27

Chronic Mountain Sickness and Cor PulmonaleLapaz-Bolivia (3,600-4,100 m)

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Summary

Among the majority of inhabitants of La Paz-Bolivia (3,200-4,100 m.), the mild elevation seen in pulmonary artery pressure (PAP) has no clinical significance and is reversible on descent to lower altitude or with administration of oxygen. Studies of normal residents versus Chronic Mountain Sickness (CMS) patients contributes to a better understanding of the mechanisms responsible for the gradual degradation of cardiorespiratory function, the pulmonary arterial hypertension (HAPH), and the natural evolution of the development of *Cor Pulmonale*. We examined 60 patients diagnosed with CMS. Their ages ranges from 16-65 years. And were hence divided in two groups: Young CMS, those patients who were $\leqslant$30 years of age (Y-CMS, n=30, mean age 22.3$\pm$4.3 years) and old CMS, $>$30 years (O-CMS, mean age 46.7$\pm$7.1 years). Each is compared with their respective control groups, Young Control (Y-C, n=30, mean age 22$\pm$2.4) and Old Control (O-C, n-27, mean age 43.5$\pm$3.4). Resting tests were performed a clinical examination and functional cardiac evaluation. These were complemented by a set of respiratory function, radiological and hematological tests. Results: Both, young and old CMS patients had arterial hypoxia and elevated hemoglobin concentrations: 19.5$\pm$0.7 and 24.0$\pm$2.3 grs/dl, respectively. Measurements of lung volumes suggested a mild altered bronchial permeability, a reduction of the 50% and up to 75% forced expiratory flow (FEF50%-75%) related to forced vital capacity observed in CMS patients. DL_{CO} (ml/min/mmHg) corrected for Hb concentration showed a moderate low value in O-CMS. The correlation between clinical cardiological examination and the ECG traces in patients and controls show 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 modestly elevated PAP that is normally observed in the inhabitants of La Paz. Conclusions: CMS occurs in young as well as older men in the absence of lung disease. Hypoventilation, due in part to a blunted hypoxia ventilatory drive, appears early and leads to a progressive worsening of hypoxemia or and polycythemia over time. Pulmonary artery hypertension (HAPH) is present in some, but not all CMS patients and does not worsen over time to Cor Pulmonale.

Introduction

Despite a number of clinical and research investigations on the pulmonary circulation, there still remain questions about the mechanisms that directly or indirectly cause the increase in pulmonary artery pressure due to chronic hypoxia secondary to high altitude residence (Antezana G., Barragan L. *et al.*, 1982; Ergueta J. *et al.*, 1971; Lockhart A. *et al.*, 1976). Where we live, in Bolivia, densely populated

towns and cities are located between 3,000-4,800 meters. Both our findings and the literature support that the most important correlate of elevated pulmonary artery pressure (PAP) is the level of altitude exposure, *i.e.* how high one lives and works. The relevant natural experiment is exemplified by La Paz, our capital, which has a population of 1.7 million persons residing between 3,200 and 4,100 meters. We have found that persons who live in the higher zones have a higher incidence of Chronic Mountain Sickness (CMS). The inhabitants of La Paz vary in the degree of which (PAP) is elevated, which is related to the extent of vascular remodeling that has occurred in the pulmonary vasculature (Heath D. *et al.*, 1981). Remodeling, may, in turn, be determined by the reflex arteriolar vasospasm induced by hypoxia. Thus both the absolute degree of hypoxia, as well as frequent changes in arterial PO_2 producing intermittent hypoxia, are relevant to the severity of elevated PAP observed. Among the majority of high altitude inhabitants, mild elevation in PAP has no clinical significance and is reversible on descent to lower altitude or with administration of oxygen (Aparicio, *et al.*, 1992). Our studies of normal residents versus CMS patients at high altitude has contributed to a better understanding of the role of changes in the pulmonary capillary circulation in relation to elevated PAP and the pathophysiology of CMS. Moreover our long-term investigation of the natural evolution of *Cor Pulmonale* has shed light on the mechanisms responsible for the gradual degradation of cardiorespiratory function

One of our long-term objectives has been to establish the normal parameters of the pulmonary circulation at high altitude. In the Instituto Boliviano de Biolog a de Altura (Antezana G., Barragan L. *et al.*, 1982), we have used cardiac catheterization to measure intracardiac pressures, pulmonary arterial pressure and pulmonary capillary pressure (wedge pressure). All the results to date are concordant in indicating that permanent residents of high altitude have resting PAPs that are higher than those at sea level; this "hypertension" has an organic basis and is characterized by differences in the size and structure of the pulmonary vessels specifically muscularisation of the pulmonary arterioles (Coudert J. *et al.*, 1971; Heath D., Smith P. *et al.*, 1981).

Prolonged residence at very high altitude produces a stable regulated and gradual series of adaptive changes that result in acclimatization for the majority of permanent inhabitants (Coudert J. *et al.*, 1974; Vargas Enrique, *et al.*, 1989; Monge Medrano C. *et al.*, 1925). Nonetheless, some of them lose their tolerance for ambient chronic hypoxia and eventually develop increased red cell mass. Excessive erythrocytosis is the most frequently observed of the physiological changes that comprise the clinical features first described in 1928 by Carlos Monge (Monge Medrano C. *et al*,. 1925), which became known as Monge's Disease or Chronic Mountain Sickness. The incidence and clinical evolution of CMS varies according to altitude. Consequently lowered ambient PO_2 is the major risk factor for the development of CMS. In Bolivia, 2/3 of the population lives at $>3,000$ meters. CMS is a health problem affecting up to 10% of the male population. Some densely populated cities, especially those associated with the mining industry, such as Chorolque, are located as high as 4,850 m, where we found that the PAP is even more elevated than in La Paz (IBBA Encuesta en la poblaci n de Chorolque, 1977).

In the highlands an appreciable percentage of residents, develop an abnormal and excessive erythrocytosis, polycythemia (Monge C. C. *et al.*, 1992; Vargas Enrique, *et al.*, 2002; Wu TY., Li W. *et al.*, 1998). The stimulus for abnormally high production of red cells, while not well understood, is not necessarily related to arterial PO_2, since many of these patients have only minimal hypoxia. The problem in determining what mechanisms are more relevant is complicated by the presence, in many patients of sub-clinical abnormalities that are both difficult to measure and to describe. Moreover, the evolution of CMS is variable within individuals (Vargas Enrique, *et al.*, 1993). The classic signs are: an abnormal increase in red cell count, hemoglobin concentration, hematocrit and arterial hypoxemia that is minimal to moderate in severity. Noteworthy is permanent cyanosis in the lips and oral-pharyngeal mucosa, which often causes worry and is the initiating factor in seeking medical consultation. Neurophysiologic symptoms are frequent, including headaches, unusual fatigue, diminished mental capacity in the form of memory and concentration, dizziness, excessive sleep or insomnia, and very often depressive states. All of these subjective symptoms are naturally quite variable. The course of the disease is prolonged; arterial hypoxia (PaO_2) eventually increases, as does carbon dioxide ($PaCO_2$). Patients develop a moderate degree of dyspnea, accompanied by the radiological signs and clinical symptoms of pulmonary arterial hypertension (HAPH) to variable degrees. These symptoms are consistent with a multifactorial disease and comprise the clinical picture of true CMS. The majority of cases are characterized by respiratory abnormalities, often including disorder in the hypoxic ventilatory

response (HVR)(Vargas Enrique, *et al.*, 2002). This is typified by a diminution in the carotid body chemoreceptor-mediated respiratory sensitivity to lowered ambient O_2 pressure and results in lowered alveolar ventilation (Lahiri S, *et al.*, 1969; Severinghaus J. *et al.*, 1966; Lefransois R. *et al.*, 1978). Other studies at altitudes higher than the Bolivian altiplano (4,100 m.) showed that from the beginning the clinical features of CMS are predominantly comprised of cardiovascular signs and symptoms, with the most severe cases suffering from severe arterial hypoxia, high hemoglobin concentration and especially, severely elevated pulmonary arterial hypertension and advanced stages of cor pulmonale (Peñaloza D. *et al.*, 1969).

Materials and Methods

We examined 60 patients diagnosed with CMS, without history or risk factors for cardiac or pulmonary disease. Their ages ranged from 16-65 and were hence divided into two groups: Young CMS, those patients who were <30 years of age (Y-CMS, n=30, mean age 22.3±4.3 years) and old CMS, >30 years (O-CMS, mean age 46.7±7.1 years). Each is compared with their respective control groups, 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 I) who met the inclusion criteria were fully informed of the study procedures and signed and informed consent as obtained 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 Instituto Boliviano de Biolog a de Altura (IBBA) and by the National Bioethics Committee of the Bolivian Health Ministry. The majority of patients in the Y-CMS and O-CMS groups have been patients within of their disease progress (Program in the Etiology and Development of CMS).

In the present study resting tests were performed included a general physical examination and cardiac evaluation. These were complemented by a set of functional, radiological and hematological tests. The functional cardiac examinations included an electrocardiogram in 12 derivations, analyzing the right derivations such as V3r and the relations of R/S in V1, 2, R in aVR and the determinations of the electrical axe (Cardiosunny Alpha) and echocardiography doppler measurements to assess the cardiac and pulmonary haemodynamics (Acuson Cipress) A chest radiograph study with a complete set of respiratory function tests was obtained. Respiratory function test included total body plethysmography with flow-volume curves (Sensor Medics MV-Autobox), and hypoxic ventilatory response (HVR), three tidal volumes of a hypoxic mixture gas inhaled (FIO2:10%, barometric pressure in La Paz: 495 mmHg, Hewlett Packard system)(Dejours P. *et al.*, 1963), arterial blood gases (Radiometer ABL 500) and lung diffusion capacity (Sensor Medics 2450). For respiratory tests, the value reflecting the subject's best performance was accepted.

The variables analysed and presented here were normally distributed and are presented as the mean standard deviation. Comparison between the four groups was made by two-way ANOVA, and relationships between variables were assessed using regression analyses. The Statview statistical program was used for statistical analyses.

Results

The 4 groups were similar in age. None of the subjects had an abnormal weight for height; subjects were excluded if BMI was ≥30, which is the upper limit for normal. Both groups of CMS patients (young and old) had elevated hemoglobin concentrations (Table 1), and it was more pronounced in the older than younger CMS group. Hemoglobin concentration (g/dl) in the two control groups (Y-C, O-C) are normal, and completely within the range of those measured in high altitude hematological studies (Vasquez Ren. *et al.*, 2001).

Table 1. Groups Characteristics

Groups	Age (yrs)	Hemoglobin grs/dl	BMI*
Young CMS	22.3 ± 4.3	19.5 ± 0.7	25.4%
Old CMS	46.7 ± 7.1	24.0 ± 2.3	27.4%
Young Control	22.0 ± 2.4	16.8 ± 0.6	23.8%
Old Control	43.5 ± 3.4	17.2 ± 0.4	27.2%

* BMI=Body Mass Index : normal <30%

Measurements of lung volumes were performed by bodyplethysmographic tests and the result showed a normal forced vital capacity (FVC) in all groups, but changes in the flow-volume force expiratory curve in Y-CMS and O-CMS patients, suggested altered bronchial permeability (FEV_1/ FVC), specially in the small pulmonary periphery branches, in fact, we observed a reduction of th 50% and up to 75% forced expiratory flow (FEF50%-75%) related to forced vital capacity. Singl breath lung diffusing capacity measurements (DL_{CO} ml/min/mmHg) corrected for Hb concentratio showed differences between the two patients groups, O-CMS had a lower value than Y-CMS, both Y-C and O-C having higher values than low altitude norms (22). (Table 2)

Table 2. Peripheral Airflow and Gas Exchange

Parameters	Y-CMS	O-CMS	Y-C	O-C
FEV/FVC %	82.0 ± 2.2	75.0 ± 1.8	86.0 ± 1.5	84.5 ± 1.2
FEF 50 % *	74.2 ± 2.5	69.2 ± 3.3	94.6 ± 2.3	104.13 ± 2.6
FEF 75% *	75.5 ± 3..3	70.1 ± 4.1	98.29 ± 2.2	89.9 ± 4.8
DL_{CO} * *	29.07 ± 1.3	23.8 ± 1.2	38.1 ± .0.9	34.6 ± 0.5
VA L/min	4.33 ± 0.8	4.08 ± 0.82	6.11 ± 0.68	5.75 ± 0.66

* Forced Expiratory Flow, related to 50% and 75% of Forced Vital Capacity (FVC).
* * Lung Diffusion Capacity and alveolar ventilation VA, (single breath of CO mixture method)

Evaluation of chemoreceptor sensitivity or the hypoxic ventilatory response (HVR) is one of the mos important tests for our purposes. The classic description of ventilatory regulation among high-altitud inhabitants indicates that there is a gradual attenuation of ventilatory sensitivity to hypoxia wit increasing years of residence. Duration of exposure to chronic hypoxia must therefore be taken int account when comparing groups as is the case in the present study. The test results (3 trials pe subject) reveal interesting differences between the groups. HVR values among Y-C and O-C, althoug showing different levels of sensitivity, were nonetheless within the normal range, while Y-CMS and C CMS differed considerably in their response to hypoxic stimuli. In the younger patients there wa moderate attenuation of HVR, as the ventilatory response to a given level of hypoxia was decrease relative to the relevant control group. In the older group of CMS patients the magnitude of respons was even more attenuated (Figure 1), suggesting that diminished chemoreceptor sensitivity to hypox is an important cause of hypoventilation in these patients.

It is well-known that hypoxia due to pulmonary disease causes polycythemia, with a considerab elevation in Hb at high altitude, or at sea level. It is evident at high altitude that the demands upo ventilatory control mechanisms are exaggerated. Despite the fact that multiple pathways contribute loss of adaptation, identification of the mechanisms contributing to failure of ventilatory contro especially among the young CMS patients, is an important objective. In the present study arteri hypoxia was variable between subjects within both groups of CMS patients (Table 3). In the Y-CM group cases had only moderate reduction in PaO_2 and had only partial respiratory insufficiency; this w more pronounced in the O-CMS group. In many cases the respiratory insufficiency could be global, would be complicated by moderate alveolar retention and rise of carbonic dioxide or markedly increas $PaCO_2$ with respiratory acidosis. But only rarely do we find true acid-base disturbance in these types patients *i. e.* an arterial pH indicative of non-compensated acidosis, due to the chronicity of the proces Rather it appears that permanent compensation for acid-base imbalance is effected by the increas concentration of Hb and the buffering action, and renal bicarbonate reabsorption.

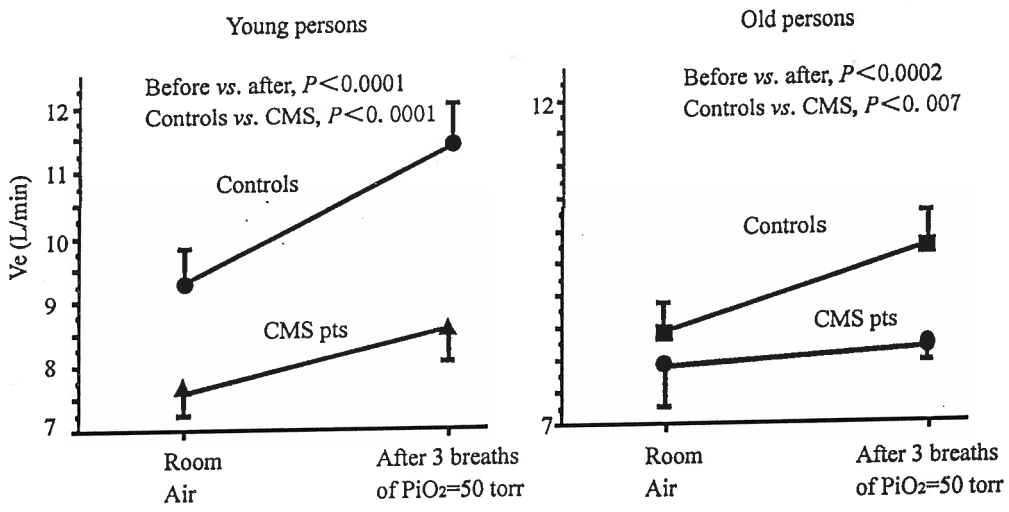

Figure1. Blunted hypoxic ventilatory response occurs early in the disease and tends to worsen with age (interaction of group *vs.* Before/after, $P=0.11$)

Table 3. Arterial blood gases and pulmonary arterial pressure

Groups	PaO_2 mmHg	Paps *	$PaCO_2$ mmHg	SaO_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

* Paps=echocardiographic systolic pulmonary arterial pressure, mmHg. (see Figure 2)

Exactly how hemodynamic factors are changed in relation to hypoxia, for example the increased polycythemia with commensurate increase in blood viscosity and in pulmonary artery pressure, is important, and likely contributes to variable degrees of elevated PAP. Nevertheless, in both CMS groups, PAP is not profoundly elevated as demonstrated by the values for systolic pulmonary pressure presented in Table 2. The electrocardiography data are typical, the P-wave shows an increase in the corresponding derivations (Ⅲ, Ⅳ, aVF), and the QRS axis is right-shifted.

These observations permit us to conclude that there is no significant relationship between the degree of arterial hypoxia, age, haemoglobin concentration, changes observed with ECG and clinical radiological findings. Moreover, as can be observed in Table 3 and Figure 2, the correlation between clinical cardiological examination and the ECG traces in 30 patients of each group, show 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 modestly elevated PAP that is normally observed in the inhabitants of La Paz.

Table 4. Electrocardiogram indicative of RVH

Group	Normal ECG	ECG probable RVH	ECG for RVH
Young CMS	8means 26.6%	12 (40%)	10(33.3%)
Old CMS	9means 30%	13 (43.3%)	8 (26.6%)
Young Controls	22means 73%	4 (13.3%)	4 (13.3%)
Old Controls	25means 92.5%	1 (3.7)	1 (3.7%)

Conclusion

The consequences of alveolar hypoxia and the increase in the blood volume in patients with CMS can be, in some cases, a cause of variable elevation in PAP. This in turn impacts upon myocardial function,

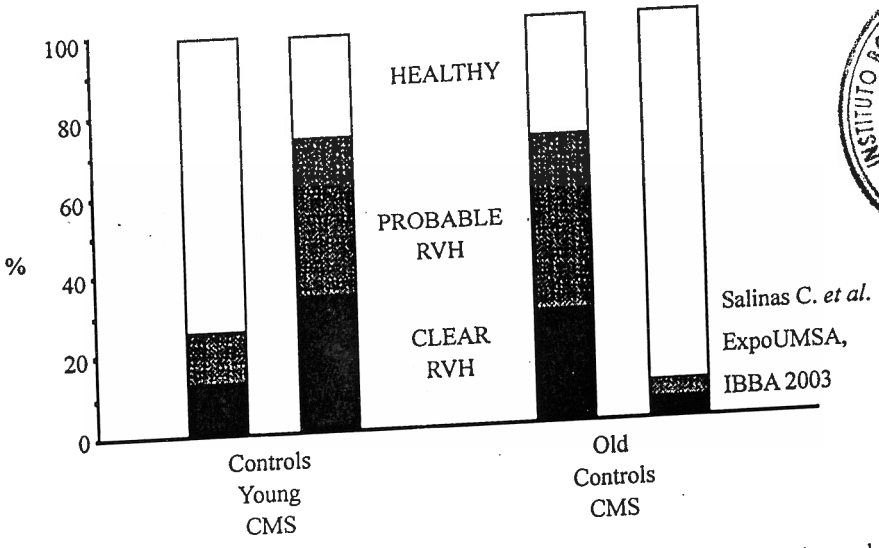

Figure 2. Electrocardiographic evidence of RVH is more common in CMS patients than controls, but the proportion does not increase with age.

not only due to the excessive increase in pulmonary artery resistance but possibly also to the alteratio produced in vascular endothelial function.

Our long-term monitoring of both the young and old groups of CMS patients, in many cases for mo than 10 years, permits us to assert that in those whose dominant pathology is altered respirati (respiratory type), the clinical and radiological findings and successive echo-and electrocardiograms not show significant aggravation of the clinical condition. In contrast, in a small percentage of case cardiovascular symptoms predominate (cardiovascular type), and we observe cardiac hypertrophy w greater frequency. This is due fundamentally to a gradual hypertrophy of the right ventricle: the co of the pulmonary artery is prominent, and the hilum vascular images, very marked, radiate towards t peripheral pulmonary zones. In most of these cases arterial hypoxia is exaggerated and haemoglo concentrations are higher.

Many patients with years of history of CMS in La Paz do not have serious degrees of hypoxia. Wh in some cases Hb concentration is high, few have severely elevation PAP and we find that progress to cor pulmonale is very rare. Nevertheless, review of individual records permits us to identify th patients in whom elevation in PAP are accentuated. They come equally from the Y-CMS or O-C groups, are of the respiratory type and have stable respiratory insufficiency, but the factor linking th patients is that the majority come from the highest zones of the city (4,100 m). They also are fo predominantly in the small group already demonstrating right ventricular hypertrophy (Figure II) thus are more likely to have their disease evolve to cor pulmonale.

These are patients whose health status requires moving to lower altitude as continuing with reside at high altitude incurs a significant risk for the development of cardiac insufficiency. For many of t a move to moderate altitude is sufficient to live without the threat of decompensation, and in many c can reverse the clinical condition of elevated PAP. In all these cases no single rule can be applied individual situations are diverse. Thus, patients of greater age and higher concentration of haemogl can evidence right ventricular hypertrophy without this signifying an incontrovertible evolution tow cor pulmonale. On the other hand, we observe that some of the young patients (16-17 years) favourably reverse their ECG findings with improvement of their oxygenation and diminution in concentration of haemoglobin in response to procedures established to improve the ventila mechanics defect by kinesitherapy, physical exercise, treatment with respiratory stimulants (Vi M. *et al.*, 1985), other medicines (Leon-Velarde F. *et al.*, 2003), descent to low zone, etc.

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