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CONCEPTS

Current concept of chronic mountain sickness: pulmonary hypertension–related high-altitude heart disease

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High-altitude heart disease, a form of chronic mountain sickness, has been well established in both Tibet and Qinghai provinces of China, although little is known regarding this syndrome in other countries, particularly in the West. This review presents a general overview of high-altitude heart disease in China and briefly summarizes the existing data with regard to the prevalence, clinical features, and pathophysiology of the illness. The definition of high-altitude heart disease is right ventricular enlargement that develops primarily (by high-altitude exposure) to pulmonary hypertension without excessive polycythemia. The prevalence is higher in children than adults and in men than women, but is lower in both sexes of Tibetan high-altitude residents compared with acclimatized newcomers, such as Han Chinese. Clinical symptoms consist of headache, dyspnea, cough, irritability, and sleeplessness. Physical findings include a marked cyanosis, rapid heart and respiratory rates, edema of the face, liver enlargement, and rales. Most patients have complete recovery on descent to a lower altitude, but symptoms recur with a return to high altitude. Right ventricular enlargement, pulmonary hypertension, and remodeling of pulmonary arterioles are hallmarks of high-altitude heart disease. It is hoped that this information will assist in understanding this type of chronic mountain sickness, facilitate international exchange of data, and stimulate further research into this poorly understood condition.

Key words: altitude, hypoxemia, heart failure, pulmonary hypertension, vascular remodeling

Introduction

Although Carlos Monge in Peru first described chronic mountain sickness (CMS) in 1928, there is no international consensus on its definition and diagnostic criteria. Therefore, its terminology and classification remain somewhat confusing. The International Consensus Group on CMS developed the following definition of CMS in 1998 in Japan[1]: Chronic Mountain Sickness is a syndrome which occurs in persons long residing at high altitude and which is characterized by excessive erythrocytosis and hypoxemia and by reversibility on descent. It may be classified as primary (without identified cause) or secondary (due to underlying conditions).

The new definition emphasizes that CMS is characterized by ''excessive erythrocytosis and hypoxemia,'' and it excludes pulmonary hypertension with and without right heart failure. However, our clinical observations in the Qinghai-Tibet Plateau showed that the most striking features in patients with CMS are severe hypoxemia, excessive polycythemia, and marked pulmonary hypertension.[2] Based on our findings in China, CMS can be defined as a clinical syndrome of maladaptation to life at high altitude, with the primary cause of the syndrome being high-altitude hypoxia, in the absence of any evidence of lung or cardiovascular disease. In clinical practice, CMS in China can be classified as 1) high-altitude polycythemia, 2) high-altitude heart disease (HAHD) without excessive polycythemia, and 3) mixed chronic mountain sickness, which includes both excessive polycythemia and pulmonary hypertension–related HAHD.[3,4] In this article, earlier and recent publications referring to HAHD in China will be reviewed, and the concept of HAHD will be introduced.

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Prevalence of high-altitude heart disease in Hans and Tibetans at various altitudes*

	Han		*Tibetan*	
Altitude	*Children*	*Adults*	*Children*	*Adults*
<3000 m	0.47	0.07	0.2	0
3000–4000 m	1.47	0.71	0.39	0.24
4000–5000 m	3.64	1.72	1.04	0.46

*Data from Wu and Ge.[6] Values are presented as percentages.

Epidemiology and prevalence

High-altitude heart disease occurs in lowlanders who reside at altitudes above 3000 m and whose clinical signs and symptoms of the disease disappear on descent to lower altitude. The first description of HAHD in China was made by Wu and Liu[5] in 1955 in Si Chuan Province. Since then, HAHD has been widely investigated, and it is now well accepted as a clinical form of CMS. It is estimated that more than 2000 cases of HAHD have been reported from Tibet, Qinghai, Xin Jiang, and Si Chuan provinces. These studies have been published in Chinese national and provincial medical journals, which are not generally known outside China, particularly in the Western countries.

Wu and Ge[6] reported from Qinghai Province that the prevalence of HAHD is higher in children than in adults, rises with increasing altitude particularly in children, but is lower both in children of Tibetan natives and in adult Tibetan natives (Table). Chen[7] reported data for 300 adults with HAHD (289 men and 11 women) in Tibet. In all cases, the patients had evidence of severe pulmonary hypertension, enlargement of right or both ventricles as shown by electrocardiography (ECG) and chest radiographic examination. Additionally, 500 cases (480 male and 20 female) were reported from Qinghai Province by Li et al.[8] Of these, 283 patients (47.6%) developed right heart failure. Echocardiography in these patients indicated a marked rise in right ventricular outflow and an increase in right ventricular internal diameter. Furthermore, pulmonary hypertension was found in most of the cases.

Diagnosis

Right ventricular enlargement and pulmonary hypertension are hallmarks of HAHD. Therefore, the diagnosis is based not only on clinical symptoms, routine physical examination, and chest radiographs, but also on ECG and Doppler-echo examination and/or cardiac catheterization. In China, the following criteria have been applied to the diagnosis of HAHD: 1) characteristic symptoms and signs, such as dyspnea, cyanosis, peripheral edema, pulmonic systolic murmur, and loud pulmonic second sound; 2) normal or slightly higher levels of hemoglobin and hematocrit (but no more than 20 g/dL of hemoglobin and 65% hematocrit); 3) normal spirometry, including vital capacity, forced vital capacity, and forced expiratory volume in 1 second, compared with healthy high-altitude individuals, except in cases of smokers, who often have a small decrease in the mean forced expiratory flow during half of the forced vital capacity (forced expiratory flow, midexpiratory phase); 4) pulmonary hypertension (mean pulmonary arterial pressure >24 mm Hg) and right ventricular hypertrophy or dilation; 5) exclusion of other cardiovascular and respiratory disorders, such as cor pulmonale and primary pulmonary hypertension; and 6) disappearance of the symptoms and signs on descent to lower altitude.

These criteria make diagnosis of HAHD fairly easy in China, but in the West, there is no accepted definition of HAHD, which commonly leads to confusion in diagnosis. For instance, preexisting lung disease, which may produce right ventricular failure that mimics HAHD at high altitude, is not excluded in some countries. Thus, HAHD, as a unique entity related to high-altitude exposure, must be differentiated from cor pulmonale with right ventricular failure, which is primarily caused by chronic airway disease, pulmonary vascular abnormality, pulmonary fibrosis, and kyphoscoliosis. It also should be emphasized that HAHD must be differentiated from physiological changes in the pulmonary circulation at high altitudes. Mild pulmonary hypertension and right ventricular hypertrophy, being a compensatory mechanism for acclimatization, are common findings in people residing at high altitudes, particularly newcomers. Halperin et al[9] reported in Lhasa, Tibet (3658 m), that right ventricular hypertrophy by ECG examination was found in 17% of healthy Tibetan natives and 29% of healthy Han immigrants. These features, however, were not associated with any symptoms, and the subjects were capable of efficiently performing heavy exercise and did not have HAHD.

Pathophysiology

An enlarged heart, right ventricular hypertrophy, and right heart failure due to severe pulmonary hypertension are the major characteristics of HAHD. Miao[10] described 6 patients with HAHD from Qinghai Province, and all patients had severe pulmonary hypertension with the mean pulmonary arterial pressure of 35 mm Hg. Also, echocardiography studies in patients with this syndrome indicated a marked rise in the right ventricular outflow

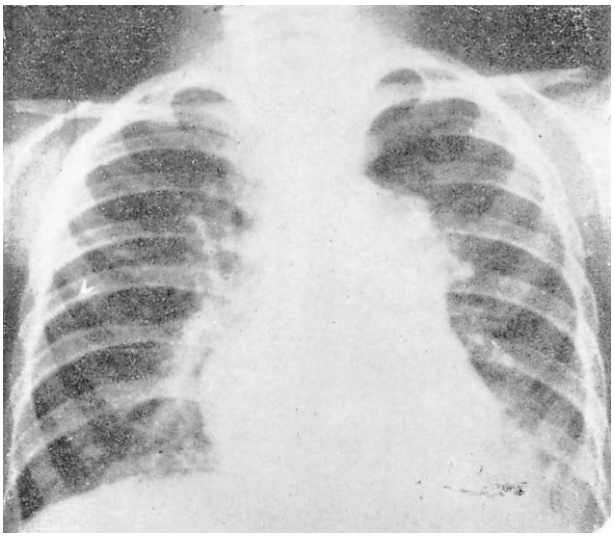

Figure 1. Chest radiograph of a 4-year-old Han boy with high-altitude heart disease. He was born at 3400 m. There is marked prominence of central pulmonary artery branches and enlargement of the right atrium and right ventricle. Data from Lin et al.[14]

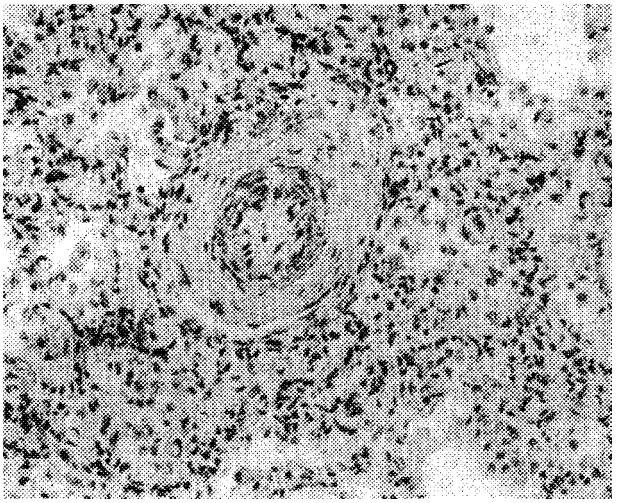

Figure 2. Lung tissue of a 4-month-old boy who died of high-altitude heart disease. There is marked medial hypertrophy of the small pulmonary artery. Data from Li and Sui.[11]

and an increase in the internal diameter of the right ventricle, which was compatible with pulmonary hypertension. Chest radiography revealed bilateral pulmonary infiltrates, a prominent pulmonary artery, and a rounded cardiac apex compatible with right ventricular hypertrophy (Figure 1).

Autopsy studies of 20 adults and 100 infants who died of HAHD were reported from Tibet by Li and Sui.[11] Major findings from the autopsies included a dilated pulmonary artery trunk, atheromas and thrombosis of the pulmonary artery, and hypertrophy and dilation of the right ventricle and right atrium. Hypertrophy of both ventricles was also found in some cases. The ratio of right to left ventricular weight was significantly greater than in the normal age-matched controls, and in some cases the weight of the right ventricle exceeded that of the left ventricle. The most significant finding from histologic examination of the lung was that the small pulmonary arteries had severe medial hypertrophy with crenation of the elastic laminae. The vessel walls were extremely thick (Figure 2), with thick smooth muscle sandwiched between inner and outer elastic laminae. The key factors in the pathogenesis of the syndrome are severe pulmonary hypertension and structural remodeling of the small pulmonary arteries. Myocardial dysfunction and ventilatory abnormalities with a blunted ventilatory response to hypoxia also contribute to development of this syndrome.

Confused terminology

The literature contains various names of subsets of pulmonary hypertension–related syndromes, such as infantile subacute mountain sickness, adult subacute mountain sickness, high-altitude pulmonary hypertension, and chronic cor pulmonale. It may be that HAHD is most similar to subacute mountain sickness, which was described by Anand and his associates in 1991.[12] According to their published data, the syndrome can occur both in infants and adults, and is called subacute infantile or adult mountain sickness, respectively. Subacute mountain sickness is characterized by congestive heart failure due to severe pulmonary hypertension. Histologic changes in this syndrome were marked medial hypertrophy of the pulmonary artery, significant muscularization with reduplication of the elastic lamina in the pulmonary arterioles, and development of a thick muscular media. Also, it is probably similar to chronic cor pulmonale, which was described by Penaloza and Sime[13] 30 years ago in Peru. They performed pulmonary hemodynamic, ECG, and chest radiographic studies in 10 patients with cor pulmonale (or CMS) and compared the results with those of 12 healthy high-altitude residents. Pulmonary artery mean pressure was significantly increased in all patients, with a mean value of 47 $\pm$ 18 mm Hg. One case had a mean pressure of 85 mm Hg. Both ECG and chest radiographic examinations revealed changes compatible with right ventricular and right atrial enlargement.

Obviously, the common feature of HAHD or subacute mountain sickness or cor pulmonale is a cardiovascular disorder, particularly the right side of the heart, such as

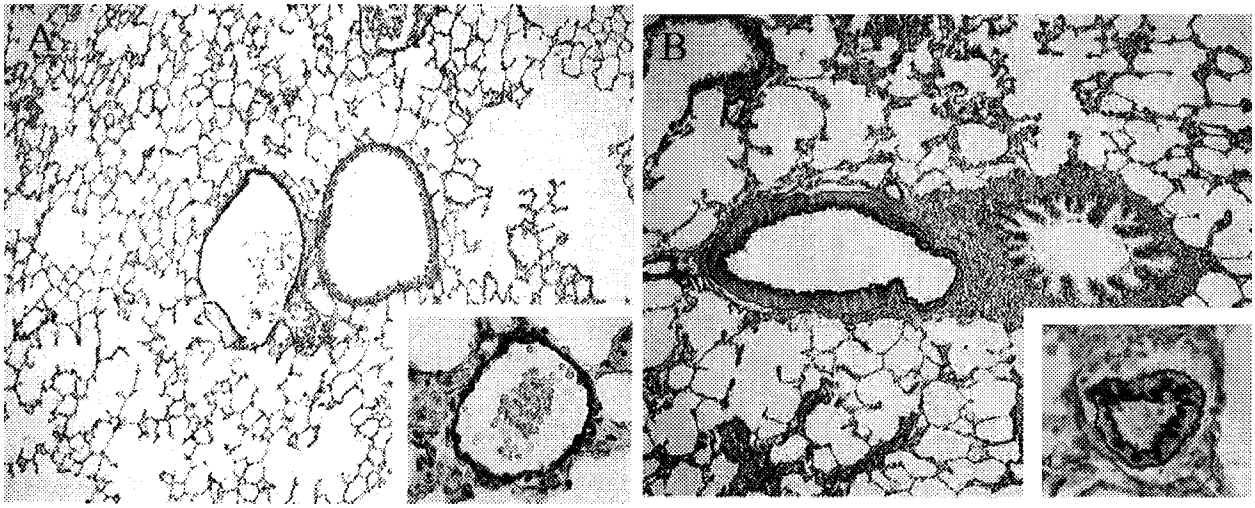

Figure 3. Lung tissues of pika (A) and rat (B) kept at altitude. In pika, there is a very thin-walled pulmonary arteriole with a wall consisting of a single elastic lamina, while in the rat there is a thick muscular wall composed of thick smooth muscle sandwiched between inner and outer elastic lamina. Data from Ge et al.[21]

right ventricular hypertrophy due to hypoxic pulmonary vasoconstriction that is manifested by pulmonary hypertension and congestive heart failure. The clinical features, laboratory findings, and pathologic changes in the 3 syndromes are quite similar, the only difference being in names applied.

Genetic influence

Interestingly, HAHD may have a familial (genetically based) inheritance. Lin et al[14] described 13 first-degree relatives of patients with HAHD (6 infants, 4 adolescents, and 3 adults) in 3 families living at altitudes between 3200 and 3500 m in Qinghai. In 1 family HAHD developed in siblings and offspring, and in 2 other families HAHD affected siblings. Three of the 6 infants died of heart failure at 3500 m, and others recovered after descent to lower altitudes. These findings suggest that HAHD demonstrates familial inheritance. In addition, the evidence from previous studies shows that Tibetan natives, despite living at very high altitudes, have a very low prevalence of HAHD when compared with Han Chinese who immigrate to high altitude. Also, the prevalence of excessive polycythemia in Tibetan natives is much lower than in the Anean Indians.[15] These conditions may be associated with their remarkable physiological feature of adaptation to high altitude. For instance, Tibetan natives, compared to Han Chinese or South American high-altitude natives, have a remarkable lack of muscularization of pulmonary arteries, low hypoxic pulmonary vasoconstrictive response, and a lower hemoglobin concentration.[16–18] This suggests that Tibetans' protection from high-altitude-related illnesses might be due to genetic factors involved. Animal studies also show that indigenous high-altitude species, such as yaks, snow pigs, and llamas, show no changes in their heart or pulmonary vessels in response to the hypobaric hypoxia at high altitude.[19,20] Previously, we compared the pulmonary hemodynamics, morphology, and hematology of pikas, a small rodent that has lived at very high altitude for many thousands of years, with Wistar rats, which have lived at high altitude for 3 generations after immigrating from sea level.[21] The study found that the pikas, compared to the rats, have a blunted pulmonary vasoconstrictive response to acute hypoxia, an extremely thin pulmonary vascular medial layer (Figure 3), no right ventricular hypertrophy, and lower concentration of hemoglobin and 2,3-diphosphoglycerate. We think that these conditions may be genetically determined.

Conclusion and prospect

Since Wu first described HAHD in 1955, it has, as a clinical form of CMS, been well recognized in China. There is, however, no accepted definition of HAHD in the West. Prevalence is progressively growing with the increase in population size at high altitude. Right ventricular enlargement, pulmonary hypertension, and structural remodeling of the small pulmonary arteries are hallmarks for developing HAHD. Millions of people permanently live in the Qinghai-Tibet Plateau, and hundreds of thousands annually go to the western territories of China, such as Tibet, Qinghai, Xin Jiang, and Si

Chuan provinces, to exploit economic resources of the remote mountain areas. Therefore, altitude-related illnesses such as HAHD are a common problem in China. We, the health care providers and medical scientists, are confronted with questions of prevention and treatment of mountain sickness. In order to help improve clinical care, to further understanding of the pathogenesis, and to facilitate international exchange of data, we must standardize the various confused terminology and establish international diagnostic criteria. Therefore, we would suggest that the International Consensus Group on CMS should consider pulmonary hypertension–related HAHD as a clinical form of CMS and include it in the CMS definition.

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