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RV Contractility and Exercise-Induced Pulmonary Hypertension in Chronic Mountain Sickness

A Stress Echocardiographic and Tissue Doppler Imaging Study

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OBJECTIVES The aim of this study was to evaluate right ventricular (RV) and left ventricular function and pulmonary circulation in chronic mountain sickness (CMS) patients with rest and stress echocardiography compared with healthy high-altitude (HA) dwellers.

BACKGROUND CMS or Monge's disease is defined by excessive erythrocytosis (hemoglobin >21 g/dl in males, 19 g/dl in females) and severe hypoxemia. In some cases, a moderate or severe increase in pulmonary pressure is present, suggesting a similar pathogenesis of pulmonary hypertension.

METHODS In La Paz (Bolivia, 3,600 m sea level), 46 CMS patients and 40 HA dwellers of similar age were evaluated at rest and during semisupine bicycle exercise. Pulmonary artery pressure (PAP), pulmonary vascular resistance, and cardiac function were estimated by Doppler echocardiography.

RESULTS Compared with HA dwellers, CMS patients showed RV dilation at rest (RV mid diameter: 36 ± 5 mm vs. 32 ± 4 mm, CMS vs. HA, $p = 0.001$) and reduced RV fractional area change both at rest (35 ± 9% vs. 43 ± 9%, $p = 0.002$) and during exercise (36 ± 9% vs. 43 ± 8%, CMS vs. HA, $p = 0.005$). The RV systolic longitudinal function (RV-S′) decreased in CMS patients, whereas it increased in the control patients ($p < 0.0001$) at peak stress. The RV end-systolic pressure-area relationship, a load independent surrogate of RV contractility, was similar in CMS patients and HA dwellers with a significant increase in systolic PAP and pulmonary vascular resistance in CMS patients (systolic PAP: 50 ± 12 mm Hg vs. 38 ± 8 mm Hg, CMS vs. HA, $p < 0.0001$; pulmonary vascular resistance: 2.9 ± 1 mm Hg/min/l vs. 2.2 ± 1 mm Hg/min/l, $p = 0.03$). Both groups showed comparable systolic and diastolic left ventricular function both at rest and during stress.

CONCLUSIONS Comparable RV contractile reserve in CMS and HA suggests that the lower resting values of RV function in CMS may represent a physiological adaptation to chronic hypoxic conditions rather than impaired RV function. (Chronic Mountain Sickness, Systemic Vascular Function [CMS]; NCT01182792) (J Am Coll Cardiol Img 2013;6:1287–97) © 2013 by the American College of Cardiology Foundation

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Chronic mountain sickness (CMS), a syndrome that begins insidiously during adult life, is characterized by excessive erythrocytosis, severe hypoxemia, and, in some cases, moderate or severe pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive heart failure. The physiopathological mechanisms of CMS remain unsettled, but chronic alveolar hypoventilation is the likely initial mechanism of a series of events leading to progressive deterioration of adaptation and development of CMS (1). On rest echocardiography, CMS patients show normal left ventricular (LV) function, pulmonary arterial hypertension associated with right heart dilation, and an increased right ventricular (RV) Tei index (2). Mild exercise induces an exaggerated increase in pulmonary pressure, interstitial lung fluid accumulation, and hypoxemia in those with CMS compared with matched healthy high-altitude (HA) dwellers (3,4). The contribution of RV function to overall cardiac performance increases with exercise, which makes the study of RV function during exercise very interesting. However, the marked change in RV load may be a potential confounder of all echocardiographic measurements related to contractility. Therefore, the aim of this study was to evaluate noninvasive pulmonary vascular behavior and LV and RV function at rest and during mild exercise. Several echocardiographic Doppler measurements were used together with a surrogate of contractility as the end-systolic pressure-volume relationship (5,6) in subjects with CMS and in a control group of healthy HA dwellers.

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ABBREVIATIONS AND ACRONYMS

CMS = chronic mountain sickness

e′ = peak early diastolic tissue Doppler imaging velocity of the mitral annulus

E = peak velocity of early mitral inflow

E/e′ = ratio of peak velocity of early mitral inflow to mitral annular early diastolic peak velocity

HA = high altitude

Hb = hemoglobin

LV = left ventricular

PAP = pulmonary arterial pressure

RV = right ventricular

RV-ESPAR = right ventricular end-systolic pressure-area relationship

RV-S′ = tissue Doppler imaging peak systolic velocity of the lateral tricuspid valve annulus

TDI = tissue Doppler imaging

tric e′/a′ = ratio of early (e′) and late (a′) diastolic tissue Doppler imaging tricuspid peak annular velocities

METHODS

Study patients. The population consisted of 46 Bolivian male patients with CMS and 40 healthy male HA dwellers of similar age consecutively enrolled in the study. All study subjects were born and permanently living in or around La Paz, Bolivia (3,600 to 4,000 m sea level). They had typical Aymara surnames, identifying themselves as Aymaras, and had similar socioeconomic backgrounds. All the patients were initially referred to the Instituto Boliviano de Biologia de Altura, and the diagnosis of CMS was based on the consensus statement on chronic HA diseases (7). Inclusion criteria for CMS patients included erythrocytosis (hemoglobin [Hb] value ≥20 mg/dl), normal pulmonary function studies (carbon monoxide diffusion capacity with single-breath technique and lung function), and no history of smoking or of lung injury from occupational exposure. All patients included in the study had Hb value ≥21 mg/dl at the time of CMS diagnosis. At study entry, however, some patients had Hb values below this threshold value because they had been treated with bloodletting. A complete clinical examination was performed on all subjects, and the CMS score was determined on the basis of the following signs and symptoms: breathlessness/palpitations, sleep disturbance, cyanosis, dilation of lower limb veins, paresthesia, headache, and tinnitus. A score between 0 and 3 was attributed, with 0 indicating an absence of CMS, 1 indicating mild, 2 indicating moderate, and 3 indicating severe signs and symptoms of CMS (5). A CMS score >5 is required for diagnosis, and the grading of the severity of CMS is as follows: mild (score of 6 to 10), moderate (score of 11 to 14), or severe (score >15).

Blood pressure and heart rate were measured at rest and at different stages of exercise. Pulse oximetry measurements were carried out at the fingertip after at least 10 min of rest, with warmed hands, and after 30 s of signal stabilization for an average of 3 consecutive measurements (Pulse-oximeter Model Tuff-Sat, Datex-Ohmeda, General Electric Healthcare Clinical System, Finland Oy, Helsinki, Finland). The experimental protocol was approved by the institutional review boards on human investigation of the University of San Andres, La Paz, Bolivia, and the University of Lausanne, Lausanne, Switzerland, and registered (NCT01182792). All studies were performed at the Instituto Boliviano de Biologia de Altura in La Paz, located at an altitude of 3,600 m sea level.

Echocardiographic examination and measurements. Echocardiography was performed using a portable fully equipped echocardiography unit (Vivid I, General Electric Healthcare Clinical System) with a

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