Progress in Cardiovascular Diseases 52 (2010) 540–549
www.onlinepcd.com

Chronic Mountain Sickness and the Heart

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Abstract Chronic Mountain Sickness (CMS) is an important high-altitude (HA) pathology in most mountainous regions of the world. Although its most characteristic sign is excessive erytrocytosis (EE), in the more severe stages of the disease, high-altitude pulmonary hypertension (HAPH), with remodeling of pulmonary arterioles and right ventricular enlargement is commonly found. The degree of ventricular hypertrophy depends on the vasoconstrictor pulmonary response, the intensity of vascular resistance and the level of altitude, and therefore on the degree of hypoxemia. This chapter briefly summarizes the existing data regarding the clinical and pathophysiological features of the cardiopulmonary system in CMS, with emphasis in findings from research in the Andes. The literature shows variability in cardiac output values in CMS, which might be related to the degree of EE. Recent findings have shown that cardiac output (l/min) is lower in CMS when compared with sea-level (SL) dwellers. Mean pulmonary acceleration time (ms) is significantly lower in CMS subjects than in SL and HA natives, and pulmonary vascular resistance index (Wood units) is higher in CMS and HA natives when compared with SL dwellers. Systemic blood pressure has similar values in CMS patients and healthy HA natives, but some differences arise in its control mechanisms. Although CMS individuals have a less effective vasoconstrictor reflex, their tolerance to orthostatic stress is similar to that of healthy HA natives which might be explained in terms of the larger blood volume present in CMS subjects. At present research is directed to design strategies on pharmacological intervention for CMS treatment. Recently, a clinical trial with acetazolamide, in patients with CMS has proven to be effective in increasing mean pulmonary acceleration time and decreasing pulmonary vascular resistance index, which might be indirectly due the reduction of hematocrit (Prog Cardiovasc Dis 2010;52:540-549)

Keywords: Chronic mountain sickness; Monge's disease; Heart; High-altitude pulmonary hypertension; High altitude

The low barometric pressure encountered at high-altitude (HA) environments results in low O_2 partial pressure (P_{O_2}) of the inspired air. This condition of hypobaric hypoxia results in decreased blood P_{O_2} or hypoxemia. The organism responds to this situation and attempts to keep a normal cellular oxygenation by modifying the behavior of the respiratory, cardiovascular, renal, and neuroendocrine systems. These physiologic responses are directed to normalize and maintain cellular oxygenation. Among them, the increase in hematocrit and hemoglobin concentration ([Hb]), and the elevation of pulmonary artery pressure (Ppa) represent key features in the response to HA chronic hypoxia[1-4] and are mainly directed toward increasing blood O_2-carrying capacity and redistributing blood toward better ventilated lung areas, respectively. An excessive increase in [Hb] and/or in Ppa, however, is associated with latent lethal illnesses such as chronic mountain sickness or Monge's disease (CMS) and high-altitude pulmonary hypertension (HAPH).[5-10] The magnitude of the erythropoietic and Ppa responses, however, varies between the different HA populations. The increase in [Hb], for example, is particularly

Statement of Conflict of Interest: see page 547.

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doi:10.1016/j.pcad.2010.02.012

Abbreviations and Acronyms

AHVR = acute hypoxic ventilatory response

CMS = chronic mountain sickness

Epo = erythropoietin

HA = high-altitude

HAPH = high-altitude pulmonary hypertension

[Hb] = hemoglobin concentration

HVR = hypoxic ventilatory response

Ppa = pulmonary artery pressure

PVR = pulmonary vascular resistance

Sao_2 = arterial blood oxygen saturation

SL = sea-level

pronounced in Andean HA dwellers[11] when compared with Tibetans and Ethiopians and even more so in those who have CMS.

Chronic mountain sickness affects people who are native or long-time residents of HA locations and usually begins insidiously in adult life; the clinical picture disappears when the patient moves to lower altitudes. Chronic mountain sickness is characterized by severe hypoxemia, excessive erythrocytosis for the altitude of residence, and various symptoms including, sleep disorders, headache, dizziness, tinnitus, paresthesias, mental and physical fatigue, and cognitive impairment.[6,12] Cyanosis is particularly visible in 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. Ultimately, CMS leads to severe HAPH and could lead to heart failure,[9] although, to date, no extensive epidemiologic study has been performed to evaluate the long-term deleterious effects of CMS. Many of the symptoms of CMS are thought to be caused by cerebral hypoxia,[13,14] and this may be exacerbated by the low cerebral blood flow caused by the high viscosity of the blood.[15]

Carlos Monge-M was the first to describe a patient with CMS and presented the case at the Academy of Medicine of Lima in 1925.[7] The patient was a native of the mining town of Cerro de Pasco located at 4300 m in the Peruvian Andes, but he was not a miner; this patient was 38 age old and showed a mean [Hb] of 21.1 g/dL Monge-M ends his presentation to the Academy, calling the attention of the Peruvian medical community and authorities, "on the need to devote their medical efforts to understand the polycythemic syndromes, in order to be able to evaluate the magnitude of impairment that these pathologies could cause to the inhabitants of the Andes." Three years later, Monge-M published an extensive article[16] on cases of CMS from Cerro de Pasco (4300 m) and Puno (3800 m), an agricultural town. Monge-M considered CMS to be a "loss of acclimatization" because it developed only after prolonged exposure to altitude in previously well-acclimatized subjects.

Historical terms used in different mountainous regions for this HA disease, which has excessive elevation of [Hb] as a common characteristic, have been: HA excessive polycythemia or erythrocytosis, excessive erythrocytosis, and HA pathologic erythrocytosis. A number of factors are known to influence the development of CMS, among them: altitude, age, sex, sleep disorders, and genetic susceptibility.[17-19]

Respiratory aspects of CMS

The primary finding in patients with CMS is excessive erythrocytosis. This excessive increase in the number of red blood cells is caused by hypoxemia, which develops mainly because differences in the respiratory pattern of CMS individuals. Compared with healthy HA natives at the same altitude, patients with CMS are relatively hypoxic and hypercapnic.[20,21] Alveolar hypoventilation is the main respiratory feature, but also, ventilation-perfusion mismatch, and widened alveolar-arterial P_{O_2} gradient has been described in subjects with CMS.[19]

Implication of the peripheral chemoreceptors as the cause of hypoxemia in CMS

The main peripheral chemoreceptors in mammals are located in the carotid bodies in the bifurcation of the carotid arteries. These small structures are heavily vascularized and have an elevated blood flow for their size. Carotid chemoreceptors stimulate ventilation in response to hypoxia. Nevertheless, in cases of prolonged residence at high altitude, this ventilatory response to hypoxia appears attenuated ("blunted") in humans and in some animals.

Chronic mountain sickness has been associated with poor hypoxic ventilatory responses (HVRs),[21,22] but there is no proof that changes in carotid body structure or function are the cause of hypoventilation in CMS.[20] To better understand the peripheral chemoreceptor function in hypoxia, short-term and sustained protocols of exposure to hypoxia have been used. An acute HVR (AHVR) protocol evaluates the immediate response to a stepwise induction of hypoxia for few minutes (6-7 minutes). A sustained protocol (15-20 minutes of hypoxia) determines the hypoxic ventilatory decline, which is the attenuation of the initial ventilatory response after the first few minutes of hypoxia. Acute HVR reflects peripheral control of breathing, whereas the hypoxic ventilatory decline may reflect attenuation of the ventilatory response by central control mechanisms although there is some debate on this point.[23]

When HA natives and individuals with CMS are exposed to acute hypoxia, from an initial end-tidal P_{O_2} (P_{ETO_2}) of 100 Torr to a final P_{ETO_2} of 45 or 34 Torr, the average values for the slope of the AHVR for both HA