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Chronic Mountain Sickness, Optimal Hemoglobin, and Heart Disease

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ABSTRACT

Vargas P., Enrique, and Hilde Spielvogel. Chronic mountain sickness, optimal hemoglobin, and heart disease. *High Alt. Med. Biol*. 7:138–149, 2006.—For the male inhabitants of La Paz, Bolivia (3200–4100 m), and other high altitude regions in America and Asia, chronic mountain sickness (CMS) is a major health problem. Since CMS was first described by Carlos Monge in the Peruvian Andes in 1925, numerous research papers have been devoted to this topic, but many unanswered questions still exist with respect to the beginning of the disease and its cause(s). The experience with CMS has shown that an excessively high hemoglobin concentration is not favorable for high altitude acclimatization, and the hypothesis of theoretically "optimal" hematocrit and "optimal" hemoglobin has been made. The calculated optimal hemoglobin concentration of 14.7 g/dL for resting men in the Andes is discussed as theoretical and not applicable in real life. The most frequent congenital and acquired heart diseases are discussed, such as patent ductus, atrial septum defect, ventricle septum defect among congenital heart diseases and the still very frequent rheumatic valve cardiopathies and Chagas disease as acquired cardiopathies. Among the typical acquired heart diseases of the high altitude dweller, special attention is given to chronic cor pulmonale as a consequence of severe CMS with pulmonary hypertension.

Key Words: high altitude; oxygen saturation; blood viscosity; pulmonary hypertension; congenital; cor pulmonale

INTRODUCTION

In Bolivia, densely populated towns and cities are located between 3000 and 4850 m. In La Paz, for instance, which has a population of 1.7 million persons residing between 3200 and 4100 m, it has been found that persons who live in the higher zones have a higher incidence of chronic mountain sickness (CMS). This fact has made it possible to examine a great number of patients with CMS over the years and to compare them with normal high altitude dwellers to try to answer such questions as when does CMS begin and what are its causes.

Since his first report, "Case of Vaquez's disease (Erythremic Syndrome of Altitude)," by Carlos Monge M. (Monge, 1925), research on excessive erythrocythemia has become of interest to physicians and physiologists working in the Peruvian and Bolivian Andes region and in other high altitude regions in the world. An appreciable percentage of high altitude residents develops excessive erythrocythemia (polycythemia) (Monge et al., 1992; Wu et al.,

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1998). In Bolivia, two-thirds of the population live at >3000 m, and CMS is a health problem affecting 8% to 10% of the male active population (Vargas et al., 2002).

The stimulus for the abnormally high production of red cells, while not well understood, is not necessarily related to arterial P_{O_2} (Pa_{O_2}), since many of the patients have only minimal hypoxia in the awake state, which might, however, increase during sleep, with repeated periods of apnea and the resulting decrease of arterial oxygen saturation (Sa_{O_2}) as previously reported (Normand et al., 1992). Moreover, the evolution of CMS is variable among individuals (Vargas and Villena, 1993). In accordance with the Consensus Statement on Chronic and Subacute High Altitude Diseases (León Velarde et al., 2005), the classic signs are an abnormal increase in red cell count, hematocrit, and hemoglobin concentration [Hb], with minimal to moderate arterial hypoxemia. Noteworthy is a permanent cyanosis of the lips and the oral–pharynx mucous membranes. Neurological symptoms are frequent, including headaches, unusual fatigue, diminished mental capacity in the form of memory and concentration loss, dizziness, excessive sleep or insomnia, paresthesias in the extremities, and very often depressive states. The course of the disease is prolonged; arterial hypoxemia eventually increases, as shown by a decrease of Pa_{O_2}, while arterial carbon dioxide pressure (Pa_{CO_2}) increases, as well as the degree of dyspnea. Radiological signs and clinical symptoms of pulmonary hypertension (HAPH) also increase by variable degrees. The majority of cases is characterized by respiratory abnormalities, with an excessive decrease of hypoxic ventilatory response (HVR) (Vargas et al., 2002). This is typified by a diminution in the carotid body chemoreceptor-mediated respiratory sensitivity to the lowered arterial O_2 pressure, which results in a decrease of alveolar ventilation (Severinghaus et al., 1966; Lefrançois et al., 1968; Lahiri et al., 1969; Ergueta et al., 1971). Studies by Peñaloza (1969), which were conducted at altitudes higher than the Bolivian Altiplano (4100 m), showed that from the beginning the clinical feature of CMS is dominated by cardiovascular signs and symptoms, with the most severe cases suffering deep arterial hypoxemia, very high [Hb], and especially severe HAPH, conducing in advanced stages to cor pulmonale (Peñaloza, 1969).

All cases of CMS reported in the literature show variable degrees of alveolar hypoventilation, either calculated, measured directly, or diagnosed by a decrease of Pa_{O_2} together with an increase of Pa_{CO_2} (Fig. 1). Therefore, our interest was always directed to measuring HVR, especially in young patients who are at the beginning of CMS. However, it is well known that hypoxia due to pulmonary disease also causes

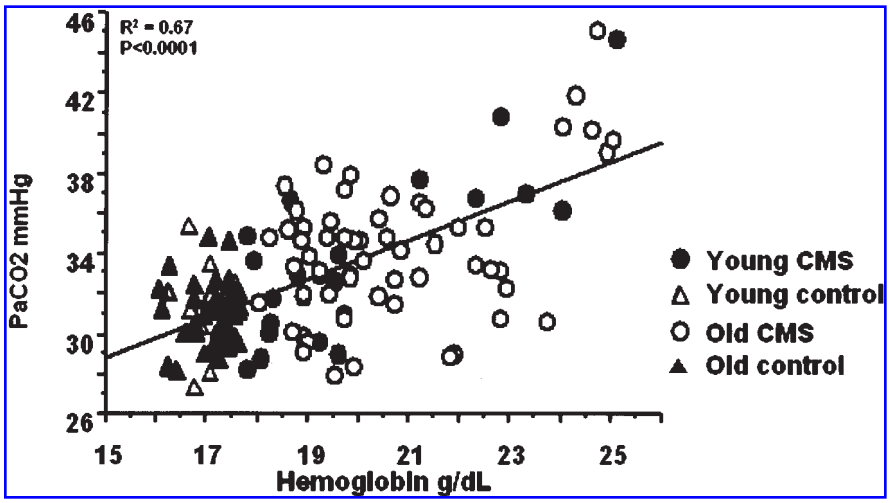

FIG. 1. Arterial carbon dioxide pressure (Pa_{CO_2}) in young and older CMS patients and their respective control groups. The graph shows the effect of hypoventilation on hemoglobin concentration.

erythrocythemia with a considerable increase of [Hb] at high altitude or at sea level. If an older patient with erythrocythemia seeks medical advice, it is very often not possible to distinguish between CMS or erythrocythemia due to cardiopulmonary function impairment.

We had the opportunity to examine 60 patients diagnosed with CMS, without history or risk factors of cardiac and chronic pulmonary disease or mechanical impairment of the respiratory function. Their ages ranged from 16 to 65 yr. Hence we assigned them to two groups: young CMS who were <30 yr of age (Y-CMS, $n = 30$, mean age 22.3 ± 4.3 yr) and old CMS, >30 yr (O-CMS, $n = 28$, mean age 46.7 ± 7.1 yr). Each group was compared with a control group of healthy men with normal cardiopulmonary function and [Hb] close to the normal mean of 17.3 g/dL, reported for normal men at high altitude in Bolivia (Vasquez and Villena, 2001) and in the same age range: young control (Y-C, $n = 30$, mean age 22 ± 2.4) and old control (O-C, $n = 27$, mean age 43.5 ± 3.4).

Patients and their controls (Table 1) were fully informed of the study procedures and signed an informed consent form prior to participation. For minors (under the age of 18), parents or guardians were asked for their approval, with full knowledge of risks and benefits. The study protocol was approved by the scientific council of IBBA and by the National Bioethics Committee of the Bolivian Health Ministry.

In the study, first, information was obtained from the patient concerning his health history; then a general physical examination and cardiac evaluation were performed. These were complemented by a set of functional, radiological, and hematological tests. The tests of cardiac function included an EKG and echocardiography doppler to evaluate cardiac and pulmonary hemodynamics. A chest x-ray with a complete set of respiratory function tests, consisting of total body plethysmography with flow-volume curves and measurement of HVR, were conducted. For this latter test, the subject in a sitting position inhaled three tidal volumes of a hypoxic mixture (F_{IO_2}: 0.08–0.1; barometric pressure in La Paz: 495 mmHg) (Dejours, 1963). Arterial blood gases and lung diffusion capacity completed the study. For statistical analysis, distributed variables are described as mean ± standard deviation, and comparisons among four groups were made by ANOVA, paired *t*-test, correlation coefficients using a Statview program.

Table 1 shows the increased [Hb] (g/dL) in both CMS groups, which was higher in the older than in the younger patients. [Hb] in the two control groups (Y-C, O-C) was around the mean of 17.3 reported in normal male high altitude residents (Vasquez and Villena, 2001).

The results of the lung volume measurements showed a normal forced vital capacity (FVC) in all groups, but changes in the flow-volume forced expiratory curve were found that suggested altered bronchial permeability (FEV1/FVC), especially in the small peripheral branches. In fact, we observed a reduction of the 50% and up to 75% forced expiratory flow (FEF 50% to 75%) related to forced vital capacity (Table 2). Single breath lung diffusing capacity measurements (DLCO mL/min/mmHg) corrected for [Hb] (Cotes et al., 1972; Graham et al., 1981) showed differences between the two patient groups, O-CMS having a lower DLCO than Y-CMS; but both control groups had higher DLCO values than low altitude norms, as indicated automatically on our Sensormedics 2400/2450 equipment for each test (American Thoracic Society, 1987).

Evaluation of chemoreceptor sensitivity or

Table 1. Age, [Hb], and Body Mass Index of the Four Study Groups

Group	*Age (yr)*	*[Hb] g/dL*	*BMI[a] (%)*
Young CMS ($n = 30$)	22.3 ± 4.3	19.5 ± 0.7	25.4
Old CMS ($n = 28$)	46.7 ± 7.1	24.0 ± 2.3	27.4
Young control ($n = 30$)	22.0 ± 2.4	16.8 ± 0.6	23.8
Old control ($n = 27$)	43.5 ± 3.4	17.2 ± 0.4	27.2

[a]BMI = body mass index.

TABLE 2. PERIPHERAL AIRFLOW AND GAS EXCHANGE

Variables	*Y-CMS*	*O-CMS*	*Y-C*	*O-C*	p *of CMS vs controls*
FEV/FVC, %	82.0 ± 2.2	75.0 ± 1.8	86.0 ± 1.5	84.5 ± 1.2	Y $p < 0.0001$ S O $p = 0.0114$ S
FEF, 50%[a]	74.19 ± 2.5	69.19 ± 3.3	94.61 ± 2.3	104.13 ± 2.6	Y $p = 0.0327$ S O $p < 0.0001$ S
FEF, 75%[a]	75.57 ± 3.3	70.1 ± 4.1	98.29 ± 2.2	89.9 ± 4.8	Y $p = 0.0133$ S O $p = 0.0003$ S
DLCO[b]	29.07 ± 1.3	23.8 ± 1.2	38.1 ± 0.9	34.6 ± 0.5	Y $p = 0.0002$ S O $p < 0.0001$ S
VA, L/min[b]	4.33 ± 0.8	4.08 ± 0.82	6.11 ± 0.68	5.75 ± 0.66	Y $p < 0.0001$ S O $p = 0.0012$ S

[a]Forced expiratory flow, related to 50% and 75% of forced vital capacity.
[b]Lung diffusion capacity and alveolar ventilation, VA (single breath of CO mixture method).
S, significant.

HVR is one of the most important tests for our purposes. The classic description of ventilatory regulation among high altitude inhabitants indicates that there is a gradual attenuation of ventilatory sensitivity to hypoxia with increasing years of residence (Weil et al., 1971). The test results (three trials per subject) reveal interesting differences between the groups. HVR values among Y-C and O-C, although showing different levels of sensitivity, were nonetheless within the normal range reported in high altitude residents ($\Delta V + 37\%$; Lefrançois et al., 1968), while the values observed in Y-CMS and O-CMS differed considerably in their response to hypoxic stimuli. In the younger patients, there was moderate attenuation of HVR, as the ventilatory response to a given level of hypoxia was decreased relative to the respective control group. In the older group of CMS patients, the magnitude of response was even more attenuated, suggesting that diminished chemoreceptor sensitivity to hypoxemia is an important cause of hypoventilation in these patients (Fig. 2). Arterial hypoxemia was variable among subjects within both groups of CMS patients (Table 3), and in the Y-CMS group, cases were moderate and had only partial respiratory insufficiency, which was more pronounced in the O-CMS group. In many cases, the respiratory insufficiency could be global and would be complicated by moderate alveolar retention and a rise of carbonic dioxide or markedly increased Pa_{CO_2} (Fig. 1) with respiratory acidosis; but only rarely do we find true acid–base

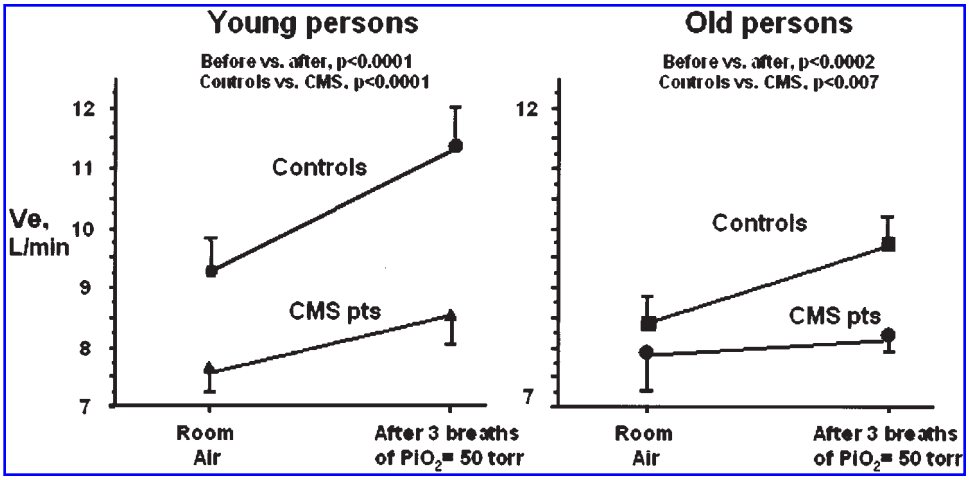

FIG. 2. HVR in younger and older CMS patients and their respective control groups. Blunted hypoxic ventilatory response occurs early in the disease and worsens with the increase of age.

Table 3. Arterial Blood Gases and Pulmonary Artery Pressure

Groups	Pa_{O_2} *(mmHg)*	*Paps*[a]	Pa_{CO_2} *(mmHg)*	Sa_{O_2} *(%)*	*pH*
Y-CMS	53.2 ± 3.6	35.0 ± 4.0	33.7 ± 4.4	86.3 ± 4.6	7.40 ± 0.02
O-CMS	49.1 ± 6.4	35.5 ± 2.4	36.5 ± 6.7	84.0 ± 5.8	7.38 ± 0.04
Y-control	60.2 ± 1.0	28.0 ± 5.0	30.6 ± 1.7	90.3 ± 1.2	7.42 ± 0.02
O-control	59.2 ± 1.3	29.4 ± 4.0	31.0 ± 1.8	89.3 ± 1.2	7.42 ± 0.03

[a]Echocardiographic systolic pulmonary arterial pressure, mmHg.

disturbance in these patients. Due to the chronic evolution of the process, rarely do we find an arterial pH indicative of noncompensated acidosis. Rather, it appears that a permanent compensation for acid–base disturbance is the effect of the increased [Hb] and its buffer action, assisted by renal bicarbonate reabsorption.

In both CMS groups, HAPH is not very much elevated, as demonstrated by the values for systolic pulmonary pressure presented in Table 4. This table compares the EKG traces in 30 patients of each group, showing that, if indeed the two groups of CMS patients have a greater tendency to right ventricular hypertrophy (RVH), the two control groups also show a degree of ventricular growth, resulting in the slightly increased HAPH that is observed in the normal inhabitants of La Paz.

Classically, excessive erythrocythemia has been described as a chronic disease (chronic mountain sickness, CMS) that results from age-related changes in cardiorespiratory function in longtime high altitude residents (Monge and Whittembury, 1982). However, the problem does not seem to be simply a matter of aging, since not all older-aged persons develop CMS.

In the present review we compare lung and heart function, blood gas data, and ventilatory response to hypoxia in younger- and older-aged lifelong male residents of high altitude with excessive erythrocythemia (EE) ([Hb] > 17.5 g/dL) with healthy controls ([Hb] < 17.5 g/dL). The purpose of our study was to determine when EE begins and to find possible causes of this disease. We wished to show that EE can occur in young men at an age when normally, no signs of aging of the cardiopulmonary function are present. Therefore, we chose a group of younger EE patients with a mean age of 22 yr and another group of older EE patients with a mean age of 46 yr for comparison with each other and with normal control groups in the same age range. By definition, both groups had higher [Hb] levels, but measures of lung function in the younger EE patients were similar to those of the respective control group with the exception of DLCO, which was decreased after correcting for [Hb] (Cotes et al., 1972).

The first study on excessive erythrocythemia was conducted at IBBA by Ergueta et al. (1971) in 20 CMS patients with an average age of 51 yr ([Hb] = 25.73 g/dL, Ht 72%). These patients were compared with a group of healthy high altitude natives with an average age of 24 yr and [Hb] of 16.51 g/dL. The most striking finding of this study was that the CMS patients had a minute ventilation similar to that of the control group ($V_{E\ BTPS}$ = 11.8 and 10.1 L/min, respectively; p = NS). However, when total ventilation was divided into its components of alveolar ventilation (VA) and dead-space ventilation (VD), it could be shown that the CMS

Table 4. EKG Indicative of RVH

Groups	*Normal EKG*	*EKG, probable RVH*	*EKG, true RVH*
Young CMS	8 (26.6%)	12 (40%)	10 (33.3%)
Old CMS	9 (30%)	13 (43.3%)	8 (26.6%)
Young controls	22 (73%)	4 (13.3)	4 (13.3%)
Old controls	25 (92.5%)	1 (3.7)	1 (3.7%)

patients had a significantly smaller VA than the normals due to a higher VD. The ratio VD/VT in the normals was 0.33, whereas in the CMS patients this ratio increased to 0.57. Alveolar hypoventilation was confirmed also by an increase of P_{CO_2} in the CMS patients. The authors attributed their findings to a blunted hypoxic and hypercapnic respiratory drive in the CMS patients.

Our results are in concordance with the results of Ergueta insofar as the older group of CMS patients had lower levels of alveolar ventilation, as shown by direct measurement (3.35 L) and by higher Pa_{CO_2} levels. HVR was almost absent in this group. The younger CMS patients did not have lower alveolar ventilation or a significantly increased Pa_{CO_2} as a group, although individual values in several subjects were higher than control values. However, HVR was more decreased in both the younger and older CMS subjects than in normal high altitude dwellers. In some older CMS patients, HVR is absent; that is, they do not increase ventilation at all when inhaling three tidal volumes of a hypoxic mixture (8% to 10% O_2). We therefore conclude that the lower arterial P_{O_2} and S_{O_2} levels in the Y-CMS than in the control groups result from an excessively reduced ventilatory responsiveness to hypoxia, whereas hypoventilation and diminished lung function were responsible for lower blood oxygen levels in the O-CMS group. Since 1968, it has been known that nonacclimatized lowlanders at high altitude in a test of HVR have a ΔV of 101%, high altitude natives 37%, and CMS patients 5% (Lefrançois et al., 1968). Based on our results, we conclude that CMS starts at a young age and that the most likely cause is an excessively decreased HVR, which leads to alveolar hypoventilation and consequently to a small to moderate degree of hypoxemia and therefore increased [Hb].

For most patients, at least the younger ones, a move to moderate altitude is advisable. But in all these cases, no single rule can be applied and individual situations are diverse. Thus, patients of greater age and higher [Hb] can have right ventricular hypertrophy without this signifying an incontrovertible evolution toward cor pulmonale. On the other hand, we have seen that some young patients (16 to 17 yr) can favorably reverse their EKG findings with improvement of oxygenation and diminution in [Hb] in response to procedures established to improve hypoventilation by kinesiotherapy, moderate physical exercise, treatment with respiratory stimulants (Villena et al., 1985), other medicines (Leon Velarde et al., 2003), and descent to low altitude.

"OPTIMAL" HEMOGLOBIN CONCENTRATION

Erythrocytes and [Hb] that are related to the oxygenation of blood and tissues show an increase according to the increment of altitude (Moulin, 1971). Oxygen transport from the environment to the cells is essential for the development and functioning of living organisms. Between the alveoli of the lung and cells, blood circulation assures this transport, which is directly related to the presence of hemoglobin, the respiratory pigment, a protein compound that conveys remarkable properties to the blood that allow for both a dynamic combination with oxygen and maintenance of the acid–base equilibrium that is necessary for the conservation of the internal medium of the cell.

For a long time, a right shift of the oxyhemoglobin dissociation curve due to an increase of 2,3 DPG inside the erythrocytes has been considered a favorable factor of chronic acclimatization to altitude hypoxia as such a shift facilitates oxygen delivery to the tissues (Aste Salazar and Hurtado, 1944; Lenfant, 1969). At sea level with an oxygen partial pressure of 150 mmHg, 99% of hemoglobin is combined in the form of oxyhemoglobin (HbO_2); in high regions like the city of La Paz with an ambient partial pressure of oxygen of 105 mmHg, HbO_2 only reaches 90%. However, arterial blood, in spite of being hypoxic in terms of oxygen partial pressure, contains more oxygen due to the increase of [Hb]. It is precisely due to the role of the oxygen vector of the blood (Krogh and Leitch, 1918–1919) that acclimatization to altitude is possible.

In low altitude regions (1600 m), breathing will have little or no influence on Sa_{O_2} or [Hb]; at higher altitudes (3100 m), breathing acquires greater power of stimulation; at 5950 m, it is a mechanism of major influence on hemoglobin

concentration, where those who ventilate better (lower P_{CO_2} values) have high Sa_{O_2} and low hemoglobin concentrations compared with persons who breathe less (higher P_{CO_2} values) (Reeves, 2002). Thus the question arises: from which altitude on is the role of ventilation over [Hb] vital; and from what conditions and values on does [Hb] become a negative mechanism for the equilibrium of the cell medium by increasing the blood volume, with the resulting impairment of the pulmonary microcirculation; and at which moment does the vicious cycle start: increase of [Hb], aggravation of arterial hypoxemia, more erythrocythemia, blood volume, and less alveolar and tissue oxygenation due to increase of the blood viscosity (Guénard, 1984).

The preceding leads us to consider the concept of an "optimal" [Hb] below which the O_2 delivery is reduced through the effect of a decrease of oxygen content and above which the same effect is produced, because the increase of viscosity provokes a decrease of cardiac output (Ward et al., 1989), an alteration of the pulmonary microcirculation, and an impairment of the VA/Q relationship (Manier et al., 1988).

The main problem of calculating this optimal value of [Hb] is the effect of blood viscosity on cardiac output (Guyton et al., 1973). Since blood is not a Newtonian fluid, an isolated value of viscosity cannot be assigned to a certain [Hb]. Obviously, the value should vary according to the measuring method in each laboratory. Physiologically, the effect of resistance changes according to the diameter of the vessels and the type of flow in velocity or turbulence (Ward et al., 1989).

Based on the work on models that permit us to calculate an optimal hematocrit and to attain an evaluation of the role of the erythrocythemia of high altitude in the oxygen transport (Whittembury et al.,1968) and on research based on the variation of mixed venous P_{O_2} (Pv_{O_2}) and its dependency on Pa_{O_2} and [Hb] (Monge and Whittembury, 1982), Villafuerte and colleagues (2004) performed a complementary analysis of all previous concepts to try to show that an excess in [Hb], far from being a beneficial role to the improvement of tissue oxygenation is rather a detrimental action. Villafuerte and colleagues used a mathematical approach by modeling the Pv_{O_2} and arterial O_2 content, considering for both the dependence on Pa_{O_2} and [Hb]. The data on which the authors based this theoretical analysis were obtained from research conducted by various authors at different altitudes in the Andes. The arguments used to demonstrate that an increase of [Hb] and elevated Ca_{O_2} in highland residents, especially in excessive erythrocythemia or CMS patients, does not improve Pv_{O_2} and tissue O_2 delivery, were the beneficial results of phlebotomy and hemodilution (Winslow et al., 1985; Manier et al., 1988).

It is a fact that a too high [Hb] represents a threat, but the situation of the numerous population living at high altitude is actually quite special because of the clinical–functional side of the problem. It is also a fact that with time the organism, and especially the cardiovascular and respiratory systems, adapts gradually to the consequences of chronic hypoxia and to the simultaneous increase of [Hb]. If it were possible to establish an optimal value of [Hb] for a healthy community that carries out its daily activities just like any group of humans at sea level, this would be ideal; and, it would be even better if these values could be maintained close to those at sea level, as seems to be the case in Himalayans (Niermeyer, 2001). Reality in the Andes, however, is different, because the people are mostly a mestizo population of Indians with Caucasian admixture, that is, with people who originally came from low altitude. Additionally, migration within the Andean region between high and low altitude is frequent.

The research conducted in La Paz that might help to identify ideal parameters to use in discussions of the theoretical analysis (Monge and Whittembury, 1976; Monge, and Whittembury, 1982) suggest the existence of an optimal [Hb] in normal persons is related to studies of pulmonary circulation in healthy high altitude natives (Antezana et al., 1982) and CMS patients (Ergueta et al., 1971; Cudkowicz et al., 1978) and coronary circulation (Moret et al., 1972). These studies report data on age, hemodynamics of pulmonary circulation, heart function, and arterial and mixed venous oxygen pressures, in addition to [Hb] and other parameters that intervene directly in the regulation of local and systemic blood flow.

From the numerous comparative studies that have been conducted by researchers from the Andean region and by others of various nationalities, we know that permanent residents of altitude regions acquire morphological, functional, and biochemical characteristics that explain their well-known tolerance of high altitude hypoxia, which permits them to lead a physiologically normal life. Of course, many other variables exist that justify a correct cardiorespiratory function at the altitude of La Paz, but we think that, in relation to the hypothesis of optimal [Hb], we should analyze the parameters that are most important for determining Pa_{O_2} and Pv_{O_2}. Therefore, we refer to Table 5, which shows variables of hemodynamic function and gas exchange in pulmonary circulation, the place where in the end good or bad tissue oxygenation is defined. This Table 5 shows the results of different studies by various authors of normal, young, male, high altitude residents (there are very few hemodynamic studies in women), with normal standards of mean pulmonary artery pressure (MPAP) whose dynamic force will establish the oxygenation of the mixed venous blood with a Pv_{O_2} that we consider adequate for sufficient O_2 reception at the alveolar–capillary level and which, distributed at a normal Pa_{O_2} (59 mm Hg), will favor the equilibrium and harmony of the internal medium.

The concept of an optimal hemoglobin concentration, however, is only theoretical and is not applicable in real life, because [Hb] is not a stable parameter, but changes quickly under certain physiological conditions. During a graded progressive exercise test to maximum, [Hb] increases within 10 to 15 min by 0.5 to 1.0 g/dL due to hemoconcentration. Furthermore, 14.7 g/dL [Hb] as calculated to be optimal by Villafuerte et al. (2004) based on Pv_{O_2} without information on iron status should not be called optimal. In a thorough study on hemoglobin distribution and functional consequences of anemia at high altitude, a cutoff point of 15.8 g/dL for [Hb] was established in 499 healthy, iron-sufficient males (Tufts et al., 1985). In this study, first, 526 subjects were selected from a survey of 600 men in La Paz (mean age 35 ± 11 yr) after exclusion of subjects that were blood donors; had chronic lung disease, ulcers, metabolic disorders, or recent major surgery; or were extremely obese or exposed to industrial toxicity. From the 526 men, those who had a transferrin saturation of less than 16% were removed, and a sample of 499 healthy, iron-sufficient subjects remained. In these subjects, mean [Hb], established by two methods, was

Table 5. Hemodynamics and Respiratory Values in La Paz, Bolivia (3600 m)

	Normal Males							
Authors, number of subjects	*Age*	*MPAP*	*Qc*	*CI*	Pa_{O_2}	Pv_{O_2}	Ca_{O_2}	*Hb*
Antezana et al., 1978 (n = 11)	22.4	22 ± 0.5	7.51	3.46	58.5 ± 1.6	37.6	18.9 ± 0.3	16.3 ± 0.6
Moret et al., 1972 (n = 10)	23.7	22.7 ± 0.3	6.0	3.49	58.4 ± 1.8	37 ± 1	20.5 ± 1.9	17.4 ± 0.5
Coudert et al., 1975 (n = 67)	23.6	21 ± 1.5	6.4	3.91	58.5 ± 1.3	36 ± 3.1	19.3 ± 0.3	16.5 ± 0.7
Cudkowicz et al., 1978 (n = 14)	24	22.9 ± 1.3	5.7	3.8	60.2 ± 1.6	37 ± 1.2	18.8 ± 1.5	16.8
	CMS Patients							
Ergueta et al., 1971 (n = 20)	51	51.5	5.98	3.3	47.9 ± 3.3	36.5	23 ± 0.6	25.7 ± 0.2
Manier et al., 1988 (n = 8)	42.6	27.4 ± 10.1	5.5	3.35	45.6 ± 5.6	32.4 ± 2.8	22.2 ± 0.8	21.5 ± 1.6

The values are means ± SD; MPAP, mean pulmonary artery pressure (mmHg) from right heart catheterization; Qc, cardiac output (L/min); CI, cardiac index (L/BSA); Pa_{O_2}, arterial partial pressure of oxygen (mmHg); Pv_{O_2}, mixed venous partial pressure of oxygen (mmHg); Ca_{O_2}, arterial oxygen content (vols. %); Hb, hemoglobin (g/dL).

18.8 ± 1.4 g/dL. Graded, progressive exercise tests to maximum were performed in three subgroups; anemic subjects had a distinct decrease of aerobic capacity in comparison to normal subjects and those with high [Hb].

So our conclusion is that "optimal" hemoglobin calculated on the basis of Pv_{O_2} values is an interesting theoretical concept. However, to be optimal for the O_2 transport that becomes essential during effort, [Hb] should rather be defined on a functional basis. We estimate that at high altitude a 20-year-old, well-trained cyclist who reaches a work load of 303 W with a $V_{O_2\,max}$ of 55 mL/kg/min in the laboratory and wins a competition for long-distance road cycling, with a [Hb] of 16.9 g/dL, must be at his optimal value for this parameter.

HEART DISEASE

With respect to heart diseases in high altitude natives and permanent residents, data have been collected by surveys, especially in hospitals of mining centers and villages on the Altiplano, as well as in hospitals in La Paz. Even though these surveys were not frequent, several conclusions can be made. The majority of the studies shows a high incidence of congenital malformations of the heart and, to the contrary, a lower frequency of diseases like systemic arterial hypertension and hypertensive cardiopathy.

Among acquired heart diseases, there are two frequent cardiopathies: diseases of the valves that are sequels of rheumatic fever and myocardiopathies due to Chagas disease caused by infection with *Trypanosoma cruzi* in residents of tropical zones and high valleys who migrate to high altitude cities. However, without any doubt, due to their connection with high altitude hypoxia, the most frequent heart diseases are congenital cardiopathies, among which patent ductus (ductus arteriosus) takes first place. The ductus or arterial channel plays a very important role in fetal circulation because it permits the blood flow from the pulmonary artery to the aorta, which receives the necessary oxygen from placenta circulation.

Statistics of the cardiac surgical service of the Instituto Nacional del Torax in La Paz, a public hospital of reference that receives patients from the whole region, including mining centers located at higher altitudes than La Paz, report that, from a total of 440 surgeries, 289 were conducted in patients with congenital heart diseases, that is, 66% of the cases (Ponce Caballero et al.,1976). Among these surgeries, 213 were of patent ductus, or 73%. Among other frequent malformations, atrial septum defect was reported in 21 cases (7.3%), ventricle septum defect in 19 cases (6.5%), coarctation of the aorta in 20 cases (6.9%), 7 cases of Fallot's tetralogy (2.4%), and 9 less severe cases (3.3%).

In 71 of the 213 patients with patent ductus, hemodynamic studies were performed by right heart catheterization. The patients were diagnosed with pulmonary hypertension prior to surgery. Only 8 patients had a MPAP that was normal for La Paz (21.6 ± 4 mmHg); while the rest had MPAPs above 30 mmHg. Approximately 45% had MPAPs over 60 mmHg, with one extreme case of 120 mmHg. There were complications after surgery in 15.9% of the patients, but mortality was zero. It is interesting that of the group of patients with congenital heart diseases, 91.5% came from places located at altitudes above 3000 m. Of the 213 ductus patients, 90.5% were residents of regions above 3000 m; 145 were females and 68 males. The mean age of the patients that underwent surgery was 9 yr (range 6 months to 47 yr) (Ponce Caballero et al., 1976). This fact seems to be in accordance with the persistence of the patron fetal (fetal pattern) as the principal cause of pulmonary hypertension (HAPA), as detected by heart catheterization and echocardiography in children of La Paz (Farfan et al., 2000; Niermeyer et al., 2002), compared to children of the tropical lowlands (Santa Cruz, Bolivia, 400 m) (Aparicio, 1991).

Aparicio and Garabito (1990) report a higher incidence of atrial septum defect in 9924 cases from the cardiac service of the Torax hospital. The principal cardiopathies of 23 that were detected (0.75% of all patients) were the atrial septum defect (17 cases); then follows pulmonary stenosis (2 cases), and patent ductus (also 2 cases). The cardiopathies secondary to rheumatic disease (13 cases) correspond to 0.42% of the total population studied and were distributed as follows: mitral insufficiency, 8 cases;

mitral stenosis, 1 case; aortic insufficiency, 2 cases; tricuspid insufficiency, 1 case; and finally aortic stenosis, 1 case. Among other heart diseases, only 2 cases of systemic hypertension were found, but 16 cases of pulmonary hypertension.

Systematically, EKGs were recorded in the whole population that was examined. The results show that right ventricular hypertrophy is predominant in a high percentage of the examined people unrelated to age, but more frequent in males than in females.

On the Bolivian Altiplano (3900–4100 m), cardiovascular epidemiological studies were conducted with the main purpose of differentiating the prevailing congenital heart diseases and others that had been reported as frequent at sea level, such as ischemic cardiopathies and systemic hypertension. The cardiologists of the Instituto Boliviano de Biología de Altura (IBBA) chose the community of Guaqui situated at the shore of Lake Titicaca at an altitude of 3900 m, where they studied 3072 persons, of which 70% were schoolchildren (Corone et al., 1976).

Finally, we refer to another cardiovascular survey conducted by IBBA, this time in the mining center of Chorolque whose camp, the village of Santa Barbara, is located at an altitude of 4850 m and has a population of about 3500 inhabitants. The most important data on cardiovascular pathology were obtained as part of a global epidemiological survey (Antezana, et al., 1978). One thousand persons were studied, of which 500 were schoolchildren of both sexes between 5 and 18 yr of age. For all of them, an EKG with standard derivations was recorded. Congenital heart diseases were distributed as follows: 13 cases diagnosed with PCA, 6 cases of atrial septum defect, and 5 cases of ventricle septum defect. Not one case of cyanotic congenital heart disease was detected.

Among acquired heart diseases, 10 patients with myocardiopathy of Chagas were found, 4 cases of rheumatic cardiopathy, and 9 cases of chronic cor pulmonale. It is remarkable that only one patient with ischemic heart disease was detected besides 10 cases of systemic hypertension.

Some concepts of Chagas disease have to be mentioned, a disease caused by infection with *Trypanosoma cruzi*, a parasite that originates in the tropical areas and high valleys of the Andean region and appears among the acquired heart diseases at high altitude due to the migrations from the countryside to the cities and mining areas. The parasite has also been transmitted by blood transfusions, which have been spreading the disease to various regions. In chagasic myocarditis, congestive heart insufficiency with overall enlargement of the heart can occur, predominantly of the right heart. In some cases, leakage into the pericardium appears, which yields a bad prognosis. Arrhythmias and impairment of the conduction are produced, most frequently bradycardia. Thromboembolisms occur due to enlargement and cardiac insufficiency, hypocontractility, and stagnant blood (Salinas Salmón, 1999).

Among acquired heart diseases at high altitude, chronic cor pulmonale (CPC) has to be included. This cardiopulmonary disease yearly reaches a percentage of 20% to 25% in the Instituto Nacional de Tórax. It affects men and women alike between 40 and 70 yr of age. Restrictive pulmonary diseases determine most cases, among them most frequently lung tuberculosis. Then follow, in order of frequency, chronic obstructive pulmonary disease (COPD), pulmonary thromboembolism, obesity, xyphoskoliosis, and impairment of the ventilatory regulation (Zuazo et al., 1982). CPC is also the consequence of long-standing severe chronic mountain sickness with pulmonary hypertension. This is one reason for which the descent to low altitude is recommended in patients with CMS. If this step is not possible, frequent blood letting has to be performed to maintain [Hb] and Ht at reasonable levels.

We are aware that most of the surveys were conducted a long time ago in rural areas. Therefore, no coronary artery disease (CAD) was found. However, in the last survey of a rural population that was carried out 2 yr ago, again no CAD was diagnosed. The rural populations of our studies in Bolivia generally were not exposed to risk factors for CAD, such as smoking, sedentary life-style, high-fat diet, and stress. However, cardiologists working in hospitals and clinics in the city of La Paz report CAD as an emerging cardiopathy due to

changes in the life-style of high altitude dwellers living in urban areas.

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