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Normal Hematological Values for Healthy Persons Living at 4000 Meters in Bolivia

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ABSTRACT

Vásquez, René, and Villena, Mercedes. Normal hematological values for healthy persons living at 4000 m in Bolivia. *High Alt Med Biol* 2:361–367, 2001.—Defining the range of normal hematocrit and hemoglobin levels in residents of high altitude is required to diagnose chronic mountain sickness (CMS) and other conditions defined, in part, by hematocrit or hemoglobin values. We studied 1,934 healthy, young (aged 15 to 29 yr) male and female residents of Potosí, Bolivia (4000 m), to determine the average and normal range of hemoglobin and hematocrit values, defining normal as within 2 standard deviations of the mean or encompassing 95% of the observed variation. Male hematocrit averaged 52.7% and hemoglobin averaged 17.3 m/dL whole blood. The corresponding female values were 48.3% and 15.8 g/dL whole blood, respectively. The range of normal values was 45% to 61% for hematocrit and 13 to 21 g/dL for hemoglobin in the men and 41% to 56% for hematocrit and 12 to 19 g/dL for hemoglobin in the women. These data indicate that hematocrit values above 61% in men or 56% in women and hemoglobin values above 21 g/dL whole blood in men or 19 g/dL whole blood in women are outside the normal range.

Key Words: hypoxia, erythropoiesis, adaptation, chronic mountain sickness, gender differences

INTRODUCTION

RESIDENTS OF HIGH ALTITUDE have hemoglobin and hematocrit levels that are above those observed at sea level (Garruto and Dutt, 1983; Moreno-Black et al., 1984; Winslow et al., 1989; Leon-Velarde et al., 1997; Beall et al., 1998; Tarazona-Santos et al., 2000). Excessively elevated levels are used to diagnose chronic mountain sickness (CMS), a syndrome characterized by shortness of breath, cyanosis, undue fatigue, headache, dizziness, memory alterations, tinnitus, and bone and muscle pain. CMS has been estimated to occur in approximately 4% of high altitude inhabitants or some 5.6 million persons worldwide (Moore et al., 1998b). CMS can be fatal, leading to pulmonary hypertension and right ventricular hypertrophy, but often results in persons moving to lower elevations.

The normal range of variation in hemoglobin and hematocrit values at a given altitude is unclear. Although hemoglobin and hematocrit data are contained in a large number of studies, sample sizes are often small, consisting only of men or including persons of uncertain health status. Our group at IBBA–Potosí has as a priority to establish the normal values for the healthy population residing at this altitude, ~4000 m. To obtain a large sample of healthy persons, we studied all male and female students, aged 15 to 29 yr, entering Thomas Frias

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University (Universidad Autonoma "Tomás Frias") in Potosí, Bolivia, over a 2-year period. Persons were judged healthy on the basis of a clinical exam and absence of known health problems and on being actively engaged in academic, athletic, and other university activities. We defined "normal" as within 2 standard deviations of the mean or 95% of the range of values observed in these healthy young men and women.

BRIEF HISTORY OF POTOSÍ

Potosí is located in the southern part of Bolivia (Fig. 1) on a high plain surrounded by rolling, 5000 to 7000 m mountains. In 1987, it was declared a UNESCO World Heritage Site for its historic role in the development of the Spanish Empire. It is a picturesque city, containing many examples of Spanish colonial architecture. Prompted by the discovery of silver, tin, and other precious metals at the nearby Cerro Rico (Rich Mountain) in 1544, Potosí became a source of great wealth for the Spanish Empire and was one of the largest cities in the world.[1] Persons emigrated there from all over the world either voluntarily, in hopes of achieving instant wealth, or conscripted to work as

[1]Early observations concerning human adaptation to high altitude were made in Potosí by the 17th century Spanish historian Antonio de la Calancha (Monge, 1948). This historic account indicates that more than one generation was required for a Spanish child to survive in Potosí. But whether it was being born and raised at high altitude or whether interbreeding with Andean populations was required is unclear. Because few European women came to Potosí during these early years, it can be expected that the inhabitants quickly became a mixture of Indian, Spanish, and other ethnicities.

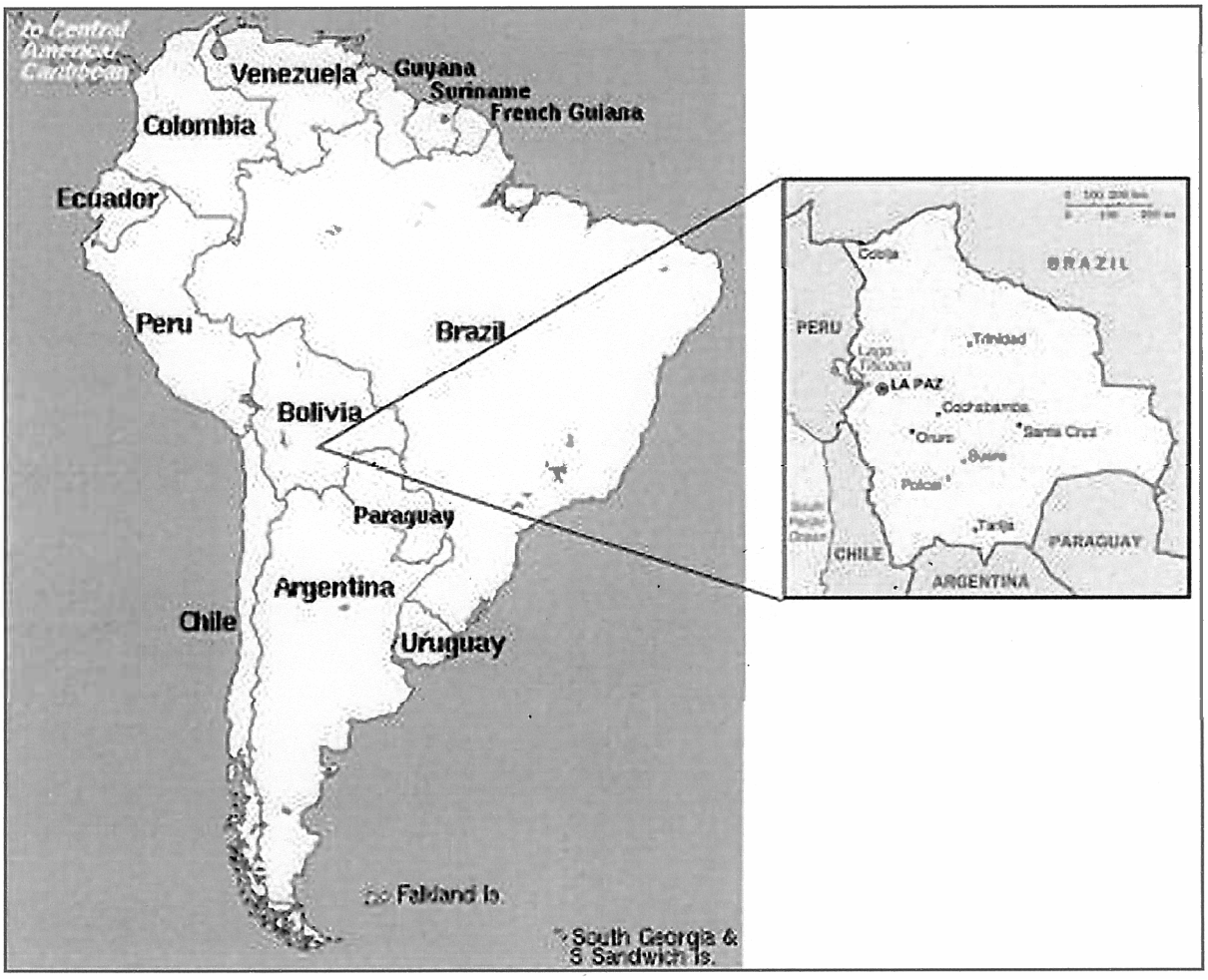

FIG. 1. Map of South American and Bolivia, showing location of Potosí.

slaves in its mines and smelters. Mines on Cerro Rico continue to be worked today under conditions that remain extremely arduous (Wicky, 2000).

MATERIALS AND METHODS

Subjects

Studies were performed on all students entering Thomas Frias University during a 2-year period (1991, 1996) following procedures approved by the University Human Subjects Review Committee. Each student was given a clinical exam, consisting of a full electrocardiogram and a complete medical history. A total of 2,162 men and women, aged 15 to 29 yr, were studied. Of these, 57 had cardiac abnormalities and 171 were above or below the age range selected for study. The remaining 1,934 were considered healthy on the basis of an absence of cardiorespiratory disease and being engaged in academic, athletic, and other university activities. None was pregnant. All were studied after an overnight fast in the resting condition in the IBBA–Potosí laboratory at an altitude of 3963 m, 18°C, and an average barometric pressure of 480 mmHg.

Blood samples (7 mL) were obtained from the antecubital vein. A tourniquet was applied to facilitate visualizing the vein, but blood samples were withdrawn after the tourniquet had been removed.

Instrumentation

Hematocrit was measured using the microcentrifuge technique, with samples centrifuged at 10,000 to 12,000 rpm for 3 min and read as percentages with a graduated scale. Hemoglobin was measured using the cyanmethemoglobin method. Samples were placed in Drabkin's solution and read at 540 nm using a spectrophotometer (Perkins Elmer model 6/8, Oakbrook, IL). Values are expressed in grams per deciliter of whole blood.

Statistics

Data are expressed as mean ± standard deviation in the tables, text, and figures. Groups were compared using two-sample *t*-tests, one- or two-way analysis of variance, or rank sum tests as appropriate using SAS (Carey, NC). Results were considered significant when $p < 0.05$.

RESULTS

The men had higher hematocrit and hemoglobin values than the women in each age group (Fig. 2 and Table 1). For both sexes, values were slightly but not significantly greater in the 20- to 29-yr compared with the 15- to 19-yr age groups. Combining the two age groups, male hematocrit averaged 52.7% and hemoglobin was 17.3 g/100 mL whole blood. The

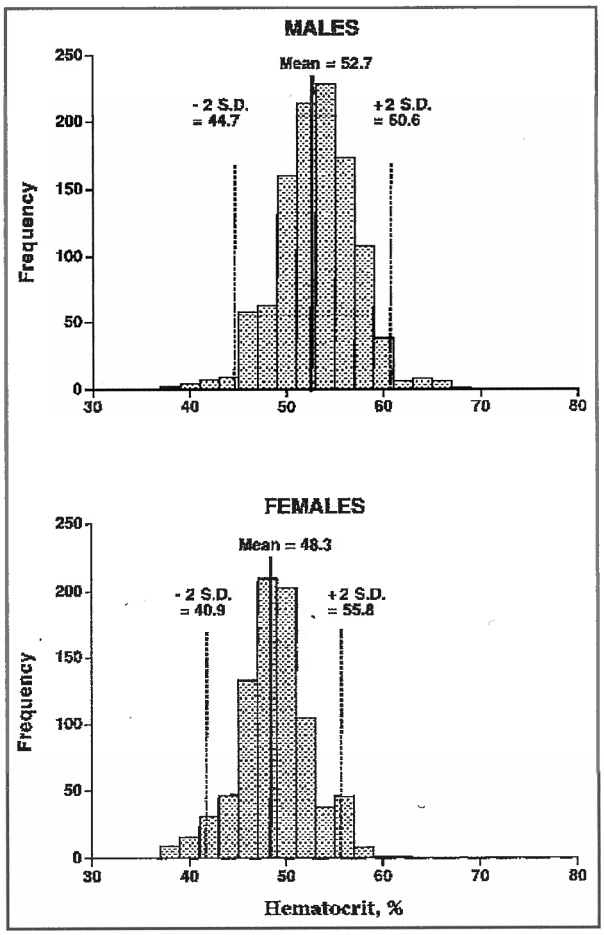

FIG. 2. Histogram showing frequency (counts) for hematocrit values and the mean and 2 standard deviation (SD) values observed in 1934, 15- to 29-yr old, healthy male and female residents of Potosí, Bolivia (elevation, 4000 m).

TABLE 1. HEMATOLOGICAL PARAMETERS IN STUDY SUBJECTS (MEAN ± STANDARD DEVIATION, SD)

Sex	*Age group*	*N*	*Hematocrit, mean ± SD*	*Hemoglobin, mean ± SD*
Males	15–19	578	52.6 ± 3.7	17.2 ± 1.9
	20–29	508	52.7 ± 4.2	17.5 ± 2.2
	All	1086	52.7 ± 4.0	17.3 ± 2.0
Females	15–19	519	48.3 ± 3.6	15.9 ± 1.4
	20–29	329	48.4 ± 3.9	15.6 ± 2.1
	All	848	48.3 ± 3.7	15.8 ± 1.7

Units: hematocrit, %; hemoglobin, g/100 mL whole blood

corresponding values in the women were 48.3% and 15.8 g/100 mL whole blood, some 10% lower.

Considering the range of normal to comprise the mean ± 2 standard deviations or 95% of the total distribution, normal hematocrit values ranged from 45% to 61% in men and 41% to 56% in women (Fig. 2). These cutoff values corresponded closely to the 2.5 percentile values (43.5% males, 40% females) and 97.5 percentile values (60% males, 56% females) for the observed distribution of hematocrit values. There were 22 men and 13 women with hematocrit values above these cutoffs, comprising 2% and 1%, respectively, of the total sample. The range of values comprising the mean ± 2 standard deviations of the hemoglobin values was 13 to 21 g/dL for men and 12 to 19 g/dL for women (Table 1).

DISCUSSION

We found that the normal range of values at 4000 m, defined as within 2 standard deviations

TABLE 2. HEMATOCRIT (%) AND HEMOGLOBIN (g/dL WHOLE BLOOD) VALUES BY REGION, SEX, AND ALTITUDE (MEAN ± STANDARD DEVIATION, SD) AND SAMPLE SIZE (*N*).

Region	*Altitude, m*		*Reference*	*N*	*Hematocrit, +2SD*		*Hemoglobin, +2SD*	
South American	3700	Ch	Winslow et al. (1989)	29	52.2 ± 4.6	61.4	18.0 ± 1.8	21.6
Males	3800–4065	Bo	Beall et al. (1998)	91			19.1 ± 0.2	19.5
	4000	Bo	This study	1086	52.7 ± 3.9	60.5	17.3 ± 1.5	20.3
	4200	Peru	Garruto and Dutl (1983)	45	51.4 ± 3.9	59.2	17.3 ± 1.5	20.3
				Average	**52.1**	**60.3**	**17.9**	**20.7**
Females	3800–4065	Bo	Beall et al. (1998)	83			17.8 ± 0.2	18.4
	4000	Bo	This study	848	48.3 ± 3.7	55.5	15.8 ± 1.7	19.2
	4300	Peru	Leon-Velarde et al. (1997)	112	47.4 ± 4.1	55.6		
				Average	**47.8**	**55.6**	**16.8**	**18.8**
			Himalayas					
Males	3000	Tib	Moore, unpub.	18	50.3		15.2	
	3560	Nep	Beall and Reichsman (1984)	126			16.1 ± 1.2	18.5
	3700	Tib	Moore, unpub.	22	54.4		17.4	
	3700	Nep	Winslow et al. (1989)	30	48.4 ± 4.5	57.4	16.9 ± 1.2	19.3
	3800–4065	Tib	Beall et al. (1998)	75			15.6 ± 0.2	16.0
	4500	Tib	Moore, unpub.	24	55.9		17.3	
	4850–5350		Beall (1997)	47			18.2 ± 1.9	22.0
				Average	**52.2**		**16.7**	**18.9**
Females	3000	Tib	Moore, unpub.	11	46.2		14.0	
	3560	Nep	Beall (1984)	100			14.4 ± 1.4	17.2
	3700	Tib	Moore, unpub.	24	45.3		13.9	
	3800–4065	Tib	Beall et al. (1998)	61			14.2 ± 0.1	14.4
	4500	Tib	Moore, unpub.	10	54.0		16.5	
	4850–5350	Tib	Beall (1997)	56			16.7 ± 1.5	19.7
				Average	**48.5**		**15.0**	**17.1**

Abbreviations: Ch, Chile; Bo, Bolivia; Tib, Tibet; Nep, Nepal.

of the mean or 95% of the variation observed in healthy, young adults (15 to 29 yr old), was 13 to 21 g/dL hemoglobin or 45% to 61% hematocrit for males and 12 to 19 g/dL and 41% to 56% hematocrit for females. Values above 21 g/dL hemoglobin or 61% hematocrit in men and above 19 g/dL hemoglobin or 56% hematocrit in women were outside the normal range and therefore considered abnormal.

Defining the range of normal variation at a given altitude is required to diagnose chronic mountain sickness (CMS) and other conditions based, in part, on hemoglobin or hematocrit values. However, there is no consensus on the normal range of hemoglobin or hematocrit values at high altitude. Cutoff values in the literature have ranged from 20 to 23 g hemoglobin/dL whole blood for men (Xie and Pei, 1981; Tufts et al., 1985; Leon-Velarde et al., 1993; Wu et al., 1998). Some (Leon-Velarde et al., 1997), but not other groups (Wu et al., 1998; Xie and Pei, 1981), have used slightly lower cutoff values for women. The need to determine the normal range of hemoglobin or hematocrit and the appropriate cutoffs for the diagnosis of CMS was recently called for in an international conference (Kobayashi et al., 1998). We therefore undertook the present investigation to establish the range of normal for healthy young persons in Potosí at an elevation of ~4000 m. We considered "normal" as within 2 standard deviations of the mean or the range encompassing 95% of the values observed in healthy young persons. Since CMS rarely occurs in young persons, we considered that choosing healthy young men and women and excluding any with cardiorespiratory diseases would permit definition of what is normal for this altitude.

When compared with literature observations from South America, our hemoglobin and hematocrit values are similar to those observed reported for men and women residing at similar altitudes (Table 2). The hemoglobin and hematocrit values reported here also agree with those of a larger study in Potosí in which similar mean values (hematocrit = 53% in men and 48% in women) were found for persons aged 15 to 34 yr (M. Villena, unpublished data). In this study, average hematocrit for persons aged 15 to 54 yr varied less than 3% in men and 1% in women, suggesting that hemoglobin and hematocrit change little across the adult age range. Using the present data in combination with that reported in the literature and defining "normal" as 2 standard deviations above the mean, hemoglobin values above 21 g hemoglobin/dL whole blood in men and 19 g hemoglobin/dL whole blood in women or hematocrits above 61% in men and 56% in women appear to be abnormal. When compared with hemoglobin or hematocrit values reported from the Himalayan region, the Andean values are somewhat higher, although there is considerable overlap in their distributions (Table 2). Probably as a result, the reported prevalence of CMS is lower in the Tibetan versus the Andean population (Moore et al., 1998a).

As is evident in this report, hemoglobin and hematocrit vary among healthy persons. Several factors are likely to contribute to this variation. There is day to day variation in red blood cell mass and plasma volume. We attempted to minimize this by studying subjects in the rested, fasted condition. Variation in normal values may be expected to be greater in women than in men, as the result of blood loss during the follicular phase (Kim et al., 1993). However, the coefficients of variation (std deviation/mean) were similar in the men and women (11.6% vs. 10.8%, respectively, for hemoglobin and 7.6% vs. 7.6%, respectively, for hematocrit), suggesting that menstrual cycle or other sex-specific factors did not greatly affect variability.

The rise in hemoglobin and hematocrit at high altitude is due to the stimulatory effects of hypoxia on erythropoietin production and hence is modulated by physiological factors affecting arterial oxygenation, red blood cell production, and plasma volume. Best studied has been the interindividual variation in ventilation. The level of hypoxic ventilatory response appears to influence the level of arterial oxygenation during high altitude acclimatization. That such variation in arterial oxygenation relates to hemoglobin or hematocrit after months to years of high altitude residence is supported by observations of lower levels of alveolar ventilation and arterial O_2 saturation in persons with excessive polycythemia than in healthy individuals at the same altitude. Particularly

marked are differences in arterial oxygenation during sleep, suggesting that repeated episodes of severe hypoxia are a likely contributor to the exaggerated polycythemia of CMS (Sun et al., 1996). The generally lower hemoglobin and hematocrit values seen in Tibetan compared with Andean high altitude residents are paralleled by higher average levels of effective alveolar ventilation (i.e., end tidal P_{CO_2} at a given end tidal P_{O_2}) when all studies are compared (Moore, 2000).

In conclusion, based on the data reported here for healthy residents of Potosí, Bolivia (~4000 m), reasonable cutoffs for exaggerated polycythemia would appear to be hematocrit values ≥61% and ≥56% or hemoglobin values ≥21 g/dL whole blood and ≥19 g/dL whole blood in men and women, respectively. Future studies are needed to determine the relative contributions of ventilatory, erythropoietic, and volume regulatory factors for exaggerating the polycythemic response to altitude and the extent to which such factors relate to the clinical signs and symptoms of CMS.

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