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

*Roman Brenner, MD; Lorenza Pratali, MD; Stefano F. Rimoldi, MD; Carla Ximena Murillo Jauregui, MD; Rodrigo Soria, MD; Emrush Rexhaj, MD; Carlos Salinas Salmón, MD; Mercedes Villena, MD; Catherine Romero, BS; Claudio Sartori, MD; Yves Allemann, MD; and Urs Scherrer, MD*

**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

**AFFILIATIONS:** From the Department of Cardiology and Clinical Research (Drs Brenner, Rimoldi, Soria, Rexhaj, and Allemann and Prof Scherrer), University Hospital Bern, Bern, Switzerland; the Institute of Clinical Physiology (Dr Pratali), Pisa, Italy; Instituto Boliviano de Biologia de Altura (Drs Murillo Jauregui, Salinas Salmón, and Villena and Ms Romero), La Paz, Bolivia; the Department of Internal Medicine (Dr Sartori), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; and Facultad de Ciencias (Prof Scherrer), Departamento de Biología, Universidad de Tarapacá, Arica, Chile.

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**CORRESPONDENCE TO:** Urs Scherrer, MD, Cardiology, University Hospital Bern, 3011 Bern, Switzerland; e-mail: urs.scherrer2@insel.ch



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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

biplane Simpson method. Using the pulsed-wave Doppler technique from the apical four-chamber view, the inflow over the mitral valve (early diastolic E and late diastolic A velocities) was obtained, with the sample volume placed at the level of the tips of the opened mitral leaflets. Doppler tissue imaging (DTI) was performed in a pulsed-wave Doppler mode. Gain and filters were adjusted as needed to eliminate background noise and to allow for a clear tissue signal and were recorded at a sweep speed of 100 mm/s. From the apical four-chamber view, a 5-mm sample volume was placed at the lateral and septal borders of the mitral annulus, and the peak early diastolic tissue velocities (DTI E) at the lateral and septal borders of the mitral annulus were measured. The ratio of the early diastolic inflow E and the mean values of the lateral and septal DTI E have the best correlations with LV filling pressures and invasive indexes of LV stiffness in subjects with a normal LV ejection fraction[14] and were therefore used for the estimation of LV filling pressure.

The LV outflow tract (LVOT) diameter was measured in the parasternal long-axis view, and its cross-sectional area was calculated assuming circular geometry. The stroke volume was calculated by multiplying the LVOT velocity time integral (VTI) by the LVOT cross-sectional area: stroke volume = $VTI_{LVOT} \times \pi \times D^2/4$. Cardiac output (CO) was then obtained by multiplying the stroke volume by the heart rate, and the cardiac index was calculated by dividing the CO by the body surface area.

The right ventricular to right atrial (RV/RA) pressure gradient as a surrogate of the estimated systolic pulmonary artery pressure was estimated by transthoracic echocardiography, as described previously.[15] After tricuspid regurgitation had been localized with Doppler color flow imaging, the peak flow tricuspid regurgitation velocity was measured using continuous-wave Doppler, and the pressure gradient between the right ventricle and the right atrium was calculated using the modified Bernoulli equation: RV/RA = 4 × (tricuspid regurgitation velocity).[2,7] All reported values represent the mean of at least three measurements. To obtain echocardiographic estimation of PVR, we used the formula proposed by Lindqvist et al[16]: PVR = (pulmonary artery mean pressure) − (pulmonary capillary wedge pressure)/CO, whereby (pulmonary artery mean pressure) = (RV/RA + 7) × 0.61 + 2 mm Hg and pulmonary capillary wedge pressure = 10 mm Hg.

All measurements were performed following the recommendations of the European Association of Echocardiography and the American Society of Echocardiography.[17,18] RV basal, midcavity dimension, RV end-diastolic area, and RV end-systolic area were obtained on an apical RV focused view. Furthermore, the subannular RV/LV ratio was calculated in the apical four-chamber view as described previously.[19] The RV function was evaluated by the percentage of RV fractional area change (FAC), defined as (RV end-diastolic area − RV end-systolic area)/RV end-diastolic area × 100.[18] RV dysfunction was defined as FAC ≤ 35%. The RV systolic function was further assessed by tricuspid annular systolic velocity. DTI velocities were obtained 1 cm more apically than were the tricuspid valve annulus within the RV lateral wall and were adjusted to cover the longitudinal excursion in both systole and diastole; careful attention was given to choosing a high frame rate acquisition and to aligning the ultrasound beam parallel to the moving direction of the RV wall.[18]

In addition, the RV function was assessed by measuring the tricuspid annular plane systolic excursion of the lateral tricuspid annulus in the four-chamber view as described previously.[18] The right ventricular end-systolic pressure-volume relationship (RV-ESPAR) was calculated as described for the left ventricle[20] using the RV end-systolic area as a surrogate of volume.[21] RV-ESPAR, in contrast to other currently used echocardiographic assessments of RV function, has been suggested to represent a load-independent parameter of RV contractility that allows one to overcome the flaws related to this problem.[22] The intraobserver variability and interobserver variability (n = 50) for the RV/RA pressure gradient, RV end-diastolic area, FAC of the right ventricle, and LV VTI were 5.3% and 7.4%, 6.4% and 8.1%, 9.6% and 10.3%, and 2.7% and 4.7%, respectively.

### *Exercise Test*

Graded semi-supine exercise was performed on a bicycle ergometer (Ergoline 900EL; Ergoline Company) with a 30° rotation to the left, starting at an initial workload of 25 W for 3 min, followed by 50 W for another 3 min, as described previously.[23] Pulmonary artery pressure, CO, and LV and RV function were estimated at rest and during mild exercise at 50 W. Transcutaneous arterial oxygen saturation was measured at a fingertip with a pulse oximeter (OxiMax N-595; Nellcor Puritan Bennett Inc). Four participants did not undergo exercise stress testing, and in two participants who underwent stress testing, measurement of the RV/RA pressure gradient at 50 W was not possible because of a poor acoustic window.

### *Statistical Analysis*

Data were analyzed using MedCalc Statistical Software, version 12.7.8 (MedCalc Software bvba). Comparisons of continuous data between the two groups were made with unpaired, two-tailed Student *t* tests and Mann-Whitney tests, as appropriate. For categorical data, the Fisher exact test was used. Correlations of ordinal and skewed distributed continuous data were given with Spearman ρ. The influence of the presence of a PFO on the different outcome variables adjusted for the CMS status and the subject's age was estimated in a multivariable regression model.

Sample size calculation based on previously reported data on pulmonary hemodynamics[22] revealed that, assuming a mean RV/RA pressure gradient difference of 10 mm Hg between the groups with and without a PFO to be clinically relevant, an SD of 10 mm Hg, and a prevalence of the PFO of 25%, 33 participants without and 11 participants with a PFO were required to detect the stated difference with a power of 80% and a type 1 error of 5%. Data are presented as mean ± SD or as median with interquartile range (IQR) as appropriate. A $P$ value < .05 was considered to indicate statistical significance.

## Results

### *Baseline Characteristics*

A PFO was found in 18 of the 57 participants (32%), of whom four had a PFO grade I, four had grade II, and 10 had grade III. Age, proportion of patients with CMS, and other baseline characteristics were similar between participants with and without a PFO (Table 1). A PFO grade I or II was found in four of 35 patients with CMS (11%) and in four of 22 healthy HA dwellers (18%), whereas a PFO grade III was found in six of 35 patients with CMS (17%) and four of 22 healthy subjects (18%) ($P$ = .96).

### *Arterial Oxygen Saturation, Pulmonary Hemodynamic, and RV Variables at Rest*

The resting RV/RA pressure gradient and PVR were similar in HA dwellers with and without a PFO (Table 2). In contrast, RV diameter, systolic and diastolic area, and RV/LV ratio were greater in participants with a PFO compared with participants without a PFO. RV-ESPAR, a load-independent proxy of RV function, was significantly

**TABLE 1** ] Baseline Characteristics at Rest According to the Presence/Absence of a PFO

| Characteristic | PFO (n = 18) | No PFO (n = 39) | *P* Value |
|---|---|---|---|
| Age, y | 54.2 (10.3) | 49.6 (10.7) | .14 |
| No. patients with CMS, No. (%) | 10 (56) | 25 (64) | .75 |
| Height, cm | 164 (7) | 165 (5) | .48 |
| Weight, kg | 78.7 (10.4) | 78.5 (13.4) | .96 |
| BMI, kg/m$^2$ | 29.2 (3.6) | 28.6 (4.2) | .62 |
| Hemoglobin, g/dL | 20.5 (2.6) | 20.2 (2.6) | .67 |
| Hematocrit, % | 57.3 (8.4) | 56.5 (9.9) | .82 |
| CMS score | 4.8 (2.6) | 4.5 (3.6) | .81 |
| LVEF, median (IQR), % | 63 (60, 65) | 63 (61, 65) | .66 |
| Stroke volume, mL | 69 (16) | 77 (25) | .21 |
| Cardiac output, mL/min | 4.8 (1.2) | 5.2 (1.7) | .44 |
| E/DTI E | 6.2 (1.5) | 6.8 (1.5) | .27 |
| Systolic BP, mm Hg | 131 (16) | 130 (15) | .82 |
| Diastolic BP, mm Hg | 82 (10) | 81 (9) | .80 |
| Heart rate, beats/min | 70 (12) | 67 (9) | .30 |

Data are given as mean (SD) unless otherwise indicated. CMS = chronic mountain sickness; E/DTI E = ratio of early mitral inflow velocity to average of the septal and lateral mitral annular tissue Doppler velocity; IQR = interquartile range; LVEF = left ventricular ejection fraction; PFO = patent foramen ovale.

lower in HA dwellers with a PFO than in those without this condition. Awake arterial oxygen saturation at rest was comparable in HA dwellers with and without a PFO (88% ± 3% vs 89% ± 2%, $P = .22$). After adjustment for age and CMS status, the differences between the groups with and without a PFO did not change significantly.

### *Arterial Oxygen Saturation, Pulmonary Hemodynamic, and RV Variables During Exercise*

We observed a 66% greater exercise-induced increase of the RV/RA pressure gradient (Fig 1A) in HA dwellers with a PFO than without a PFO, resulting in a roughly 20% higher RV/RA pressure gradient during mild

**TABLE 2** ] Pulmonary and Right Ventricular Hemodynamic Variables Assessed at Rest in High-Altitude Dwellers With/Without a PFO

| Variable | PFO (n = 18) | No PFO (n = 39) | Adjusted Difference[a] (SE) |
|---|---|---|---|
| RV/RA pressure gradient, mm Hg | 24.4 (5.3) | 24.8 (3.6) | −1.2 (1.1) |
| PAMP, mm Hg | 21.7 (2.8) | 21.4 (2.2) | 0.1 (0.6) |
| PVR, Wood units | 2.5 (0.8) | 2.4 (0.8) | 0.0 (0.3) |
| RV basal diameter, mm | 32.2 (3.5)[b] | 27.1 (3.3) | 5.4 (1.1)[b] |
| RV midventricular diameter, mm | 29.8 (2.7)[c] | 26.7 (4.2) | 3.6 (1.2)[c] |
| RV to LV ratio | 0.9 (0.1)[d] | 0.8 (0.1) | 0.06 (0.03)[d] |
| RV EDA, cm$^2$ | 17.5 (2.6)[c] | 14.9 (2.8) | 2.6 (0.9)[c] |
| RV ESA, cm$^2$ | 11.4 (1.6)[b] | 9.3 (1.9) | 2.2 (0.6)[b] |
| FAC, % | 34 (4) | 37 (6) | −3 (2) |
| TASV, cm/s | 10.6 (1.3) | 11.1 (1.5) | −0.1 (0.4) |
| TAPSE, mm | 19.6 (3.2) | 21.0 (3.2) | −1.3 (1.2) |
| RV-ESPAR, mm Hg/cm$^2$ | 2.2 (0.5)[b] | 2.8 (0.8) | −0.9 (0.2)[b] |

Data are presented as mean (SD). EDA = end-diastolic area; ESA = end-systolic area; FAC = fractional area change; LV = left ventricular; PAMP = pulmonary artery mean pressure; PVR = pulmonary vascular resistance; RV = right ventricular; RV-ESPAR = right ventricular end-systolic pressure to area ratio; RV/RA = right ventricular to right atrial; TAPSE = tricuspid annular plane systolic excursion; TASV = tricuspid annular systolic velocity. See Table 1 for expansion of other abbreviations.

[a]Difference adjusted for participant's age and CMS status.

[b]$P < .001$.

[c]*P* value between .001 and .01.

[d]*P* value between .01 and .05.

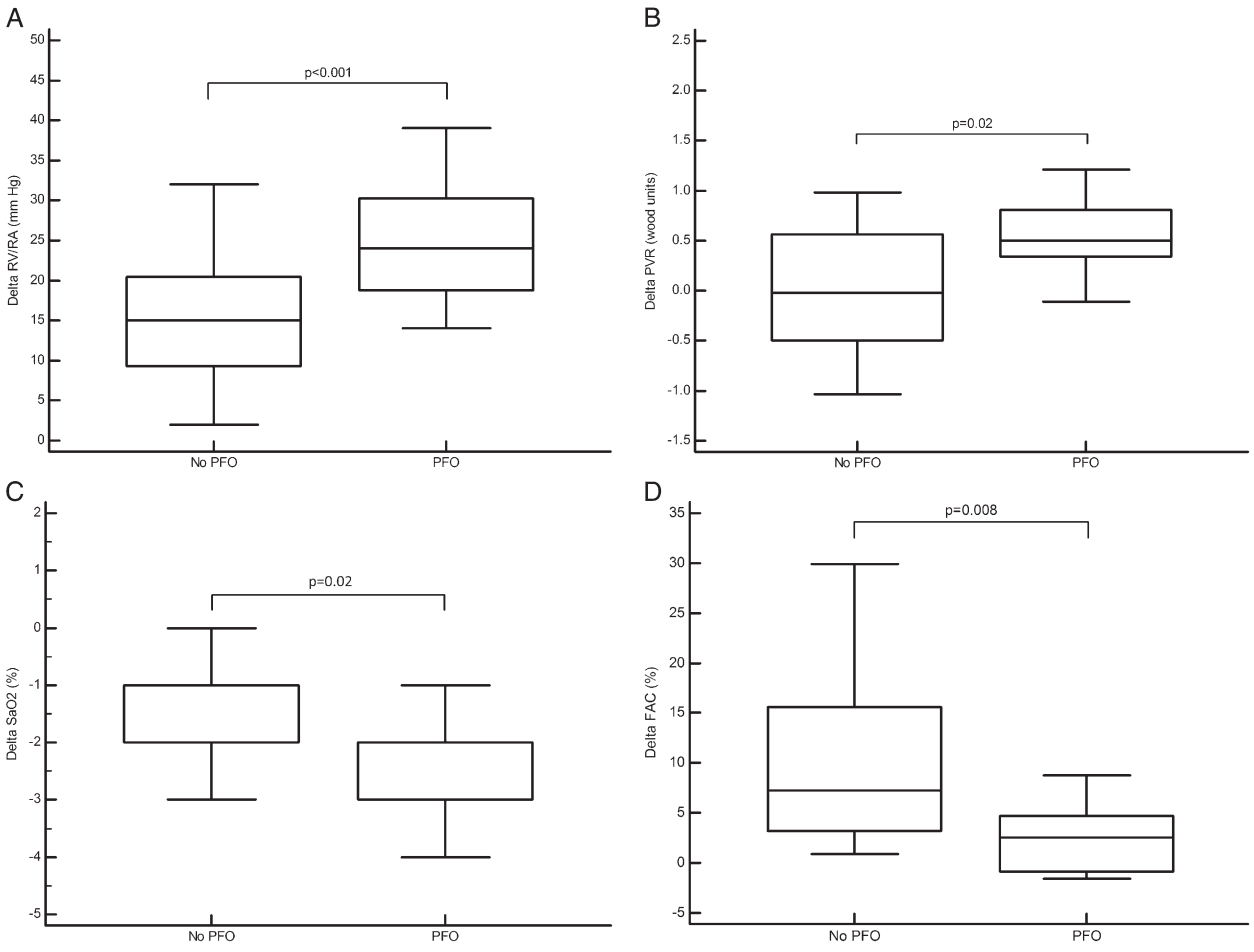


Figure 1 – *Exercise-induced changes in high-altitude dwellers with (n = 18) and without (n = 39) a PFO. A, RV/RA. B, PVR. C, SaO2. D, FAC. The boxplots represent median with interquartile range; the whiskers symbolize the maximal and minimal values. FAC = fractional area change of the right ventricle; PFO = patent foramen ovale; PVR = pulmonary vascular resistance; RV/RA = right-ventricular-to-right-atrial pressure gradient; SaO2 = arterial oxygen saturation.*

exercise in participants with a PFO (Table 3). This was because of a greater increase in PVR in individuals with a PFO (Fig 1B). CO (PFO vs no PFO, 9.0 ± 2.2 L/min vs 9.1 ± 2.8 L/min; $P = .85$) and the estimated LV filling pressure (ratio of mitral E to DTI E) (PFO vs no PFO, 6.8 ± 1.4 vs 7.6 ± 1.7; $P = .31$) were similar in the two groups. Of note, none of the patients had significant mitral regurgitation. During mild exercise, arterial oxygen saturation was significantly lower in participants with a PFO compared with participants without a PFO (85.1 ± 3.2 vs 87.1 ± 2.9, $P = .03$), because the exercise-induced decrease of arterial oxygen saturation was significantly greater in HA dwellers with a PFO than in those without a PFO (Fig 1C).

PFO size and arterial oxygen desaturation during exercise appeared to play a role in these responses during mild exercise. The drop of arterial oxygen saturation during exercise was related to PFO size ($\rho = 0.36$, $P = .001$), exercise-induced increase in the RV/RA gradient ($\rho = 0.40$, $P = .003$), and PVR ($\rho = 0.30$, $P = .03$). Similarly, the exercise-induced increases in the RV/RA gradient ($\rho = 0.52$, $P < .001$) and PVR ($\rho = 0.33$, $P = .02$) were also directly related to PFO size.

During mild exercise, the RV systolic and diastolic areas remained significantly greater in participants with a PFO compared with participants without a PFO (Table 3). Moreover, RV function increased significantly less during exercise (FAC, 3% [−1%, 5%] vs 7% [3%, 12%]; $P = .008$ [Fig 1D]; tricuspid annular systolic velocity, 2.0 cm/s [0.3, 2.8 cm/s] vs 3.0 cm/s [2.0, 4.8cm/s], $P = .007$) and was significantly lower in HA dwellers with a PFO compared with participants without a PFO. Accordingly, RV dysfunction (FAC ≤ 35%) during mild exercise was significantly more frequent in HA dwellers with a PFO compared with those without a PFO (five of 17 [27%] vs one of 36 [3%], $P = .048$). Similar to the pulmonary hemodynamic variables, the exercise-induced increase in RV function was related to PFO size (FAC, $\rho = -0.43$,

**TABLE 3** ] Pulmonary and RV Hemodynamic Variables Assessed at 50-W Exercise in High-Altitude Dwellers With/Without a PFO

| Variable | PFO (n = 18) | No PFO (n = 39) | Adjusted Difference[a] (SE) |
|---|---|---|---|
| RV/RA gradient, mm Hg | 49.7 (9.6)[b] | 40.3 (9.1) | 8.4 (2.6)[b] |
| PAMP, mm Hg | 36.6 (5.8)[b] | 30.8 (5.6) | 5.1 (1.6)[b] |
| PVR, Wood units | 3.1 (0.9)[c] | 2.5 (1.0) | 0.6 (0.3)[c] |
| RV EDA, $cm^2$ | 18.2 (1.8)[b] | 15.2 (2.9) | 3.0 (0.9)[b] |
| RV ESA, $cm^2$ | 11.4 (1.2)[b] | 8.1 (2.0) | 3.4 (0.6)[d] |
| FAC, % | 37 (4)[d] | 47 (7) | −10 (2)[d] |
| TASV, cm/s | 12.3 (2.2)[c] | 13.8 (1.7) | −1.5 (0.6)[c] |
| TAPSE, mm | 23.4 (3.2)[b] | 27.7 (4.6) | −4.4 (1.6)[c] |
| RV-ESPAR, mm Hg/$cm^2$ | 4.5 (0.9)[c] | 5.2 (1.1) | −0.6 (0.4) |

Data are presented as mean (SD). See Tables 1 and 2 for expansion of abbreviations.
[a]Difference adjusted for participant's age and CMS status.
[b]*P* value between .001 and .01.
[c]*P* value between .01 and .05.
[d]*P* < .001.

$P = .003$; tricuspid annular systolic velocity, $\rho = -0.39$, $P = .008$; and tricuspid annular plane systolic excursion, $\rho = -0.36$, $P = .04$). After adjustment for age and CMS status, the differences between the RV dimension, RV function, and pulmonary hemodynamic responses in participants with and without a PFO did not change significantly (Table 3).

Maximal achieved heart rate during exercise (103 ± 11 beats/min vs 99 ± 11 beats/min, $P = .23$), heart rate reserve (33 ± 11 beats/min vs 32 ± 9 beats/min, $P = .73$), and percentage of maximal predicted heart rate (60% ± 7% vs 57% ± 6%, $P = .1$) were not different between subjects with and without a PFO. Moreover, systolic BP (152 ± 24 mm Hg vs 147 ± 22 mm Hg, $P = .43$) and LV ejection fraction (67% ± 4% vs 69% ± 4%, $P = .16$) during exercise were also comparable between the two groups.

### *Pulmonary Hemodynamic and RV Variables at Rest and During Exercise in Participants With and Without CMS*

Table 4 shows that, as expected,[8,22] in patients with CMS, pulmonary artery pressure was slightly increased at rest, and that the exercise-induced increase was exaggerated compared with participants without CMS. Most importantly, in patients with CMS, a PFO was associated with more marked pulmonary hypertension and RV dysfunction during exercise than in patients with CMS without a PFO. Finally, a PFO in healthy HA dwellers appeared to have similar effects on pulmonary hemodynamics and RV function as CMS alone.

## Discussion

In disease states associated with hypoxemia at low altitude, a PFO is associated with increased pulmonary artery pressure.[6,7] Surprisingly, in HA dwellers there is no information on the prevalence of PFO and its potential consequences on pulmonary artery pressure and RV function. Here, we believe for the first time, we show that although the prevalence of PFO in HA dwellers (32%) was similar to the one reported in low-altitude populations,[24] its presence was associated with important alterations in pulmonary artery pressure, RV morphology and function, and arterial oxygenation. Compared with subjects without a PFO, mild exercise resulted in an exaggerated increase in pulmonary artery pressure and PVR in HA dwellers with a PFO that was associated with impaired RV function, RV enlargement, and exaggerated arterial oxygen desaturation. These findings suggest that at HA, a PFO appears to facilitate RV and pulmonary hemodynamic changes during mild physical activity frequently performed in everyday life. These pulmonary hemodynamic alterations during physical activity may also have contributed to the RV enlargement at rest observed in HA dwellers with a PFO.

The current estimations of pulmonary artery pressure responses to mild exercise in HA dwellers are comparable to those reported in earlier reports[8,22] and confirm the relatively large interindividual variability in these responses. The current findings suggest that in both patients with CMS and healthy HA dwellers, the presence and size of a PFO explains part of this interindividual

**TABLE 4** ] Pulmonary and RV Hemodynamic Variables in High-Altitude Dwellers With/Without CMS and Subgroup Analysis of Patients With CMS and Healthy High-Altitude Dwellers According to the Presence of a PFO

| Variable | CMS (n = 35) | No CMS (n = 22) | CMS With PFO (n = 10) | CMS Without PFO (n = 25) | Healthy With PFO (n = 8) | Healthy Without PFO (n = 14) |
|---|---|---|---|---|---|---|
| Values assessed at rest | | | | | | |
| RV/RA gradient, mm Hg | 25.6 (3.9)[a] | 23.3 (4.3) | 27.0 (5.0) | 25.0 (3.2) | 22.3 (3.0) | 24.0 (4.4) |
| PVR, Wood units | 2.4 (0.7) | 2.5 (0.9) | 2.5 (0.5) | 2.3 (0.8) | 2.6 (1.1) | 2.5 (0.9) |
| RV basal diameter, mm | 31.3 (3.7)[b] | 28.8 (4.0) | 33.0 (4.0)[a] | 29.7 (3.6) | 32.3 (3.1)[b] | 26.9 (3.1) |
| FAC, % | 36 (6)[b] | 41 (7) | 33 (5)[a] | 38 (6) | 39 (8) | 38 (7) |
| Values assessed at 50-W exercise | | | | | | |
| RV/RA gradient, mm Hg | 46.0 (10.9)[a] | 39.4 (7.8) | 52.2 (10.8)[a] | 43.1 (9.8) | 46.3 (6.7)[b] | 36.1 (6.1) |
| PVR, Wood units | 3.0 (1.1) | 2.5 (0.9) | 3.2 (0.8) | 2.7 (1.2) | 3.0 (1.2) | 2.2 (0.6) |
| FAC, % | 38 (7)[b] | 45 (8) | 33 (4)[b] | 41 (7) | 39 (3)[b] | 48 (7) |

Data are presented as mean (SD). See Tables 1 and 2 for expansion of abbreviations.
[a]Comparison with respective value of the group without the condition: *P* value between .01 and .05.
[b]Comparison with respective value of the group without the condition: *P* value between .001 and .01.

variability. Consistent with previously reported findings in HAPE-susceptible mountaineers that showed that the size of the PFO, rather than its mere presence, is a determinant of the pulmonary artery pressure response during acute HA exposure,[5] significant correlations were observed between the PFO size and the exercise-induced increase in pulmonary artery pressure, PVR, and exercise-induced arterial oxygen desaturation in HA dwellers. Thus, the current findings lend support to the hypothesis that in HA dwellers with a PFO, the exercise-induced pulmonary vasoconstriction initiates a vicious cycle by shunting deoxygenated blood from the right to the left atrium, which, in turn, aggravates hypoxemia, resulting in reduced mixed venous oxygen tension, greater alveolar hypoxia, and greater pulmonary hypertension.[25]

There is evidence that, at low altitude, in patients with sleep-disordered breathing, a PFO is associated with more severe nocturnal oxygen desaturation[26] and pulmonary hypertension.[27] It is possible that in HA dwellers with a PFO who suffer from sleep disordered breathing, this may represent an additional mechanism contributing to pulmonary and RV remodeling. The current observation of load-independent RV dysfunction at rest (as evidenced by lower RV-ESPAR) in HA dwellers with a PFO could be consistent with this speculation. Moreover, subgroup analysis of our findings suggests that in HA dwellers with pulmonary vascular dysfunction, as may be the case for CMS,[22,28,29] a PFO predisposes to more marked pulmonary hypertension and RV dysfunction than in healthy HA dwellers and may therefore represent a risk factor for right-sided heart failure in this subpopulation. Regarding this, some findings suggest that fetal programming of pulmonary vascular dysfunction in the offspring of mothers with preeclampsia and children generated by assisted reproductive technology predisposes to exaggerated hypoxic pulmonary hypertension at HA.[30,31] Further study is needed to assess the effects of a PFO on pulmonary hemodynamics and RV function in these populations. Finally, for ethical reasons we did not perform invasive assessments of RV and pulmonary vascular function. However, there is good agreement between invasive and echocardiographic assessments of resting pulmonary artery pressure at HA[15] and pulmonary artery pressure responses to exercise at low altitude.[32]

## Conclusions

In conclusion, we show, for the first time to our knowledge, that in HA dwellers, the presence and the size of a PFO appear to have important hemodynamic consequences. At rest it's presence was associated with RV enlargement and, even more importantly, during mild exercise expected to be frequently associated with daily activity, a PFO in HA dwellers was related to exaggerated pulmonary hypertension and pulmonary vasoconstriction that was associated with RV enlargement and dysfunction.

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