

CARDIOPULMONARY FUNCTION IN HIGH ALTITUDE RESIDENTS OF LADAKH

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Abstract

We studied residents of high altitude in Ladakh, India to determine effects of altitude, age, gender, and ethnicity on gas exchange and pulmonary function. Physical examinations, including pulse oximetry, hemoglobin concentration, end-tidal PCO₂, and pulmonary function were conducted on resting Ladakhi and Tibetan subjects at altitudes of 3300 m, 4200 m, and 4500 m. A total of 574 men and women, ranging in age from 17 to 82, were studied. At 3300 m, Ladakhis had higher heart rates than Tibetans in both genders and higher P_{ET}CO₂ in women. Above 4000 m, 21 of the 141 men studied (15%) had Hb concentrations higher than 20 g/dL with one confirmed case of Monge's Disease. There was no gender difference in SaO₂ at any altitude except for pregnant women. At 4600 m, Tibetans had significantly higher peak flows and lower P_{ET}CO₂ than Ladakhis. Ladakhi men had higher diastolic BP than women (91 vs. 81) with no difference in systolic BP. There was no gender difference in BP for Tibetans. An important spirometry finding for both groups was high air flows with mid maximal expiratory flow (MMEF) at 130 – 150% of predicted values compared with 85% for sojourner controls and FEV₁/FVC at 115% compared with sojourner controls at 98 %). Improved lung mechanics may be an important adaptation to the lifelong sustained increased in resting ventilation as well as indoor biomass smoke and outdoor dust exposure of these populations at high altitude.

Key Words Altitude Spirometry Lung Mechanics Hemoglobin
Pulmonary Function Himalayas

Introduction

Physiological adaptations to high altitude and genetic differences among ethnic groups have been studied in resident populations of high altitude in the Andes, Tibet, Nepal, North America, and Europe (reviewed by Beall, 2000; Hochachka and Monge, 2000). Much less is known about high altitude natives in India. Ladakh is one of the most remote regions of India, located with the Karakoram to the northwest, the Himalayas in the southwest, and the Trans-Himalayas at its core. The region was not open to foreigners until 1974. Altitudes range from about 2750 to 7672 m with permanent villages as high as 4650 m.

Increased ventilation is an important and prominent feature of adaptation of sojourners to high altitude. This is not always seen in Natives of high altitude. Some populations, e.g., in the Andes and Colorado, show an acquired blunting of hypoxic ventilatory response (Chiodi, 1957). Other populations including Tibetans and Nepalese Sherpas have lifelong sustained high resting ventilation similar to that of newcomers and a moderate hypoxic ventilatory response (Beall et al., 1997; Hackett et al., 1980; Moore, 2000).

A higher rate of ventilation at high altitude is facilitated by decreased air density, which lowers the resistance to turbulent flow. Accordingly, peak expiratory flow (PEF) increases linearly with increasing altitude (Thomas et al., 1990; Pollard et al., 1996, 1997). Anatomical factors may also favor higher rates of ventilation. High altitude natives often show increased lung volume and compliance (Mortola et al., 1996). Vital capacity is higher in natives of the Andes (Hurtado, 1932; Choidi, 1963; Monge and Monge, 1966), Nepal

(Bangham and Veale, 1976), Bhutan (Cotes and Ward, 1966), Poland (Wolański and Pyzuk, 1972), and Ladakh (Malik and Singh, 1979). Larger airways and improved lung mechanics might accompany increased lung volume.

In contrast, ventilation of high altitude natives is compromised by the high levels of indoor pollution from biomass stoves and environmental dust to which they are exposed. Ladakhis show a high incidence of chronic bronchitis (Norboo et al., 1991) and non-occupational silicosis associated with frequent dust storms (Norboo et al., 1991; Saiyed et al., 1991).

The present study examined pulmonary function in residents of Ladakh as a function of ethnicity, age, gender, altitude, and life style (sedentary versus nomadic). In addition, we obtained other measures of cardiopulmonary function related to high altitude life including hemoglobin concentration, blood pressure, heart rate, arterial saturation, and end-tidal PCO₂.

Methods

Study subjects and sites

We studied natives of Ladakh, Tibetan refugees and Tibetan nomads living in Ladakh. A total of 574 subjects, men and women, ranging in age from 17 to 82 were studied. Data were collected as part of physical exams provided at rural clinics operated by the S.N.M. Hospital in Leh. Six male sojourners, all the members of our group, ages 19 to 57 were also studied. The appropriate institutional review committees reviewed protocols and informed consent was obtained. Subjects were seated and resting for a minimum of 20 minutes before

being tested. Studies were conducted indoors or in shaded locations. Specific study sites and subjects were as follows:

- Tibetan refugee camp near Leh at 3300 m; 70 women, ages 23 to 83; 46 men, ages 24 to 79.
- Village of Phey near Leh at 3300 m; 55 women, ages 20 to 85; 17 men, ages 20 to 81.
- Obstetrics/gynecology clinic at S.N.M. Hospital at 3300 m in Leh.
- Village of Chumathang, 140 km from Leh, at 4193 m; 47 women, ages 20 to 81; 29 men, ages 20 to 82.
- Lake Tsokar, at 4540 m, during a gathering of Tibetan nomads celebrating the Dalai Lama's birthday (July 6); 57 women, ages 17 to 83; 38 men, ages 23 to 80.
- Village of Karzok at 4550 m; 70 women ages 16 to 77; 84 men, ages 18 to 78. The village is near Lake Tsomoriri in upper Rupshu valley, 240 km from Leh. The village is the only permanent settlement in the Rupshu.

Measurements

Subjects were surveyed as to age, exposure to indoor smoke, tobacco use, and exposure to environmental dust. Height and weight were measured and body mass index was calculated as weight (kg)/height (meters)².

Hemoglobin concentration was determined on blood obtained from venipuncture using a portable, battery powered photometer (Hemocue AB, Sweden). This instrument uses a modified azidemethemoglobin reaction

(Vanzetti, 1966) and is calibrated to an accuracy of ± 0.3 g/dl and is linear over the range 0-25.6 g/dl.

End-tidal PCO₂, pulse oximetry (SpO₂), respiratory rate, and pulse rate were measured using a portable, battery powered capnograph (Nellcor Puritan Bennett NPB-75). Accuracy of the measurements is ± 2 mm Hg for PETCO₂, and $\pm 2\%$ for SpO₂ (over the range of 70-100%) tested at altitudes up to 4572 m (http://www.nellcor.com/_Catalog/PDF/Product/NPB-70_75SalesCard.pdf). Our measurements controlled (seated, resting, warm) or accounted for most of the factors known to affect accuracy of the oximetry measurements (e.g., motion artifact, hypotension, vasoconstriction, hypothermia, and anemia), except for carboxyhemoglobinemia, methemoglobinemia (Sinex, 1999). Blood pressure was measured using a sphygmomanometer.

Pulmonary function tests were performed using a portable spirometer (MicroLoop; Micro Medical, UK) on subjects who had been resting for at least 15 min. This is a fixed orifice spirometer that utilizes turbine technology. Accuracy is $\pm 3\%$. Prior studies have shown that results are not affected by either climate or altitude, unlike other spirometers using different technologies (Pedersen et al., 1994; Pollard et al., 1996).

Instructions for performing the forced vital capacity were explained to subjects in their native language (Tibetan, Ladakhi, Hindi, or English) by a member of the S.N.M. Hospital staff or member of the research team. Subjects wearing nose clips performed maneuvers in the seated position. Subjects performed 3 to 6 forced expiratory maneuvers in order to obtain at least 2 reproducible results.

In addition to measured values of lung volume and flows, the spirometer provided data on predicted values based on age, height, race (Caucasian or non-Caucasian), and gender referenced to normal values published by the European Coal and Steel Community (ECCS) (Quanjer et al. 1993). Individuals from other races tend to have smaller lung volumes for the same height and age - a factor adjusted for in the MicroLoop spirometer by multiplying final values by an adjustment factor of 0.9. We also compared our data to a more recent study that provides spirometric reference values for Caucasians, African-Americans, and Mexican-Americans 8 to 80 years old (Hankinson et al., 1999) and to available normalized values for Asians (Jain and Ramiah, 1969; Chin et al., 1997; Korotzer et al., 2000)

Most of the data were analyzed by parametric or non-parametric (Kruskal-Wallis) analysis of variance. Data for percentage of predicted values were analyzed by a one-sample t test or Wilcoxon test (for non-parametric analysis) to determine whether the values in each column differ significantly from a theoretical mean of 100. Regression data were fitted using reduced major axis Model-2 regression, an appropriate method when both variables are measured with error (Pearson, 1901; Kermack and Haldane, 1950). In this method, the regression line is fit to pass through the mean value for the 'x' data and 'y' data with a slope equal to the standard deviation for the y data divided by the standard deviation for the x data.

Results¹

While tobacco use was uncommon, exposure to indoor smoke and environmental dust approached was almost universal. The low use of tobacco is attributable to cultural factors (Ladakhi women generally do not smoke), economic factors (very low disposable income; esp. for nomads), and low availability (esp. for nomads).

At 3300 m, Ladakhis had higher heart rates than Tibetans in both genders and higher PETCO₂ in women. As predicted, Hb was higher in men for both groups with no difference between Tibetans and Ladakhis. There was no gender difference in SaO₂ at any altitude except for pregnant women where the saturation was significantly elevated. Ladakhi men had higher diastolic BP than women (91 vs. 81) with no difference in systolic BP. There was no gender difference in BP for Tibetans.

End-tidal PCO₂ was highly variable. There was no significant altitude effect except for Tibetan women at 4500 m compared to 3300 m. At 4500 m, end-tidal PCO₂ was significantly lower in Tibetan men and women compared with Ladakhis at the same altitude.

Pulmonary function tests were remarkable for all parameters except peak expiratory flow. PEF was not different from predicted values except for Tibetan women at 3300 m and Ladakhi women at 4500 m, where mean values were significantly less than predicted. At 4600 m, Tibetans had significantly higher peak flows than Ladakhis. Finding PEF values not higher than predicted was

¹ Tabular data are available on request from the author at: swood@mountain-research.org.

surprising, given that reduced air density at high altitude should result in higher than predicted peak flows, as seen in the sojourner controls. In contrast, the forced expiratory volume in 1 second (FEV_1) and the mid-maximal expiratory flow (MMEF), were significantly elevated in both Ladakhis and Tibetans compared to % predicted for any race and to sojourners. As shown in Figure 1, MMEF as a percentage of predicted values, was significantly elevated ($P < 0.002$) in both Tibetans and Ladakhis at each altitude except for Tibetan women at 3300 m. Sojourners studied at 4500 m did not show higher than predicted values of MMEF or FEV_1/FVC . Both FEV_1 and forced vital capacity (FVC) were significantly higher than predicted in both Tibetans and Ladakhis at each altitude and there was no gender difference. As shown in Figure 2, the ratio FEV_1/FVC was also significantly higher than predicted for both Tibetans and Ladakhis, independent of gender, at each altitude.

Blood pressure, in general, was not affected by gender, ethnic group, or altitude except for mean arterial blood pressure, which was significantly elevated ($P < 0.05$) at 4500 m vs. 3300m in both Tibetan and Ladakhi males but not females. Also, MAP was significantly higher ($P < 0.0101$) in Ladakhi vs. Tibetan males at 4500 m. Tibetan nomads, both male and female, had significantly lower body mass index than Tibetans living in refugee camps. Blood pressure was not different between nomads and refugees.

Gender and age had predictable effects on spirometry, with slopes of parameter as a function of age similar to those found in Caucasians. Results for FVC and FEV_1 are shown in Figure 3. Data were combined since slopes did not differ for the altitude groups. Linear regression revealed a significant effect of

age, with males having a significantly higher slope than females. Average age did not differ significantly among altitude groups. The slopes and intercepts for males did not differ significantly from those reported for Indian males living at lower altitudes reported by Verma et al. (2002).

Discussion

The most important result of this study is the finding of improved air flow in residents of high altitude. Improved lung mechanics could be an important adaptation to the sustained high levels of ventilation of this population by reducing the work of breathing. Also, the intrinsic improved mechanics might be of special importance to these populations where there is a high incidence of respiratory symptoms due to high exposure to indoor biomass smoke and outdoor dust.

Error Analysis. Because all of the subjects were naïve and instructions for the forced vital capacity maneuver had to be translated, a random sample of 80 flow volume loops were stored and later analyzed for potential artifacts in the data. For example, a falsely high mid expiratory flow rate could result from a delay in the onset of peak expiration (resulting in a sigmoidal versus hyperbolic flow – time curve). This was found to be the case in 10% of the stored samples, a finding that does not alter the conclusions of our study.

Ethnic differences. Small but statistically significant differences ($P < 0.05$) between Ladakhis and Tibetans were present in a few of the parameters we measured; e.g., peak flow, $P_{ET}CO_2$, blood pressure, but in general the two groups were very similar. The general similarity is not surprising

since Ladakhis are a mixture of Mongoloid and Aryan races. The Aryans who settled originally in the sub-continent's northern parts were the early Buddhist people from Kashmir and the Dards from Gilgit. The Mongolian stock is traced to Tibet, from where the shepherds and nomads came to the valleys of Ladakh to graze their flocks. The present day population of Ladakh is the result of blending together of Dards and the Mongolians (Husain, 1987).

Hemoglobin and Arterial Saturation. Although highly variable in our subjects Hb was generally elevated as seen in other high altitude populations. Ethnic differences in this regard have been reported; e.g., Winslow et al. (1989) confirmed that male Sherpas have lower hematocrits than Quechua Indians do at the same altitude of 3700 m (48.4 vs. 52.2). The male Ladakhis and Tibetans we studied at 3300 m had hematocrits of ca. 49% (assumes a MCHC of 33%). There was a significant effect of altitude ($P < 0.001$) in both groups for both saturation and hemoglobin. There was a significant gender effect for hemoglobin ($P < 0.001$) but not saturation in both groups at all altitudes.

We found 21/141 men studied (15%) had excessive polycythemia (Hb > 20 g/dL) and one confirmed case of Chronic Mountain sickness. Assuming mean cell hemoglobin of 33%, hemoglobin concentration of 20 g/dL is associated with a hematocrit of 60%. Polycythemia is a well-recognized adaptation to high altitude that sometimes becomes excessive leading to chronic mountain sickness (Monge's Disease; Monge, 1925).

The etiology of Monge's Disease remains unclear. Winslow and Monge (1987) suggest an important role of hypoventilation in augmenting hypoxia and

subsequent erythropoiesis. Reeves and Weil (2001) provide a metanalysis of data on hemoglobin, arterial saturation, and ventilation to examine the hypothesis put forth by Winslow and Monge. They analyzed hemoglobin concentration (response) as a function of arterial saturation (stimulus). They found that over the range of SaO₂ of 50 to 100% there was a significant inverse relationship between hemoglobin concentration and SaO₂ for both men (r=0.72) and women (r=0.68). Our data cover a narrower range of SaO₂ (70 to 100 %) but show the same pattern. As shown in Figure 4, hemoglobin concentration is significantly related to saturation for both men and women. Although the slope is highly significant (P = 0.0001), the relatively narrow range of saturation and high variability results in r² of 0.11 and 0.10; i.e., only 10-11% of the variation in hemoglobin values is accounted for by saturation. SaO₂ shows higher temporal variation at high altitude due to the greater effect of breathing or apnea on saturation when values are on the steeper portion of the oxygen dissociation curve.

We found no effect of ethnicity or gender at any altitude on SaO₂ except in the case of pregnant women where SaO₂ was significantly elevated. This finding is consistent with previous data on high altitude pregnancy (Moore et al., 1982) and is due to progesterone stimulated ventilation (Lopatin, 1979)

Blood Pressure. The prevalence of hypertension is one of the highest in the world and stroke is the leading cause of death in Ladakh. The mechanism is not known although current efforts are to decrease the sodium intake of local men from 183.6 mmol, in 24 hours (the present average in Ladakh).

Ventilation. The low end tidal PCO_2 of our subjects indicate a significant degree of hyperventilation at rest. For example, the typical end tidal PCO_2 seen in our subjects above 4000 m (30 mm Hg) indicates an approximate 33% elevation of alveolar ventilation (assuming no change in metabolic rate and a $P_{ET}CO_2$ at sea level of 40 mm Hg). This confirms previous data for Tibetans and Nepalese Sherpas showing sustained high resting ventilation similar to that of newcomers and a moderate hypoxic ventilatory response (Beall et al., 1997; Hackett et al., 1980; Moore, 2000). At 4500 m, Tibetans showed significantly higher levels of resting ventilation than Ladakhis with $P_{ET}CO_2$ s of 28 and 31 respectively.

Spirometry. Other cardiopulmonary parameters we measured are generally similar to previous data for high altitude residents in Asia including Nepalese Sherpas who also have high resting ventilation (Beall et al., 1997; Hackett et al., 1980; Moore, 2000) and high vital capacity (Bangham and Veale, 1976). Our data on FVC confirm previous reports of increased thoracic volume and vital capacity of high altitude natives in the Andes (Hurtado, 1932; Choidi, 1963; Monge and Monge, 1966), Nepal (Bangham and Veale, 1976), Bhutan (Cotes and Ward, 1966), Poland (Pyzuk and Wolański, 1972), and Ladakh (Malik and Singh, 1979).

Our data on FVC and FEV_1 agree in part with that of Malik and Singh (1979) and Malik and Pandey (1993) who measured ventilatory capacity in Ladakhi teenage men and women. They concluded, based on regression analysis, that there was higher FVC and FEV_1 in the high altitude subjects. Our data, showing elevated FEV_1/FVC , differs from their study. Although they had

the data, they did not publish the ratio FEV_1/FVC . Analysis of their data for the older teenagers shows no significant difference between the low and high altitude males with respect to either FVC or FEV_1 and there was likewise no significant difference in the ratio FEV_1/FVC calculated from their data with both groups ranging from 84 to 89%. Predicted values for these ages and heights range from 89 to 90% (Hankinson et al., 1999). Likewise, in their study of 171 Indian men at sea level, Verma et al. (2002) measured FVC and FEV_1 as a function of age. They did not calculate FEV_1/FVC , but analysis of their data shows a range from 78% in younger subjects to 71% in older subjects.

In the present study we found that FVC was significantly higher than predicted whereas PEF was not higher than predicted based on age, race, and height and less than predicted based on altitude. The reason PEF might be low is unclear. Since the English speaking sojourners did show expected elevation of PEF, it may have been a problem in the translation of instructions given to the subjects resulting in a sub-maximum effort during forced expiration. This would reduce PEF and FEV_1 without altering FVC or MMEF. Consequently, the values for FEV_1/FVC , while being exceptionally high in our subjects, may be conservative. Similar findings of values for PEF that are less than predicted were reported for natives of Kashmir (1600 m altitude) by Jeelani et al. (1992). They reported FEV_1 values for men and women (3.4 and 2.5 L/sec) similar to the present data and to norms for Caucasians but values of PEF (8.8 and 5.8 L/sec) that were less than predicted but similar to the present data. They did not report data for FVC.

The higher vital capacity of natives to high altitude is not seen in sojourners where, if anything, vital capacity decreases. For example, Mason et al. (2000) studied sojourners during an ascent from 2800 to 5300 m in Nepal. They found a progressive fall in FVC and increase in PEF with increasing hypobaric hypoxia while FEV₁ remains unchanged. They speculated that the fall in FVC may be due to reduced inspiratory force; subclinical pulmonary edema; an increase in pulmonary blood volume, or changes in airway closure.

Ladakhis and Tibetans differ from Peruvian natives of high altitude with respect to improved lung mechanics. Brody et al. (1977) found that despite the larger volumes in highlanders, density-corrected maximum flow rates were similar in highlanders and lowlanders, and flow expressed in FVC'S-S-1 was less in highlanders. They concluded that airways, which form in fetal life, do not participate in adaptation to altitude, and that the large lungs of highlanders result from postnatal environmental hypoxic stimulation of lung growth.

Age. The effect of age on FVC and FEV₁ was not the same for men and women. The slope of the regression of both parameters as a function of age was significantly higher in men. A similar gender difference in age regression coefficients has been reported for Caucasians, with the FVC decreasing by 14-30 ml/year in men and 15-24 ml/year in women and FEV₁ decreasing by 30 ml/year in men and 23 ml/year in women (Anderson and Tockman, 2002). In their review of literature on age effects on spirometry, the American Thoracic Society (1991) provided age regression coefficients for Caucasian men and women from 5-7 studies. The average age regression coefficient for FVC was significantly lower for women than men (-0.020 versus -0.028) but was not significantly

different for FEV₁ (-0.026 versus -0.028). The present study has similar coefficients for men for FVC and FEV₁ (-0.025 and -0.0265) but the coefficients for women are much smaller (-0.015 and -0.016) than those for men and those reported for Caucasian women. However, the present data closely agree with data obtained for Indian men and women living at sea level by Chin et al. (1997) reporting age coefficients for FVC and FEV₁ of -0.024 and -0.026 for males and -0.010 and -0.013 for females.

One possible explanation for the gender difference in spirometry – age relationships would be a difference in the height – age relationship, since height is an important predictor of pulmonary function values. However, analysis of this relationship for the present subjects showed that the height of men did not change significantly with age, whereas there was a significant decline (0.10 cm/yr) for women, opposite to the results that might explain the spirometry – age findings.

Spirometry Standards. Spirometry results are usually standardized according to ethnicity, gender, age, and height and reported as a percentage of predicted values. A recent and comprehensive data set for normal spirometry comes from the NHANESIII study (Hankinson et al., 1999). They showed in a study of 7429 subjects that Caucasian and Mexican American subjects had similar values of FEV₁ and FVC with respect to height and that African Americans had lower values.

The present study shows that Tibetans and Ladakhis have substantially higher values for FEV₁/FVC and MMEF than predicted for Caucasians in both the European Coal and Steel Community (ECCS) (Quanjer et al. 1993) and the

NHANES III studies. There is little prior data on pulmonary function of Tibetans or Ladakhis. However, available literature on spirometry of Asian subjects, including Indians, indicates similar or lower values than those for Caucasians (Jain and Ramiah, 1969; Korotzer et al. 2000; Chin et al. (1997) again pointing to a conservative nature of our data compared with predicted values.

Physiological Significance. The present data point to markedly improved lung mechanics in Ladakhis and Tibetans at high altitude. For example, as it is measured when the lung is about half empty, MMEF describes the function of the mid size airways and, because it is presumed to be independent of effort, a reliable indicator of lung mechanics *per se*.

What is the physiological significance of the improved lung mechanics of these residents of high altitude? One possibility would be improved gas exchange. However, when data for FEV₁/FVC or MMEF were plotted against gas exchange parameters (end-tidal PCO₂ and saturation) there were no correlations. On the other hand, improved lung mechanics could be an important adaptation to the sustained high levels of ventilation by reducing the work of breathing. Also, the intrinsic improved mechanics might be of special importance to these populations where there is a high incidence of respiratory symptoms due to high exposure to indoor biomass smoke and outdoor dust.

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Legends for Figures

Ladakhi subjects are indicated by square symbols; Tibetan subjects are indicated by round symbols; Sojourners are indicated by triangles; women are indicated by open symbols; men are indicated by closed symbols.

Figure 1. Relationship of mid-maximal expiratory flow, expressed as percentage of values predicted for non-Caucasians (Quanier et al., 1993) to altitude in men and women. * Indicates that the actual mean is significantly different from the theoretical mean (100) with a P of < 0.002 or less. Values for sojourner males were significantly lower than those for Ladakhis ($P < 0.01$) and Tibetans ($P < 0.001$) at 4500 m.

Figure 2. Relationship of FEV_1/FVC , expressed as percentage of values predicted for non-Caucasians (Quanier et al., 1993) to altitude in Ladakhi and Tibetan men and women at three altitudes. * Indicates that the actual mean is significantly different from the theoretical mean (100) with a P of < 0.001 (all groups except Ladakhi males at 3200 m where $P < 0.006$). Values for sojourner males were significantly lower than those for Ladakhis ($P < 0.01$) and Tibetans ($P < 0.001$) at 4500 m.

Figure 3. Effects of gender and age on FVC and FEV_1 in subjects from each altitude group. Data for altitude groups were combined since slopes did not differ among the groups. Data for Ladakhis and Tibetans did not differ and were combined.

Regression equations are:

FVC = $3.215 - 0.0151$ for females and $4.58 - 0.0254$ for males; slopes are significantly different ($P = 0.004$)

$FEV_1 = 3.147 - 0.0163$ for females and $4.366 - 0.0265$ for males; slopes are significantly different ($P = 0.003$)

Figure 4. Relationship of hemoglobin to arterial saturation in men (top panel) and women (bottom panel). The line of best fit for men is reproduced in the panel for women as a dashed line indicating that the gender difference in Hb is constant over the range of saturation measured. Data for Ladakhis and Tibetans did not differ and were combined.





