The Heart and Pulmonary Circulation at High Altitudes
Healthy Highlanders and Chronic Mountain Sickness

Dante Penaloza, MD; Javier Arias-Stella, MD, FRCP

Abstract—More than 140 million people worldwide live >2500 m above sea level. Of them, 80 million live in Asia, and 35 million live in the Andean mountains. This latter region has its major population density living above 3500 m. The primary objective of the present study is to review the physiology, pathology, pathogenesis, and clinical features of the heart and pulmonary circulation in healthy highlanders and patients with chronic mountain sickness. A systematic review of worldwide literature was undertaken, beginning with the pioneering work done in the Andes several decades ago. Original articles were analyzed in most cases and English abstracts or translations of articles written in Chinese were reviewed. Pulmonary hypertension in healthy highlanders is related to a delayed postnatal remodeling of the distal pulmonary arterial branches. The magnitude of pulmonary hypertension increases with the altitude level and the degree of exercise. There is reversal of pulmonary hypertension after prolonged residence at sea level. Chronic mountain sickness develops when the capacity for altitude adaptation is lost. These patients have moderate to severe pulmonary hypertension with accentuated hypoxemia and exaggerated polycythemia. The clinical picture of chronic mountain sickness differs from subacute mountain sickness and resembles other chronic altitude diseases described in China and Kyrgyzstan. The heart and pulmonary circulation in healthy highlanders have distinct features in comparison with residents at sea level. Chronic mountain sickness is a public health problem in the Andean mountains and other mountainous regions around the world. Therefore, dissemination of preventive and therapeutic measures is essential. (Circulation. 2007;115:1132-1146.)

Key Words: altitude • altitude sickness • hypertension, pulmonary

People native to high altitude (HA) environments live in an environment of hypobaric hypoxia with low ambient partial pressure of oxygen. As a consequence, they develop alveolar hypoxia, hypoxemia, and polycythemia. Despite this, healthy highlanders are able to perform physical activities similar to and often even more strenuous than those of people living at sea level (SL). This phenomenon has been ascribed to adaptive mechanisms that occur at sequential steps of the oxygen transport system with the main purpose of decreasing the total pO2 gradient from ambient hypoxic air to mixed venous blood at the tissue level.

The heart and pulmonary circulation in healthy people living at HA exhibit important physiological and anatomical characteristics, which resemble those that occur in chronic clinical conditions associated with alveolar hypoxia, hypoxemia, and polycythemia. Healthy HA natives have pulmonary hypertension (PH), right ventricular hypertrophy (RVH) and increased amount of smooth muscle cells (SMCs) in the distal pulmonary arterial branches. All these findings become exaggerated when healthy highlanders lose their capacity for adaptation and develop chronic mountain sickness (CMS). The physiological, pathological, pathogenic, and clinical features of the heart and pulmonary circulation in healthy highlanders and patients with CMS, as described in the pioneering work done in the Andes several decades ago, will be reviewed in the light of the subsequent research performed in other geographic areas.

Healthy Highlanders

Pathogenesis of Human Chronic Hypoxic Pulmonary Hypertension

In a recent historical review, Reeves and Grover highlighted the fact that Peruvian scientists were the first to demonstrate the pathogenesis of human chronic hypoxic PH, a concept that has been verified by numerous subsequent studies. These authors further emphasized the considerable impact of these findings on research in the area of hypoxic PH, although the origin of these concepts remained unnoticed for decades.1

In the present review, we summarize the sequence of events that led us to develop this concept. The story dates back >4 decades when our team carried out electrocardiographic (ECG) and vectorcardiographic studies in healthy HA natives who lived in Morococha, Peru, an Andean community located at 4540 m. In Table 1, some respiratory and hematologic parameters in SL residents and HA natives are compared. We studied 8 groups of HA natives who ranged from newborn to 60 years of age, and the results were compared with similar groups of SL residents. We found that, in the...
newborn at both HA and SL, there is RVH. After birth, however, a clear divergence rapidly emerges. At SL, the RVH decreases promptly and is replaced by left ventricular predominance by 4 to 6 months. In contrast, at 4540 m the RVH decreases slowly and electrical evidence of RVH is persistent throughout life. These findings were confirmed by anatomic observations of heart specimens obtained from highlanders and lowlanders aged from newborn to 80 years who had died in accidents or from acute diseases without cardiopulmonary involvement. These observations led us to postulate that at HA the postnatal changes of the pulmonary artery pressure (PAP) and pulmonary vascular structure would probably differ from what was already described at SL. Therefore, cardiac catheterization studies were carried out in 32 children aged 1 to 14 years and 38 adult HA natives who lived at 4540 m. Later, an additional group of HA newborns was also studied. PH with a mean value of PAP (Ppa) of ≈60 mm Hg was found in HA newborns, a finding similar to that described at SL. After birth, however, the changes in PAP were very different. In contrast to the fast decline at SL, Ppa at HA decreased slowly, and a mild or moderate degree of PH remained until adult age (Figure 2A). A Ppa value of 55 mm Hg was recorded 72 hours after birth and 45 mm Hg in children aged 1 to 5 years. HA adolescents and adults had Ppa of 28±10.5 mm Hg in contrast to 12±2.2 mm Hg obtained in 25 SL residents. The calculated pulmonary vascular resistance (PVR) was 5 times greater at HA than at SL. Heart rate, cardiac output, right atrial pressure, and pulmonary wedge pressure were similar at both levels (Table 2). The postnatal delayed decline of PAP at HA has recently been confirmed by noninvasive methodology in Bolivian and Chinese children. Ultrasound also confirmed the slow decrease of RVH in Bolivian infants.

Quantitative histological observations of distal pulmonary arterial branches were performed in 30 HA natives and in 30

TABLE 1. Respiratory and Hematologic Parameters in SL Residents and HA Natives

<table>
<thead>
<tr>
<th>Location</th>
<th>PaCO₂, mm Hg</th>
<th>PaO₂, mm Hg</th>
<th>SaO₂, %</th>
<th>Hb, g/dL</th>
<th>Hct, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lima (150 m; P₀=753 mm Hg)</td>
<td>40</td>
<td>90</td>
<td>97</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>Morococha (4540 m; P₀=445 mm Hg)</td>
<td>29</td>
<td>50</td>
<td>79</td>
<td>20</td>
<td>60</td>
</tr>
</tbody>
</table>

Values are average of several studies. P₀ indicates barometric pressure; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; SaO₂, arterial oxygen saturation; Hb, hemoglobin concentration; and Hct, hematocrit. Data derived from Hurtado.

Figure 1. A, Relation of AQRS° to age in HA natives and SL residents studied at their respective locations. RVH as indicated by AQRS° >135° is similar in SL newborns and HA newborns (4540 m). Postnatal changes diverge. RVH slowly decreases and remains until the adult age in people born at HA. By contrast, RVH is replaced early by left ventricular predominance in infants born at SL. B, Left ventricle/right ventricle (LV/RV) weight ratio confirms different postnatal changes at SL and HA. C, Transverse sections of heart specimens show absence of RVH involution in children born at HA. Each section shows the right ventricle on the right and the left ventricle on the left. Data for A and B derived from Penaloza et al, Arias-Stella and Recavarren, and Recavarren and Arias-Stella; C is reproduced from Penaloza et al with permission of the American Academy of Pediatrics. Copyright 1984.
SL residents who had died in accidents or from acute noncardiopulmonary diseases, who ranged from newborn to 76 years of age. There were no differences among newborns or stillborns of HA and SL. Both groups showed the “fetal pattern” characterized by increased amount of SMCs in the small pulmonary arteries and muscularization of the arterioles, which implied thickening of the walls and narrowing of the lumen of these vessels. This histological pattern remained, with slight variation, in children and adults native to HA. In contrast, the SL subjects exhibited prompt decrease of SMCs in the distal arteries and absence of SMCs in the arterioles and consequently exhibited thinning of the vascular walls and widening of the lumen. This implies that in HA natives there is delayed remodeling of the distal pulmonary arteries.

**Figure 2.** A, Relation of PPA to age in HA natives (4500 m) in comparison to data described at SL. PPA of 45 mm Hg is similar in SL newborns and HA newborns (4540 m). Postnatal changes diverge. PH slowly declines and remains until the adult age in people born at HA, in contrast to the fast decline of PPA described in subjects born at SL. Numbers in parentheses indicate number of cases. B, Schematic representation of remodeling at the distal pulmonary arterial branches. There is prompt vascular remodeling in infants born at SL by contrast with a delayed process in infants born at HA. Data derived from Penaloza et al,6 Sime et al,7 Penaloza et al,8 Gamboa and Maticorena,9 Arias-Stella and Saldaña,13 Arias-Stella and Castillo,14 Penaloza et al,15 and Arias-Stella16.

**TABLE 2.** Hemodynamic Values in Healthy Highlanders by Comparison With SL Residents Studied at Their Respective Locations

<table>
<thead>
<tr>
<th></th>
<th>HA Children 1 to 5 Years Old (n=7)</th>
<th>HA Children 6 to 14 Years Old (n=32)</th>
<th>HA Adults 18 to 33 Years Old (n=38)</th>
<th>SL Adults 17 to 23 Years Old (n=25)</th>
<th>P, HA Adults vs SL Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct, %</td>
<td>43.9±3.87</td>
<td>48.0±3.25</td>
<td>59.1±7.20</td>
<td>44.1±2.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>14.1±0.66</td>
<td>15.7±1.07</td>
<td>19.5±1.97</td>
<td>14.7±0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>78.2±2.76</td>
<td>77.3±5.76</td>
<td>78.4±4.81</td>
<td>95.7±2.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, L · min · m⁻²</td>
<td>4.4±0.60</td>
<td>4.5±1.39</td>
<td>3.7±1.64</td>
<td>3.9±0.97</td>
<td>NS</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>2.8±1.57</td>
<td>1.8±1.46</td>
<td>2.6±1.69</td>
<td>2.6±1.31</td>
<td>NS</td>
</tr>
<tr>
<td>PPA, mm Hg</td>
<td>45±16.6</td>
<td>28±10.2</td>
<td>28±10.5</td>
<td>12±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWP, mm Hg</td>
<td>6.7±2.21</td>
<td>5.0±1.00</td>
<td>5.4±1.96</td>
<td>6.2±1.71</td>
<td>NS</td>
</tr>
<tr>
<td>PVR, dyne · s · cm⁻⁵</td>
<td>...</td>
<td>459±273.7</td>
<td>332±212.6</td>
<td>69±25.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD. CI indicates cardiac index; RAP, right atrial pressure; PWP, pulmonary wedge pressure; and NS, not significant. Data derived from Sime et al7 and Penaloza et al.3
vasculature in contrast with what is observed at SL (Figures 2B, 3A, and 3B).

Taken together, these findings indicate a different evolutionary pattern at HA in the PAP, remodeling of the pulmonary vasculature, and anatomic and electrical ventricular predominance. The postnatal persistence of PH at HA implies a delayed closure of ductus arteriosus and, as a consequence, an increased prevalence of patent ductus arteriosus at HA. The evidence indicates that the main factor responsible for PH in healthy highlanders is the increased amount of SMCs in the distal pulmonary arteries and arterioles, which increases the PVR. Vasoconstriction is a secondary factor because the administration of oxygen decreases the PAP only by 15% to 20%. Hypervolemia, polycythemia, and increased blood viscosity, although considered causal factors in earlier studies, are now considered secondary factors. The main role of the structural changes in the pulmonary vasculature is confirmed by the slow decline of PAP, which becomes normal after 2 years of residence at SL. The recent exciting developments in the cellular and molecular mechanism of chronic hypoxic PH are beyond the scope of this review.

**PAP, Arterial Oxygen Saturation, and Level of Altitude**

The level of altitude has an inverse relation to arterial oxygen saturation (SaO₂) and a direct relationship to the PAP.

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**Figure 3.** Transverse sections of distal pulmonary arterial branches obtained in an 8-year-old boy native to HA. A, Small pulmonary artery at the level of alveoli that shows a thick medial layer caused by increased SMC between the elastic layers. Elastic Van Gieson stain, ×25. B, Muscularized pulmonary arteriole with a mean diameter of 15 μm and a distinct muscular media sandwiched between internal and external elastic laminae. This finding is in contrast with the SL pulmonary arterioles that have a single elastic lamina without muscular layer. Weigert’s fuchsin-resorcin stain, ×25. Data derived from Arias-Stella and Saldana, Arias-Stella and Castillo, Penaloza et al, and Arias-Stella.

**Figure 4.** A, Level of altitude as related to PPA. There is a direct relationship represented by a parabolic line so that above 3000 m moderate increments in altitude correlate to great increases in PPA. There are 2 exceptions to this correlation (○). PPA in Leadville, Colo (3100 m), is greater than expected for this altitude. PPA in Lhasa, Tibet (3600 m), is lower than expected for this altitude. B, Level of altitude as related to SaO₂. There is an inverse relationship between these 2 variables. Notice that Leadville and Lhasa follow the general tendency, different from what occurs with PPA. See Table 3 for PPA and SaO₂ values at various altitudes.
TABLE 4. Exercise-Induced Hemodynamic Changes in Healthy Highlanders (4540 m) and SL Residents Studied at Their Respective Locations

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Location</th>
<th>Altitude, m</th>
<th>P_{PA}, \text{mm Hg (n)}</th>
<th>Sa_{O2}, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grover (20)</td>
<td>Denver, Colo</td>
<td>150</td>
<td>12±2 (25)</td>
<td>96±2.1 (25)</td>
</tr>
<tr>
<td>Michelis et al (21)</td>
<td>Mexico City, Mexico</td>
<td>2240</td>
<td>15±2 (21)</td>
<td>92 (21)</td>
</tr>
<tr>
<td>Miao et al (23)</td>
<td>Xining, Qinghai, China</td>
<td>2261</td>
<td>14±2 (34)</td>
<td>93 (34)</td>
</tr>
<tr>
<td>Ordoñez (22)</td>
<td>Bogota, Colombia</td>
<td>2600</td>
<td>13±3 (18)</td>
<td>90 (18)</td>
</tr>
<tr>
<td>Grover (20)</td>
<td>Leadville, Colo</td>
<td>3100</td>
<td>24±7 (50)</td>
<td>89 (50)</td>
</tr>
<tr>
<td>Antezana et al (24)</td>
<td>La Paz, Bolivia</td>
<td>3600</td>
<td>22±1 (11)</td>
<td>90±0.8 (11)</td>
</tr>
<tr>
<td>Groves et al (29)</td>
<td>Lhasa, Tibet</td>
<td>3600</td>
<td>15±1 (5)</td>
<td>88±1.8 (5)</td>
</tr>
<tr>
<td>Yang et al (26)</td>
<td>Yushu, Qinghai, China</td>
<td>3680</td>
<td>22±4 (17)</td>
<td>...</td>
</tr>
<tr>
<td>Hultgren et al (25)</td>
<td>La Oroya, Peru</td>
<td>3700</td>
<td>22±4 (26)</td>
<td>85 (27)</td>
</tr>
<tr>
<td>Yang et al (27)</td>
<td>Chengdu, Qinghai, China</td>
<td>3950</td>
<td>26±2 (22)</td>
<td>...</td>
</tr>
<tr>
<td>Yang et al (26)</td>
<td>Madou, Qinghai, China</td>
<td>4280</td>
<td>23±3 (12)</td>
<td>...</td>
</tr>
<tr>
<td>Penaloza and Sime (28)</td>
<td>Cerro de Pasco, Peru</td>
<td>4340</td>
<td>23±5 (12)</td>
<td>81±4.6</td>
</tr>
<tr>
<td>Penaloza et al (8)</td>
<td>Morococha, Peru</td>
<td>4540</td>
<td>28±11 (38)</td>
<td>78±4.8 (38)</td>
</tr>
</tbody>
</table>

Values for P_{PA} are mean±SD. Values for Sa_{O2} are mean or mean±SD.

TABLE 3. Pulmonary Arterial Pressure and Arterial Oxygen Saturation at Various Altitudes

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Location</th>
<th>Altitude, m</th>
<th>P_{PA}, \text{mm Hg}</th>
<th>Sa_{O2}, %</th>
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Values for P_{PA} are mean±SD. Values for Sa_{O2} are mean or mean±SD.
at HA, and some of them may develop severe PH and heart failure (HF) because of the excessive amount of pulmonary vascular SMCs. A similar condition has been induced experimentally in young steers and in newborn calves at 4300 m.

### Pulmonary Pressure and Arterial Oxygen Saturation During Exercise

Earlier studies on the cardiopulmonary response to exercise in Andean natives were carried out by Peruvian investigators. Thirty-five highlanders were studied in Morococha, Peru, at 4540 m and the results were compared with those obtained in 25 SL residents. Both groups were submitted to mild supine exercise with a workload of 50 watts. Pulmonary pressure responses were quite different at HA and SL, despite similar increases in oxygen consumption and cardiac output. PPA increased from 29 ± 10 to 60 ± 17 mm Hg in highlanders and from 12 ± 2.2 to 18 ± 2.7 in lowlanders. These changes correspond to increments of 100% at HA and 50% at SL (Table 4). Exercise-induced PH in highlanders was confirmed in subsequent studies performed in Leadville, Colo,19,20; La Paz, Bolivia24; and La Oroya, Peru.25 The magnitude of the pressure response was related to the level of altitude and the degree of submaximal workload. The probable influence of a genetic factor was demonstrated by Asian investigators who found a lower pulmonary pressure response to exercise in Tibetan natives than in Chinese Han immigrants, who are relative newcomers to HA.26

PH induced by exercise in highlanders is related to increased SMCs and narrowing of the distal pulmonary arteries and arterioles and consequently to increased PVR, which is already high in the basal state. Therefore, the pulmonary vascular bed is unable to dilate and accommodate the increased blood flow during exercise, contrary to what occurs in SL residents. Consequently, PVR does not decrease and even increases during physical activity in people who live at HA. Vasoconstriction is a contributing factor to increased PVR because of greater hypoxemia during exercise. These findings are in contrast to the reduced cardiac output response to exercise at HA observed in both athletes and sedentary SL residents. Similar findings have also been observed in athletes of European ancestry native to Leadville, Colo (3100 m).41 The remarkable exercise performance of Andean natives, despite a relative hypoventilation, has been ascribed to a superior oxygen transport system that includes the preservation of a normal cardiac output response. This was first reported by us for mild exercise and confirmed by subsequent studies for submaximal and maximal exercise. These findings are in contrast to the reduced cardiac output response to exercise at HA observed in both athletes and sedentary SL residents. Similar findings have also been observed in athletes of European ancestry native to Leadville, Colo (3100 m).41 The remarkable exercise performance of Andean natives, despite a relative hypoventilation, has been ascribed to a superior oxygen transport system that includes the preservation of cardiac output, increased pulmonary diffusion capacity, and probable adaptation at the tissue level.

### Reversal of HA PH After Long Residence at SL

There are only a few reports on measurements of pulmonary hemodynamics in HA natives after they descend to SL. We studied 11 HA natives who resided at 4340 m and repeated the studies after 2 years of residence at SL. After prolonged residence at SL, the PPA became normal, and this finding was associated with reduction of heart rate, increased cardiac output, and augmented stroke volume (Table 5).

The decrease in heart rate was highly significant, and 7 of the 11 subjects had a resting heart rate <60 beats/minute. A slight decrease in heart rate has been observed in highlanders after short stays at SL, and this has also been observed at HA after oxygen inhalation. This phenomenon has been ascribed to an increased parasympathetic activity.

Cardiac output increased moderately after 2 years of residence at SL. The increase in cardiac output is not related to an increased oxygen uptake, but correlated with a reduction of the arterial-venous oxygen difference and with a decrease in the arterial oxygen content caused by a significant reduction of the hemoglobin concentration (Hb). The moderate
increase of cardiac output and in particular the great decrease of heart rate explain the highly significant increase of stroke volume observed in highlanders after 2 years of residence at SL.

The PAP and PVR also decreased significantly after 2 years at SL and reached levels similar to those found in normal SL residents. By contrast, only a partial reduction of PAP and PVR is obtained by short-term oxygen inhalation in highlanders while living at high altitude. These observations reinforce the importance of the structural remodeling of the distal pulmonary arteries and arterioles in the mechanism of PH at HA. There is an additional argument that supports this mechanism. Despite the normal PAP after 2 years at SL, the pulmonary pressure response to exercise was similar to that observed at HA, a 100% increase in the PAP. This observation suggests that the involution of the thick pulmonary vessels is not complete even after long residence at SL. Similar observations were made by Grover et al about an adolescent of European ancestry who had had severe PH when he lived in Leadville, Colo, and then spent 1 year at SL.45

Role of HA PH in the Process of Altitude Adaptation

Altitude adaptation implies changes in the oxygen transport system. The role of PH in this process has not been clearly established. HA PH is a marker of chronic hypoxia, but a causal relationship to the altitude adaptation has not been proven, and some teleological hypotheses have not been confirmed. PH is an epiphenomenon during altitude adaptation. In an environment of chronic hypoxia, with few exceptions, there is a direct relationship between the level of altitude, the degree of alveolar hypoxia, and the magnitude of PH. A mild or moderate PH is compatible with normal life at HA. A severe degree of PH is associated with HA diseases. HA PH and the associated vascular changes gradually regress after prolonged residence at SL. In contrast to PH, HA polycythemia is a fundamental component of the oxygen transport system and the adaptation to altitude; however, excessive polycythemia is also associated with HA disease.

New knowledge in HA biology has illuminated the controversial topic of the relationship between high-altitude PH and the process of altitude adaptation. Unexpectedly normal PAP and minimal hypoxic pulmonary vascular reactivity were discovered in Tibetan natives who lived in Lhasa at 3600 m.29 This feature was consistent, however, with the finding of a normal amount of SMCs in the distal pulmonary arteries and a lack of SMCs in the arterioles.46 In addition, Tibetans have higher SaO2 and lower Hb in comparison with Chinese Han immigrants and Andean natives. Tibetans also have greater ventilatory capacity and hypoxic ventilatory response as well as greater physical performance.

Taken together, these findings indicate adaptive changes in the oxygen transport system, and they suggest that Tibetan natives would have reached optimal adaptation to HA following a process of natural selection through millennia and numerous generations of life on the most extensive and elevated plateau in the world. By contrast, Andean natives would still be immersed in the slow process of adaptation that would take millennia. Tibetans would have reached genotypic adaptation, whereas Andean natives would be involved in a process of phenotypic adaptation.47-49

Further support for this hypothesis is found in animal adaptation. Animals native to HA such as yaks, snow pigs, and pika of the Himalayas, which preceded human life by millennia, have normal PAP and pulmonary vasculature. In contrast, domestic animals like cows, pigs, and guinea pigs, which were transported to the Andes by the Spanish conquerors, have PH and thick pulmonary arteries and arterioles.50 There would be genotypic adaptation in the first group and phenotypic adaptation in the second one.50,51 The results of an elegant experiment of a cross-breed between yak and cow further support this hypothesis.52

Taken together, this new knowledge would indicate that normal PAP and pulmonary vasculature in HA residents are evidence of full adaptation. In contrast, PH and thick pulmonary arteries and arterioles would be evidence of incomplete adaptation that is compatible with normal life at HA.29,50 A severe degree of PH is associated with HA disease and risk of death if there is not early management of this clinical condition.

Chronic Mountain Sickness

Seven decades ago Professor Carlos Monge, Sr, was the first to describe the clinical picture of CMS in the Peruvian Andes,
and he emphasized excessive polycythemia as the main characteristic feature of this disease.\textsuperscript{53} Later, Professor Alberto Hurtado pointed out that alveolar hypventilation is the primary mechanism in CMS, which leads to severe hypoxemia and hence to exaggerated polycythemia.\textsuperscript{38} Rotta et al were the first to describe PH in 1 case of CMS,\textsuperscript{17} and then Penaloza et al, who worked at Cerro de Pasco, Peru (4340 m), carried out investigations on the heart and pulmonary circulation in 10 patients with CMS.\textsuperscript{28,54} Afterward, Bolivian investigators reported 2 studies.\textsuperscript{55,56} Further cardiac catheterization studies on CMS have not been performed in the Andean region. Chinese and Kyrgyz investigators have also published interesting observations on CMS and related diseases, as discussed in the following sections.

**Definition of CMS**

An international consensus statement on chronic and subacute HA diseases has recently been published, and the definition of CMS has been established as follows: “A clinical syndrome that occurs to native or long-life residents above 2500 m. It is characterized by excessive erythrocytosis (females, \(Hb \geq 19\) g/dL; males, \(Hb \geq 21\) g/dL), severe hypoxemia, and in some cases moderate or severe PH, which may evolve to cor pulmonale, leading to congestive HF. The clinical picture of CMS gradually disappears after descending to low altitude and reappears after returning to HA.”\textsuperscript{57}

**Prevalence of CMS and Excessive Erythrocytosis**

The concept of excessive erythrocytosis (EE) is closely related to the prevalence of CMS. This topic has been investigated in Peru, Bolivia, China, and Kyrgyzstan. Peruvian investigators performed an epidemiological approach to the study of EE in healthy highlanders who resided in Cerro de Pasco at 4340 m, and studied the Gaussian distribution of Hb in 5 age groups. A threshold Hb value of 21.3 (mean, 18 ± 2 SD) was proposed as criterion for EE. The prevalence of EE increased from 6.8% in the youngest group (20 to 29 years of age) to 33.7% in the oldest group (60 to 69 years of age) with an average prevalence of 15.6%.\textsuperscript{58} At the same altitude, these investigators described a prevalence of EE as high as 32.4% in cases associated with lung diseases.\textsuperscript{59}

Bolivian investigators have reported a CMS prevalence of 6% to 8% in the male population of La Paz (3600 m).\textsuperscript{60} Other studies in La Paz described a hospital frequency of 28%, with most of the patients diagnosed with associated respiratory diseases.\textsuperscript{61} Chinese investigators carried out epidemiological studies on CMS and EE in the Qinghai-Tibetan plateau at 3 levels of altitude and found an overall prevalence of 5.6% in Chinese Han immigrants and 1.2% in Tibetan natives.\textsuperscript{62} Kyrgyz studies at the Tien-Shan and Pamir Mountains (3000 to 4200 m) found a prevalence of HA cor pulmonale in 4.6% of the male population.\textsuperscript{63} Prevalence of CMS and EE is higher in men than in women, and increases with altitude, aging, association of lung diseases, smoking, and environmental pollution.

**Pathogenesis of CMS**

Hyperventilation is a characteristic feature of healthy HA residents. A gradual reduction of hyperventilation that varies to a relative hypventilation is the probable initial mechanism of a cascade of events that leads to progressive deterioration of adaptation and the development of CMS. A lower level of alveolar ventilation induces hypoxemia of greater degree than in healthy highlanders. In consequence, there is increased erythropoietin response, exaggerated polycythemia, and a greater degree of PH. The complex interaction of the respiratory and hematologic changes induces the appearance of neuropsychic symptoms.

CMS is a variety of chronic alveolar hypventilation that results in a complex syndrome that integrates 4 main components. Respiratory features are characterized by alveolar hypventilation, relative hypercapnia, V/Q mismatch, widened (A-a) \(pO_2\) gradient, and increased hypoxemia. Hematologic features are excessive polycythemia, increased blood viscosity, and expanded total and lung blood volume. Cardiopulmonary abnormalities include moderate or severe PH and RVH, which may evolve to hypoxic cor pulmonale and HF. Neuropsychic symptoms include sleep disorders, headache, dizziness, and mental fatigue.

The symptomatic complex of CMS resembles the clinical picture, which may result as a complication that evolves from other chronic alveolar hypventilation syndromes such as chronic obstructive pulmonary diseases, obesity hypventilation syndrome, obstructive sleep apnea syndrome, central sleep hypventilation syndrome, neuromuscular disorders, and chest wall deformities.\textsuperscript{64}

**Clinical Picture of CMS**

Peruvian investigators carried out pioneering cardiopulmonary studies of CMS in 10 male patients from 22 to 51 years of age who were born and lived near Cerro de Pasco (4340 m). The patients did not have any history of pulmonary diseases and had never worked in mines or in any other dusty occupation. Clinical and hemodynamic studies were performed in these patients and the results were compared with a group of healthy natives who resided at the same altitude.\textsuperscript{28,54} Respiratory studies have been published by Peruvian and North American investigators.\textsuperscript{65,66} In recent decades Asian investigators studied a great number of patients with CMS and described a clinical picture\textsuperscript{67,68} that closely resembles the classic description by Peruvian investigators.\textsuperscript{28,54}

Frequent symptoms in patients with CMS are decreased exercise tolerance, sleep disorders, headaches, dizziness, tinnitus, paresthesias, physical weakness, and mental fatigue. Physical examination shows that the ruddy or erythremic color usually seen in healthy highlanders becomes cyanotic. Cyanosis can vary and is particularly visible at the nail beds, ears, and lips. In some cases the face is almost black, and the mucosa and conjunctiva are dark red. Clubbing of fingers is a frequent finding. The pulmonary second sound is increased and often associated with a soft mid-systolic ejection murmur. Signs of mild or moderate HF are found in some cases. The systemic diastolic blood pressure is often increased, which has been related to excessive polycythemia.\textsuperscript{28,54}

Heart size is significantly increased on chest x-ray as compared with healthy highlanders, and this feature is caused by increased size of the right chambers. Prominence of the main pulmonary artery is found in all patients, and pulmonary
Cardiac Catheterization and Pulmonary Hemodynamics in CMS

Rotta et al were the first to perform a cardiac catheterization in 1 case of CMS in Morococha, Peru (4540 m). This patient had Hb 26 g/dL, PPA 35 mm Hg, and SaO2 78%. Then we performed cardiac catheterization studies in 10 cases of CMS in Cerro de Pasco (4340 m) and the mean values for Hb, SaO2, and PPA were 25±2 g/dL, 70±5%, and 47±17 mm Hg, respectively, which indicated greater degrees of polycythemia, hypoxemia, and PH in comparison with healthy highlanders. PPA was >25 mm Hg in all patients, and the highest value was 85 mm Hg. The relationship of PPA with SaO2 is depicted in Figure 5, which shows that as SaO2 decreases PPA increases, and the patient with the lowest SaO2 value has the highest PPA. Differences among CMS patients, healthy highlanders, and normal SL subjects are shown in Table 6.

The hemodynamic response to exercise was studied by our group in 6 patients submitted to mild workloads and the changes observed were as follows: Cardiac index increased from 4.05 to 7.24 L/min per M2, SaO2 fell from 71.3% to 61.4%, and PPA increased from 37 to 82 mm Hg. Because cardiac output increased in a normal fashion, the great increment of PPA is ascribed primarily to increased PVR caused by the thick SMC coat and in part to vasoconstriction caused by increased hypoxemia. When patients with CMS were moved to SL, SaO2 became normal, whereas Hb, hematocrit, and PPA decreased gradually, and the greatest changes occurred in patients with the longest residence at SL. However, PPA did not reach the SL value after 2 months, probably because of an incomplete remodeling of the pulmonary vascular structure.

Pulmonary hemodynamics in CMS have been studied in other geographic regions as well. Hecht and McClement reported a 28 year-old-man with a clinical picture of CMS in Fairplay, Colo (3015 m). After 2 years of residence in Los Angeles, Calif, there was partial recovery, although a certain degree of hypoxemia, polycythemia, and PH remained, which was ascribed to a subclinical lung disease. Bolivian investigators carried out 2 studies on CMS in La Paz, Bolivia (3600 m). Ergueta et al found average values of Hb 26 g/dL, PPA 51 mm Hg, and SaO2 84% in 2 patients studied in La Paz. Manier et al reported Hb 21±1 g/dL and PPA

TABLE 6. Hemodynamic Values in CMS in Comparison With Healthy Highlanders and SL Subjects

<table>
<thead>
<tr>
<th></th>
<th>SL Controls (n=25; Age 17 to 23 Years)</th>
<th>Healthy Highlander Controls (n=12; Age 19 to 38 Years)</th>
<th>CMS Subjects (n=10; Age 22 to 51 Years)</th>
<th>P, CMS vs Healthy Highlanders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dL</td>
<td>14.7±0.88</td>
<td>20.1±1.69</td>
<td>24.7±2.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hct, %</td>
<td>44.1±2.59</td>
<td>59.4±5.4</td>
<td>79.3±4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>95.7±2.07</td>
<td>81.1±4.61</td>
<td>69.6±4.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>2.6±1.31</td>
<td>2.9±1.4</td>
<td>3.9±1.8</td>
<td>NS</td>
</tr>
<tr>
<td>PPA, mm Hg</td>
<td>12.2±2.2</td>
<td>23.4±5.1</td>
<td>47±17.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWP, mm Hg</td>
<td>6.2±1.71</td>
<td>6.9±1.4</td>
<td>5.7±2.3</td>
<td>NS</td>
</tr>
<tr>
<td>PVR, dyne·s·cm⁻³</td>
<td>69±25.3</td>
<td>197±57.6</td>
<td>527±218.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>3.9±0.97</td>
<td>3.8±0.62</td>
<td>4.0±0.93</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. Hct indicates hematocrit; RAP, right atrial pressure; PWP, pulmonary wedge pressure; CI, cardiac index; and NS, nonsignificant. Data derived from Penaloza et al54 and Penaloza and Sime.28
27 ± 10 mm Hg as mean values obtained in 8 patients with CMS.56

Chinese investigators have made important clinical and epidemiological studies in the last 2 decades. There are limited observations of pulmonary hemodynamics, however. Pei et al studied 17 patients of CMS in Lhasa, Tibet (3600 m), most of them men of Chinese Han origin, all smokers. Five patients had cardiac catheterization, and the average PPA was 40 mm Hg, which greatly exceeded the normal value for healthy highlanders.67 Yang et al reported a PPA of 31 mm Hg in 6 male Han patients studied at Chengdou (3950 m). Wu et al reported 18 subjects who developed CMS at 3700 to 4200 m but were studied 1 week later during recovery in Xining (2261 m), and only 5 patients had mild to moderate PH. According to the authors, this result is ascribed to the lower altitude where the study was performed.70 This low degree of PH is in contrast to the RVH detected by ECG in patients with CMS in Peru, Bolivia, and China. Table 7 shows the studies of pulmonary hemodynamics performed in patients with CMS in various geographic regions.

### Primary and Secondary CMS

The high prevalence of lung diseases at HA and the increased morbidity and mortality related to this cause have been reported in Bolivia, Colorado, China, and Kyrgyzstan. Professor Monge was the first to mention the possible association of CMS and lung diseases, and this association has been demonstrated in different geographic areas.59–62,71–73 The rare pathological reports from patients who died with the diagnosis of CMS and HF showed evidence of mild or moderate pulmonary diseases and/or conditions such as severe obesity and kyphoscoliosis, which indicates that these cases were actually secondary forms of CMS. One patient with these characteristics was studied by us, and the autopsy showed severe RVH and dilation (Figure 6A), excessive muscularization of peripheral pulmonary arterial branches, thickened adventitia, and thrombi in some.

#### Table 7. PAP in CMS, HAHD, and SMS

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Location</th>
<th>Altitude, m</th>
<th>Diagnosis</th>
<th>PPA, mm Hg (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotta et al (17)</td>
<td>Morococha, Peru</td>
<td>4540</td>
<td>CMS</td>
<td>35 (1)</td>
</tr>
<tr>
<td>Penaloza and Sime (28)</td>
<td>Morococha, Peru</td>
<td>4540</td>
<td>CMS</td>
<td>47 ± 17 (10)</td>
</tr>
<tr>
<td>Ergueta et al (55)</td>
<td>La Paz, Bolivia</td>
<td>3600</td>
<td>CMS</td>
<td>51 (2)</td>
</tr>
<tr>
<td>Manier et al (56)</td>
<td>La Paz, Bolivia</td>
<td>3600</td>
<td>CMS</td>
<td>27 ± 10 (8)</td>
</tr>
<tr>
<td>Pei et al (67)</td>
<td>Lhasa, Tibet</td>
<td>3600</td>
<td>CMS</td>
<td>40 ± 11 (5)</td>
</tr>
<tr>
<td>Yang et al (27)</td>
<td>Chengdu, Qinghai, China</td>
<td>3950</td>
<td>CMS</td>
<td>31 (6)</td>
</tr>
<tr>
<td>Wu et al (70)</td>
<td>Guolok, Qinghai, China</td>
<td>3700 to 4200</td>
<td>CMS</td>
<td>18 ± 8 (18)</td>
</tr>
<tr>
<td>Wu et al (63)</td>
<td>Qinghai-Tibetan Plateau, China†</td>
<td>3000 to 5000</td>
<td>HAHD</td>
<td>36 ± 3 (108)</td>
</tr>
<tr>
<td>Cheng et al (84)</td>
<td>Qinghai-Tibetan Plateau, China†</td>
<td>3000 to 5000</td>
<td>HAHD</td>
<td>28 ± 4 (10)</td>
</tr>
<tr>
<td>Aldashev et al (63)</td>
<td>Tien-Shan &amp; Pamir Mountains, Kyrgyzstan‡</td>
<td>2800 to 3100</td>
<td>HACP</td>
<td>32 ± 4 (11)</td>
</tr>
<tr>
<td>Ma Ru-Yan et al (77)</td>
<td>Qinghai-Tibetan Plateau, China†</td>
<td>2440 to 3700</td>
<td>SMS</td>
<td>72 ± 17 (55)</td>
</tr>
</tbody>
</table>

Values for PPA are mean or mean ± SD. HACP indicates high altitude cor pulmonale.

*Cardiac catheterization in Xining, 2261 m.
†Doppler echocardiography in Xining, 2261 m.
‡Cardiac catheterization in Bishkek, 760 m.

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Figure 6. Postmortem findings in a 45-year-old-woman who was born and lived in Cerro de Pasco, Peru (4300 m). She died with the diagnosis of CMS and pronounced kyphoscoliosis. A. Severe right ventricular hypertrophy and dilatation with prominent pulmonary trunk are shown. B. Distal small pulmonary arterial branch with definite medial muscular layer between 2 elastic lamina and thickening of the adventitia by collagen fibers. Elastic Van Gieson stain, ×25. C, small pulmonary arterial branch with similar findings and a partially organized thrombus. Hematoxylin-Eosin, ×40. Reproduced from Arias-Stella et al with permission of British Medical Journals. Copyright 1973.
medium and small pulmonary arteries (Figure 6A through 6C).74

CMS may be considered as a disease with a wide spectrum. At 1 end of the spectrum there is the genuine or primary CMS, well known as Monge’s disease, and at the other end of the spectrum is the secondary variety of CMS associated with obvious lung diseases. However, most cases are in the middle of the spectrum, and these may represent unrecognized respiratory abnormalities because it is not easy to rule out the influence of smoking and environmental pollution, factors often mentioned in papers dealing with CMS. The primary type of CMS is diagnosed after exclusion of lung diseases by pulmonary function testing. This type of CMS is caused by alveolar hypoventilation, and is related to aging, increased weight, sleep disorders, and other factors that at HA become important determinants of hypoxemia because of the shape of the hemoglobin-oxygen dissociation curve.

Differential Diagnosis of Chronic Mountain Sickness With Other HA-Related Diseases

Subacute Mountain Sickness
Fifty years ago, a spontaneous form of right HF named brisket disease was described in some strains of young calves after their first exposure to grazing at altitudes between 2500 and 3700 m in the Rocky Mountains of the United States of America. Excessive PH, exaggerated cardiac enlargement with RVH, and medial muscular hypertrophy of the small pulmonary arteries were found. These animals died if they remained at altitude. They had prompt and spontaneous remission of HF and pulmonary hemodynamics after descending to lower levels, however.75 Afterward, this clinical picture and pulmonary hemodynamics were experimentally induced in steers at 3900 m, and PH was mainly ascribed to vasoconstriction caused by excessive hypoxic pulmonary vasoreactivity of the very thick pulmonary small arteries in these young animals.34

Five decades ago Chinese investigators described the human counterpart of brisket disease with the name of HA heart disease (HAHD) of pediatric type.76 This entity is observed in infants of Chinese Han origin who are born at low altitude and then brought to HA, where they develop HF within a few weeks or months with a fatal outcome if the infants are not moved down to lower places. The first paper in English was published in 1988 with the name of infantile subacute mountain sickness (SMS), and it described an extreme medial hypertrophy of the small pulmonary arteries as well as massive hypertrophy and dilatation of the right ventricle.33 Severe PH assessed by Doppler-echocardiography has been recently described in children with SMS (Table 7).77 SMS in adults has also been described in soldiers who patrolled at very HA of the Himalayan Mountains with prompt recovery after a return to lower altitude.78 A review of SMS in Asia has recently been published.79 SMS is not frequent in the Andes, but some cases have been observed in infants who died in a Peruvian community at 4700 m (Figure 7A and 7B).

There are fundamental differences on clinical and pathophysiological grounds between CMS and SMS. CMS (Monge’s disease) is a chronic entity that occurs in adults after long residence at HA. SMS is a subacute disease rarely seen in adults. It mainly occurs in infants from low altitudes after their arrival at HA. Patients with SMS have a severe degree of PH, RVH, and HF, whereas hypoxemia and polycythemia are only of slight degree. The primary mechanism in CMS is hypoventilation, whereas the initial mechanism in SMS is vasoconstriction caused by exaggerated hypoxic pulmonary vasoreactivity of the small pulmonary arteries, which are excessively muscularized. In short, the basic mechanism is respiratory in CMS, but it is vascular in SMS54,80 (Figure 8).

HAHD of Adult Type
Four decades ago Chinese investigators described the adult variety of HAHD. This is a chronic disease of maladaptation to altitude that occurs in lowlanders who have migrated to HA for prolonged residence. Adult HAHD has a lower prevalence than CMS and is characterized by clinical evidence of PH, RVH, and HF in absence of significant
hypoxemia and polycythemia.\textsuperscript{81,82} However, most Chinese publications on adult HAHD describe cases with polycythemia of variable degree, which include the last original article published in 1990.\textsuperscript{83} Moreover, Wu et al have recognized that publications on adult HAHD, most of them from their own group, actually correspond to CMS.\textsuperscript{85} In addition, the clinical evidences of PH obtained by ECG, vectorcardiographic, and chest x-ray in patients with adult HAHD are no different from those found in patients with CMS.

Chinese investigators mention that there are no reliable measurements of PAP via cardiac catheterization in adult HAHD. There are only 2 reports of PAP obtained by Doppler echocardiography after 1 week of residence at the lower altitude of Xining (2261 m), and the calculated PPA values were 36/11006 and 28/11006 mm Hg,\textsuperscript{83,84} values lower than most of those reported in CMS (Table 7).

**HA Cor Pulmonale**

Kyrgyz investigators do not have publications with the name of CMS. Five decades ago they described a clinical picture named HA PH, which may evolve to HA cor pulmonale (HACP) and HF. This clinical entity is observed in people who live at the HA of the Tien-Shan and Pamir Mountains (2800 to 4200 m), and its prevalence is 4.6% in the male population.\textsuperscript{63,73,86} HACP is characterized by a variable degree of PH, RVH, and HF in the absence of significant hypoxemia and polycythemia.

The heart auscultation and the findings obtained by the ECG and chest x-ray resemble those found in patients with CMS\textsuperscript{28,85} and adult HAHD.\textsuperscript{52,83} Cardiac catheterization studies have been carried out in several surveys and hundreds of subjects. A PPA value of 32±4 mm Hg (range 20 to 64 mm Hg) was reported recently in 11 subjects with clinical evidence of cor pulmonale.\textsuperscript{63} This value is lower than most described in CMS (Table 7). It should be noted, however, that catheterization studies were performed after 1 week of residence at low altitude (Bishkek, 760 m). In brief, the main difference from CMS is the absence of severe hypoxemia and polycythemia, which may in part be ascribed to the low altitude where the patients were studied.

**Comparison of Pulmonary Hemodynamics in Chronic HA Diseases**

Currently there is no available information that indicates significant differences of pulmonary hemodynamics among CMS, HAHD, and HACP. Most publications describe moderate degrees of PH in these entities. Severe degrees of PH (Ppa≥40 mm Hg) have only been reported in CMS, however (Table 7). In addition, there are no significant clinical differences in the magnitude of PH as assessed by ECG, vectorcardiography, and chest x-ray. It appears that CMS, HAHD, and HACP are basically the same entity with some different shades. Consequently, some amendments in the consensus statement on chronic HA diseases\textsuperscript{57} would be timely, and a reappraisal of this document has recently been proposed.\textsuperscript{87}
Prevention and Treatment of CMS

CMS is a public health problem in the Andean populations as well as in other mountainous regions of the world. Therefore, government authorities, medical institutions, health care providers, and private organizations should be involved in the dissemination of preventive measures directed toward modifiable risk factors such as smoking, obesity, domestic and industrial air pollution, and lung diseases.57

The traditional and definitive treatment of CMS is a descent to lower altitudes or SL. After this, a prompt improvement of the subjective symptoms and sleep disorders is observed. Alveolar hypoxia, hypoxemia, and cyanosis disappear. Polycythemia decreases, and after a few weeks or months Hb and hematocrit return to SL values. PH and RVH gradually reverse and disappear after 1 or 2 years.28,54

Bloodletting alone or isovolemic hemodilution are palliative procedures to reduce the exaggerated polycythemia with partial improvement of signs and symptoms.85,89 Other procedures are directed to improve ventilation with respiratory stimulant drugs such as medroxyprogesterone and acetazolamide, with consequent reduction of hematocrit and improvement of symptomatology.66,90

Vasodilators are being tested to reduce high-altitude PH. Calcium-channel blockers such as nifedipine, already used for treatment and prevention of high-altitude pulmonary edema, have also been tested on CMS, which resulted in transient and partial reduction of PH.91 Selective pulmonary vasodilators, currently used for idiopathic pulmonary arterial hypertension, are being tested for long-term treatment of high-altitude PH. Sildenafil, a phosphodiesterase-5 inhibitor, has been tested in symptomatic highlanders with PH, and after several months improvement in pulmonary hemodynamics and exercise tolerance was observed.92 Prostacyclin analogues and endothelin inhibitors, already used in idiopathic pulmonary arterial hypertension, may be future options for therapy of CMS. Inhaled nitric oxide, useful in high-altitude pulmonary edema, may be an option for transient relief of an acute hypoxic emergency in patients with CMS.

Conclusions

Pioneering studies by Peruvian investigators contributed to elucidation of the pathogenesis of high-altitude PH and RVH in healthy people born and living at HA. Delayed postnatal remodeling of the distal pulmonary arterial branches is the main factor responsible for the peculiar cardiopulmonary condition of healthy highlanders. There is a direct relation of the altitude level to the magnitude of PAP. However, the level of altitude itself and the degree of hypoxia are not the only determining factors of the PAP level. There is evidence that the number of generations living at HA is a contributing determinant of the magnitude of PAP elevation. This factor explains higher PAP in a relatively new HA population of Leadville, Colo, in contrast with normal PAP in Tibetan natives who have the oldest altitude ancestry in the world.

CMS is the consequence of the loss of the capacity for altitude adaptation. Hypoventilation induces severe hypoxemia, exaggerated polycythemia, and moderate to severe PH. Peruvian investigators pioneered studies on pulmonary hemodynamics in CMS. The clinical picture of CMS resembles complex syndromes that result from other varieties of chronic alveolar hypoventilation. CMS also resembles other HA-related diseases such as adult HAHD described in China and HACP described in Kyrgyzstan. PH is a common denominator of these chronic altitude diseases, whereas hypoxemia and polycythemia are more significant in CMS. CMS differs from SMS, a distinct clinical entity characterized by severe PH and HF as a consequence of excessive amount of SMC in the distal pulmonary arterial branches and exaggerated hypoxic vasoreactivity. CMS is a public health problem in the Andean mountains and other mountainous regions around the world. Therefore, dissemination of preventive and therapeutic measures is essential.

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Disclosures

None.

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