample size and greater statistical power of the present study may explain why the sex difference was detected. Recalculating the adult sex differences for individuals 20–49 years of age from several published Tibetan samples reveals that adult females had about 1% higher SaO_2 at 3939 and 4545 m, but 0.4% lower SaO_2 at ~5000 m where both males and females had very low SaO_2 (recalculated from samples reported in Beall and Goldstein, 1990). In contrast, adult females in an Andean Aymara sample had lower SaO_2 than males (Beall et al., 1999). An explanatory mechanism for higher SaO_2 of Tibetan females and lower SaO_2 of Andean females, relative to males, is not apparent. Ventilation and hemoglobin concentration are lower, not higher, among females in this age range in both Tibetan and Andean samples (Beall et al., 1997b). However, ventilation as a function of metabolic rate and their simultaneous influence on SaO_2 have not been examined. The absence of an adolescent growth spurt of SaO_2 and the population contrasts in the adult sex differences argue against a simple hormonal explanation for the sex differences. There is potential for women to experience intermittent progesterone-mediated increases in ventilation and perhaps SaO_2 during the luteal phase of the menstrual cycle. Some of the women in the sample were surely experiencing this progesterone peak. However, that seems unlikely to account for the higher SaO_2 of reproductive age Tibetan women relative to men. That is because some of the Andean women would have been experiencing the same progesterone stimulus to breathe yet they had lower SaO_2 relative to men. Information on progesterone levels and ventilatory response to progesterone would be required to explore this possibility further. Whatever the mechanism, from an evolutionary perspective it is noteworthy that the present study found that the mean SaO_2 was better maintained during the female reproductive span, which is shorter and more circumscribed than the male reproductive span.

This study was consistent with others reporting lower SaO_2 at older ages during adulthood at high altitude (Beall and Goldstein, 1990; Beall et al., 1992, 1997, 1999) and sea level (Cotes, 1979). The progressively larger age differences in mean SaO_2 at older adult ages and the larger standard errors observed in the present study reflect progressively larger standard deviations that are characteristic of many biological aging processes (Comfort, 1979). The standard deviations increased from 3.0% in the 20- to 29-year age range to 4.4% in the 60- to 69-year age range. The larger variance at older ages is usually interpreted as reflecting individual variation in the systems that are failing and causing the deterioration of homeostasis.

The present study identifies two life-cycle stages of particular interest for future studies of ongoing evolution in this population: the first decade of life and the female reproductive span. Natural selection is most powerful when acting on variation expressed early in life rather than late because progressively fewer individuals remain alive at older ages (Finch, 1990). Natural selection can also be powerful when acting during the reproductive span because differential fertility is one means (along with differential survival) of effecting evolutionary change. For natural selection to operate on traits that increase SaO_2, some of the variation in SaO_2 must have a genetic basis. Previous studies provided evidence for a genetic basis to SaO_2 among Tibetans. Significant heritability (h^2) of SaO_2 and an autosomal dominant major gene for 5–6% higher SaO_2 were reported in two different samples (Beall et al., 1994, 1997b).

CONCLUSION

The present study of 1582 healthy high altitude native Tibetans residing in villages at altitudes from 3800 to 4200 m found an age-related increase in SaO_2 during the first decade of life from an average of 83.6% during the first year to an average of 89.8% at 11 years of age. There was no adolescent increase in SaO_2.

A plateau of SaO_2 was maintained through the 40–49 year age range among females, whereas average male SaO_2 began to decrease in the 20–29 year age range, indicating that aging phenomena were manifest earlier among males than females.

ACKNOWLEDGMENTS

This research was supported by the National Science Foundation through award No. SBR-9706980 and by the Henry R. Luce Foundation. The Tibet Academy of Social Sciences, Lhasa hosted this research. Ms. Beimatsho and Mr. Kesang Yishi of the Tibet Academy of Social Sciences successfully accomplished the huge task of collecting the measurements of SaO_2 and interviews in the 905 households. Their patience, hard work, and excellent interpersonal skills are gratefully acknowledged. We also thank the officials and the study participants for their generous cooperation and hospitality.

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Received January 3, 2000; accepted in final form January 25, 2000