CHEST

Exaggerated Pulmonary Hypertension and Right Ventricular Dysfunction in High-Altitude Dwellers With Patent Foramen Ovale

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BACKGROUND: There is considerable interindividual variability in pulmonary artery pressure among high-altitude (HA) dwellers, but the underlying mechanism is not known. At low altitude, a patent foramen ovale (PFO) is present in about 25% of the general population. Its prevalence is increased in clinical conditions associated with pulmonary hypertension and arterial hypoxemia, and it is thought to aggravate these problems.

METHODS: We searched for a PFO (transesophageal echocardiography) in healthy HA dwellers (n = 22) and patients with chronic mountain sickness (n = 35) at 3,600 m above sea level and studied its effects (transthoracic echocardiography) on right ventricular (RV) function, pulmonary artery pressure, and vascular resistance at rest and during mild exercise (50 W), an intervention designed to further increase pulmonary artery pressure.

RESULTS: The prevalence of PFO (32%) was similar to that reported in low-altitude populations and was not different in participants with and without chronic mountain sickness. Its presence was associated with RV enlargement at rest and an exaggerated increase in right-ventricular-to-right-atrial pressure gradient (25 ± 7 mm Hg vs 15 ± 9 mm Hg, $P < .001$) and a blunted increase in fractional area change of the right ventricle (3% [−1%, 5%] vs 7% [3%, 16%], $P = .008$) during mild exercise.

CONCLUSIONS: These findings show, we believe for the first time, that although the prevalence of PFO is not increased in HA dwellers, its presence appears to facilitate pulmonary vasoconstriction and RV dysfunction during a mild physical effort frequently associated with daily activity.

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ABBREVIATIONS: CMS = chronic mountain sickness; CO = cardiac output; DTI = Doppler tissue imaging; FAC = fractional area change of the right ventricle; HA = high altitude; HAPE = high-altitude pulmonary edema; IQR = interquartile range; LV = left ventricular; LVOT = left ventricular outflow tract; PFO = patent foramen ovale; PVR = pulmonary vascular resistance; RV = right ventricular; RV-ESPAR = right ventricular end-systolic pressure-volume relationship; RV/RA = right ventricular to right atrial; TEE = transesophageal echocardiography; VTI = velocity time integral

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Pulmonary vasoconstriction is a hallmark of the adaptation to high-altitude (HA) hypoxia.[1] In the Andes and other mountain regions of the world, millions of people are chronically exposed to hypoxia.[2] There is considerable interindividual variability in pulmonary artery pressure among HA dwellers, with a substantial proportion displaying pulmonary hypertension.[3] The reason for the variability in the pulmonary artery pressure response in HA dwellers is poorly understood.

Observations in low-altitude residents susceptible to HA pulmonary edema (HAPE), a condition characterized by exaggerated hypoxemia and pulmonary hypertension during acute HA exposure,[4] suggest that a patent foramen ovale (PFO) could represent an underlying mechanism.[5] In a study by Allemann et al,[5] a PFO was found to be more frequent in HAPE-prone participants than in mountaineers resistant to this condition, and spontaneous right-to-left-shunting was found in these subjects at HA. These findings suggest that in HAPE-prone individuals with a PFO, the acute hypoxic pulmonary vasoconstriction initiates a vicious cycle by causing right-to-left shunting across a PFO, which, in turn, aggravates hypoxemia, resulting in reduced mixed venous oxygen tension and greater pulmonary hypertension.[5]

At low altitude, a PFO is present in approximately 25% of the general population, and its prevalence is increased in clinical conditions associated with increased pulmonary artery pressure.[6,7] To our knowledge, there is no information on the prevalence of a PFO in HA dwellers and its potential consequences on pulmonary artery pressure and right ventricular (RV) function. We speculated that in HA dwellers, the presence of a PFO is associated with increased pulmonary artery pressure and/or RV dysfunction. To test this hypothesis, in healthy HA dwellers and in patients with chronic mountain sickness (CMS) living permanently at 3,600 to 4,000 m (a study population expected to encompass a wide range of pulmonary artery pressure), we searched for PFO by transesophageal echocardiography (TEE) and studied its effects on pulmonary artery pressure, pulmonary vascular resistance (PVR), and RV function at rest and during mild exercise, an intervention designed to further increase pulmonary artery pressure and facilitate the detection of RV dysfunction.[8]

Materials and Methods

Study Design and Participants

The study population consisted of 35 male patients with CMS and 22 healthy male HA dwellers living permanently in the city of La Paz or its surroundings (3,600-4,000 m altitude), enrolled consecutively in the study. All participants had typical Aymara surnames and self-identified themselves as Aymaras (the major indigenous population living in this region).

The patients with CMS were recruited at the Instituto Boliviano de Biologia de Altura, where the diagnosis of CMS was established based on the previously published consensus statement criteria of chronic HA diseases.[9] Briefly, patients with CMS were required to have erythrocytosis (hemoglobin value $\geq$ 21 mg/dL at the time of diagnosis), 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. At the time of the study, some patients had hemoglobin values $<$ 21 mg/dL because of bloodletting. Additionally, a CMS score $>$ 5 was required for the diagnosis of CMS according to the consensus statement of chronic HA diseases.[9]

Healthy control subjects born and living permanently in the city of La Paz or its surroundings (3,600-4,000 m altitude) were sought through advertising and were prospectively enrolled in the study. All healthy participants had normal pulmonary function tests and no history of smoking or working in the mining industry, and after a thorough workup did not fulfill the diagnostic criteria for CMS mentioned previously.

The study was conducted in accordance with the amended Declaration of Helsinki. The experimental protocol was approved by the institutional review board on human investigation of the University of San Andres La Paz, Bolivia (CEI UMSA No. 128-2012). All participants provided written informed consent. All studies were performed at the Instituto Boliviano de Biologia de Altura in La Paz (3,600 m).

Doppler Echocardiography

Transthoracic echocardiography and TEE were performed with real-time, phased-array sector scanners (Philips CX50; Koninklijke Philips NV and GE Vivid I; GE Healthcare) with an integrated color Doppler system and a transducer-containing crystal set for imaging (3.5 MHz, 7MHz for the TEE omniplane probe) and for continuous-wave Doppler recording (1.9 MHz). The recordings were stored on videotape for offline analysis by two investigators who were unaware of the participants' clinical history.

Transesophageal Echocardiography

TEE was performed under mild sedation (IV midazolam, 1-4 mg according to the clinical response) following pharyngeal local anesthesia with lidocaine 10% spray. TEE, in combination with an injection of 2 mL of echo contrast medium (ad hoc sonicated mixture of 0.2 mL air plus 1.8 mL plasma expander [Physiogel; Pharmacy of the University Hospital, Inselspital]) into the right antecubital vein and the Valsalva maneuver, were used for the search for a PFO in at least two orthogonal image planes.[10,11] The contrast bolus injection was given at the start of the strain phase of the Valsalva maneuver. The maneuver was considered successful when immediately after the release of the strain phase (lasting 5-10 s), a leftward deviation of the interatrial septum in the fossa ovalis region was observed (related to the short right atrial preload and pressure increase). The diagnosis of a PFO required the crossing of bubbles from the right to the left atrium within four heart beats following the release of the strain. The size of the PFO was graded semiquantitatively according to the maximal number of bubbles crossing into the left atrium, using a scoring system of 0 to III: grade I, less than six bubbles; grade II, six to 20 bubbles; grade III, $>$ 20 bubbles.[12,13] We did not encounter any complications in performing TEE.

Transthoracic Echocardiography

Left ventricular (LV) end-systolic and end-diastolic volumes were measured, and the ejection fraction was calculated using the modified