CHEST

Original Research

PULMONARY HYPERTENSION

Exaggerated Pulmonary Hypertension During Mild Exercise in Chronic Mountain Sickness

Thomas Stuber, MD; Claudio Sartori, MD; Marcos Schwab, MD; Pierre-Yves Jayet, MD; Stefano F. Rimoldi, MD; Sophie Garcin, MD; Sébastien Thalmann, MD; Hilde Spielvogel, MD; Carlos Salinas Salmòn, MD; Mercedes Villena, MD; Urs Scherrer, MD; and Yves Allemann, MD

Background: **Chronic mountain sickness (CMS) is an important public health problem and is characterized by exaggerated hypoxemia, erythrocytosis, and pulmonary hypertension. While pulmonary hypertension is a leading cause of morbidity and mortality in patients with CMS, it is relatively mild and its underlying mechanisms are not known. We speculated that during mild exercise associated with daily activities, pulmonary hypertension in CMS is much more pronounced.**

Methods: **We estimated pulmonary artery pressure by using echocardiography at rest and during mild bicycle exercise at 50 W in 30 male patients with CMS and 32 age-matched, healthy control subjects who were born and living at an altitude of 3,600 m.**

Results: **The modest, albeit significant difference of the systolic right-ventricular-to-right-atrial pressure gradient between patients with CMS and controls at rest (30.3 ± 8.0 vs 25.4 ± 4.5 mm Hg, $P = .002$) became more than three times larger during mild bicycle exercise (56.4 ± 19.0 vs 39.8 ± 8.0 mm Hg, $P < .001$).**

Conclusions: **Measurements of pulmonary artery pressure at rest greatly underestimate pulmonary artery pressure during daily activity in patients with CMS. The marked pulmonary hypertension during mild exercise associated with daily activity may explain why this problem is a leading cause of morbidity and mortality in patients with CMS.** ***CHEST 2010; 137(2):388–392***

Abbreviations: CMS = chronic mountain sickness; DLCO = carbon monoxide diffusion capacity; VA = alveolar volume

Chronic mountain sickness (CMS) is an important public health problem characterized by exaggerated hypoxemia, erythrocytosis, and pulmonary hypertension. Pulmonary hypertension in CMS is relatively mild.[1,2] It is, however, a leading cause of morbidity and mortality, and its underlying mechanisms are not known.[3,4]

Exercise is known to increase pulmonary artery pressure.[5,6] The exercise-induced increase in pulmonary artery pressure is exaggerated by preexisting pulmonary hypertension.[7] Moreover, hypoxemia, which is universally associated with high-altitude exposure, is also known to increase exercise-induced pulmonary hypertension.[8] We speculated that light-to-moderate exercise associated with daily activities induces a much larger increase in pulmonary artery pressure in patients with CMS than in control subjects.

Manuscript received June 9, 2009; revision accepted August 11, 2009.

Affiliations: From the University Hospital of Bern, Cardiology (Drs Stuber, Rimoldi, and Allemann), Bern, Switzerland; Department of Internal Medicine and Botnar Center for Clinical Research (Drs Sartori, Schwab, Jayet, Garcin, Thalmann, and Scherrer), University Hospital, Lausanne, Switzerland; and Instituto Boliviano de Biologia de Altura (Drs Spielvogel, Salmòn, and Villena), La Paz, Bolivia.

Funding/Support: This work was supported by grants from the Swiss National Science Foundation, the Prof Dr Max Cloëtta Foundation, the Placide Nicod Foundation, the CardioMet Foundation, the Leenaards Foundation, the Novartis Foundation, and the Eagle Foundation.

Correspondence to: Yves Allemann, MD, Swiss Cardiovascular Center Bern, University Hospital, CH-3010 Bern, Switzerland; e-mail: yves.allemann@insel.ch

DOI: 10.1378/chest.09-1355

To test this hypothesis, we estimated pulmonary artery pressure by using echocardiography at rest and during mild, semisupine bicycle exercise in patients with CMS and normal control subjects who were all born and permanently living at an altitude of 3,600 to 4,000 m. To discriminate between anatomic and functional defects, we measured the carbon monoxide diffusion capacity (DLCO) (a proxy of the extent of the pulmonary microcirculation) and we tested the effects of nitric oxide inhalation on pulmonary artery pressure in the two groups.

Materials and Methods

Thirty male Bolivian patients with primary CMS (mean ± SD age, 47 ± 13 years) and 32 healthy, age-matched control subjects (mean ± SD age, 46 ± 11 years, $P = .71$) who were born and had been permanently living in the city of La Paz or its surroundings (altitude 3,600–4,000 m) were included in the study (Table 1). All patients and control subjects had typical Aymara surnames, self-identified themselves as Aymaras, and had similar socio-economic backgrounds.

All patients were initially referred to the Instituto Boliviano de Biologia de Altura with clinical symptoms of CMS. Inclusion criteria for CMS patients were excessive erythrocytosis with hemoglobin concentrations > 20 g/dL, normal pulmonary function studies, and no history of working in the mining industry. None of the subjects was a smoker or taking any medications. A complete clinical exam was performed, and the CMS score was determined.[9] For each of the seven items (breathlessness/palpitations, sleep disturbance, cyanosis, dilation of veins, paresthesias, headache, tinnitus) a score between 0 and 3 was attributed, with 0 indicating the absence of the symptom; 1, mild symptoms; 2, moderate symptoms; and 3, severe, incapacitating symptoms.

The institutional review boards on human investigation of the University of San Andres in Bolivia and of the University of Lausanne in Switzerland approved the experimental protocol, and all subjects provided written informed consent. All studies were performed at the Instituto Boliviano de Biologia de Altura in La Paz (altitude 3,600 m).

Doppler Echocardiography

Transthoracic Doppler echocardiography was performed in all subjects to rule out structural heart disease. Echocardiographic recordings were obtained with a real-time, phased-array sector scanner (Siemens Acuson Cypress; Siemens; Mountain View, CA) with an integrated color Doppler system and two different transducers containing crystal sets for two-dimensional imaging (3.6 and 6.0 MHz) and for continuous-wave Doppler recording (2.15 and 3.6 MHz). To estimate systolic pulmonary artery pressure, we measured the peak systolic transtricuspidal jet velocity and calculated the right-ventricular-to-right-atrial pressure gradient, as previously described.[10] This method has the best reproducibility of all noninvasive measurement methods.[11] It has been validated against invasive measurements at high altitude[10] and is widely accepted for use during exercise testing.[5,6,8,12] In two subjects (one patient, one control), the systolic right-ventricular-to-right-atrial pressure gradient could not be measured.

The recordings were stored on MO-discs and S-VHS videotapes for off-line analysis by three of us (T.S., Y.A., C.S.S.) who were unaware of the patient's group assignment. All reported values represent the mean of at least three measurements.

Cardiac output was determined by measuring the diameter of the left ventricular outflow tract and its time-velocity integral. The left ventricular outflow tract diameter was measured in the parasternal long axis view, and assuming the cross-sectional area to be a circle, its surface was calculated. The pulsed-wave Doppler time-velocity integral in the left ventricular outflow tract was measured from the apical five-chamber view. The stroke volume was calculated by multiplying the left ventricular outflow tract time velocity integral by the cross-sectional area. Cardiac output was then obtained by multiplying the stroke volume by the heart rate.[13] The intraobserver and interobserver variability for the systolic right-ventricular-to-right-atrial pressure gradient estimations were 1.5 ± 1.2 mm Hg and 1.6 ± 2.2 mm Hg, respectively (n = 30), and for the cardiac output measurements, 10.7% ± 10.2% and 7.2% ± 4%, respectively (n = 30). The right-ventricular-to-right-atrial pressure gradient divided by the cardiac output was used as a proxy of pulmonary vascular resistance.

Exercise Test

The exercise test was performed on a bicycle ergometer (Ergoline 900EL; Ergoline Company; Bitz, Germany) in the semisupine position with a 30° rotation to the left. Pulmonary artery pressure was estimated using measurements of peak systolic transtricuspidal jet velocity at rest and during mild exercise at 50 W. During exercise, at least one technically acceptable measurement of pulmonary artery pressure was obtained in 65% of subjects, with valuable baseline measurements. In the remaining subjects, body and diaphragmatic movements made it impossible to locate the transtricuspidal regurgitation jet during exercise.

Pulmonary Function and DLCO

To examine whether pulmonary hypertension in patients with CMS was related to a reduced size of the pulmonary microcirculation, we assessed DLCO and lung function (Sensor-Medics 2200 Pulmonary Function System SP; Sensor-Medics; Bilthoven, The Netherlands). In the presence of a normal pulmonary function, the DLCO is a good indicator of pulmonary blood flow and, in turn, lung capillarization.[14] DLCO was measured with the single-breath technique following American Thoracic Society recommendations.[15] Adjustments for altitude, hemoglobin concentration, and age of the subjects were made according to these recommendations. To adjust for hemoglobin, the following equation was used: Hb-adjusted DLCO = observed DLCO (10.22 + Hb)/1.7 Hb). To adjust for altitude, the following equation was used: altitude-adjusted DLCO = measured DLCO × (1.0 + 0.0035 [Pa_{O_2} − 120].To correct for lung volume, the DLCO was divided by the alveolar volume (VA)

Table 1—*Patient Characteristics*

Characteristics	Patients With CMS	Control Subjects	*P* Value
No.	30	32	
Age, y	47 ± 13	46 ± 11	$P = .71$
Hb, g/dL	21.5 ± 1.7	16.6 ± 0.9	$P < .001$
Hematocrit, %	66 ± 7	50 ± 3	$P < .001$
CMS score	11.9 ± 3.7	0.6 ± 0.6	$P < .001$
Sa_{O_2}, %	83 ± 5	92 ± 2	$P < .001$
Height, cm	168 ± 11	168 ± 7	$P = .97$
Weight, kg	79 ± 11	80 ± 14	$P = .96$
DL/VA, mL CO/min/mm Hg/L	6.6 ± 1.1	6.3 ± 1.0	$P = .52$

CMS = chronic mountain sickness; DL = diffusion capacity; Hb = hemoglobin; Sa_{O_2} = arterial oxygen saturation; VA = alveolar volume.

determined during the lung function measurements and expressed as DL/VA (mL CO/min/mm Hg/L).

Nitric Oxide Inhalation

To examine whether pulmonary hypertension was reversible, we assessed the effects of nitric oxide inhalation on pulmonary artery pressure. Subjects breathed for 20 min through a facemask that was connected to a nonrebreathing circuit consisting of a gas delivery system with a 50-L reservoir bag containing 40 ppm of nitric oxide.

Oxygen Saturation

Transcutaneous arterial oxygen saturation and heart rate were measured at a fingertip with a pulse oxymeter (OxiMaxN-595' Nellcor; Pleasanton, CA).

Statistical Analysis

All statistical analyses were done with Statview 4.5 (Abacus Concepts Inc.; Piscataway, NY) and SAS 9.1 for Windows (SAS Institute; Cary, NC). Patient characteristics were compared using analysis of variance factorial analysis or the χ^2 test for categorical data. The Fisher *post hoc* least significant difference test was used for *post hoc* analysis of mean differences between the groups. Data are presented as mean ± SD. A P value $< .05$ was considered to indicate statistical significance.

Results

The characteristics of patients and controls are shown in Table 1. By definition, hemoglobin and hematocrit levels were higher in patients than in control subjects. As expected, CMS scores were higher and arterial oxygen saturation was lower in patients with CMS than in control subjects (Table 1). Pulmonary function was normal in all subjects, and DL/VA was comparable in patients with CMS and control subjects.

At rest, the right-ventricular-to-right-atrial pressure gradient was slightly, but significantly, higher in patients with CMS than in control subjects (30.3 ± 8.0 vs 25.4 ± 4.5 mm Hg, $P = .002$) (Fig 1*A*). Heart rate (70 ± 9 vs 60 ± 9 beats/min, $P < .001$) was faster in patients, whereas cardiac output (4.2 ± 0.9 vs 4.1 ± 0.9 L/min, $P = .60$) and estimated pulmonary vascular resistance (7.2 ± 2.3 vs 6.4 ± 1.7 mm Hg/(L/min), $P = .20$) were similar in the two groups.

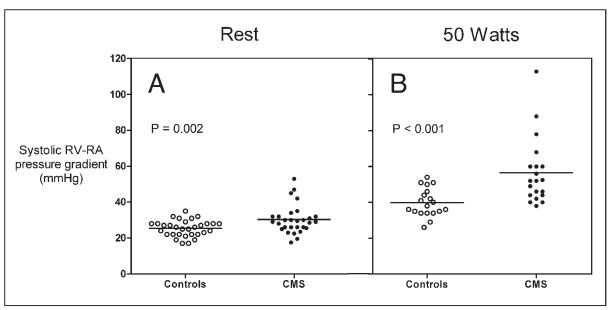

Figure 1. Systolic right-ventricular-to-right-atrial pressure gradient at rest (*A*) and during mild bicycle exercise at 50 W (*B*) in patients with CMS and control subjects at an altitude of 3,600 m. CMS = chronic mountain sickness; RV-RA = right-ventricle-to-right-atrial.

During light bicycle exercise at 50 W, the increase in the pressure gradient was almost twice as large in patients than in control subjects (+ 25.1 ± 15.7 vs + 13.8 ± 5.1 mm Hg, $P = .01$). Thus, during mild exercise, pulmonary artery pressure was much higher in patients with CMS than in control subjects (56.4 ± 19.0 vs 39.8 ± 8.0 mm Hg, $P < .001$) (Fig 1*B*), and the pressure gradient difference between the two groups was more than three times greater than at rest (16.6 vs 4.9 mm Hg). During exercise, the arterial oxygen saturation decreased significantly ($P < .001$) in both groups (from 83% ± 5% to 79% ± 8% in patients, and from 92% ± 2% to 90% ± 2% in control subjects), but the exercise-induced decrease tended to be greater in patients than in control subjects (4.4% ± 3.5% vs 2.6% ± 1.3%, $P = .07$). The heart rate was similar in the two groups (99 ± 9 vs 99 ± 19 beats/min, $P = .88$).

During nitric oxide inhalation, pulmonary artery pressure decreased significantly and comparably in the two groups (by 6.2 ± 4.5 and 4.9 ± 2.5 mm Hg, patients vs control subjects, $P = .31$), but remained significantly higher in patients than in control subjects (25.1 ± 3.4 vs 20.2 ± 2.8 mm Hg, $P < .001$).

Discussion

These data represent the first direct comparisons of echocardiographic estimations of pulmonary artery pressure at rest and during mild exercise between Andean high-altitude dwellers with CMS and healthy control subjects born and living at the same altitude. At rest, pulmonary artery pressure was slightly, albeit significantly, higher in the patients with CMS than in the control subjects. During mild exercise similar to that expected to be associated with daily activities, this difference in pulmonary artery pressure between the two groups was more than three times larger than expected. Structural vascular defects appeared to contribute to exaggerated pulmonary hypertension in patients with CMS. These findings indicate that in patients with CMS, measurements at rest greatly underestimate pulmonary artery pressure during daily activity, and they may explain the clinical observation that right ventricular failure is a leading cause of morbidity and mortality in these patients.[3,4]

The present echocardiographic estimations of pulmonary artery pressure at rest in the control subjects were comparable to those recently reported in a roughly 10-years-younger population with similar ethnic and socioeconomic backgrounds living at the same altitude.[16] In the patients with CMS, the present estimations were slightly lower than those recently

reported by Maignan et al.[1] The somewhat higher values in the latter report were probably due to the higher study altitude (4,300 m). Earlier uncontrolled studies using invasive measurements in small groups of patients with CMS reported mean pulmonary artery pressure values at rest ranging from 27 to 42 mm Hg.[2,17] The relative wide range of these invasive pressure values might be related to differences in study altitude (3,600-4,340 m) and, in turn, more severe hypoxemia, or duration of stay at high altitude and patient selection, since secondary forms of CMS were not excluded. In the present study, we were careful to exclude all secondary forms of CMS, to include only patients who were born at high altitude, and to compare them with control subjects with the same ethnic and socio-economic high-altitude backgrounds. Differences in patient selection, socio-economic status, concomitant disease, and study altitude (4,340 m), resulting in much more severe exercise-induced hypoxemia (arterial oxygen percent saturation, 61%), may also explain the difference between the present findings during exercise and those of Peñaloza and Sime,[2] who were the first to measure invasively the hemodynamic response to exercise in six patients with CMS and reported an increase of the mean pulmonary artery pressure from 37 mm Hg at rest to 82 mm Hg during mild exercise. Since cardiac output also increased during exercise, the authors attributed this dramatic increase in pulmonary artery pressure to increased pulmonary vascular resistance related to vascular remodeling.

While echocardiography did not allow us to measure pulmonary vascular resistance during exercise, our data at rest are consistent with the concept that vascular remodeling of the pulmonary circulation contributes to pulmonary hypertension in patients with CMS. The present data indicate that pulmonary hypertension in patients with CMS was not related to a difference in the extent of the pulmonary microcirculation, since the DLCO was comparable in patients and control subjects. The observation that during nitric oxide inhalation, pulmonary artery pressure decreased similarly in the two groups indicates that the physiologic role of nitric oxide is intact in patients with CMS. Importantly, however, pulmonary artery pressure during nitric oxide inhalation remained significantly higher in patients than in control subjects. This finding suggests that a structural defect, possibly related to remodeling of the pulmonary vascular wall, contributes to pulmonary hypertension in patients with CMS.[18] In line with this hypothesis, after a descent to low altitude, pulmonary artery pressure takes several years to normalize in patients with CMS.[2] The mechanism causing this structural defect is not known. CMS, as in the present studies, is characterized by exaggerated hypoxemia, possibly related to a blunted hypoxic ventilatory response[3,4] or to some unknown mechanism. Chronic hypoxia is well known to cause pulmonary vascular remodeling,[19] and may represent a candidate mechanism.

In conclusion, we found that in patients with CMS estimations of pulmonary artery pressure at rest greatly underestimate pulmonary artery pressure during mild exercise, as expected to be associated with daily activities. A structural vascular defect of the pulmonary vasculature, possibly related to exaggerated chronic hypoxemia, appears to contribute to this exaggerated exercise-induced response. We speculate that exaggerated pulmonary hypertension during daily activity explains why this problem is a leading cause of morbidity and mortality in patients with CMS.

Acknowledgments

Author contributions: *Dr Stuber:* was involved in the clinical examinations, including echocardiography, and exercise testing, and wrote a draft of the paper.
Dr Sartori: was involved in the study design, data analysis and interpretation, and final writing of the paper. He also participated in the clinical examinations and lung function testing, and was responsible for recruiting patients and control subjects.
Dr Schwab: was involved in the clinical examinations and lung function testing, and was responsible for recruiting patients and control subjects.
Dr Jayet: was involved in the clinical examinations and lung function testing.
Dr Rimoldi: was involved in the clinical examinations, echocardiography, and exercise testing.
Dr Garcin: was involved in the clinical examinations, including exercise testing and lung function testing.
Dr Thalmann: was involved in the clinical examinations, including exercise testing and lung function testing.
Dr. Spielvogel: was involved in the clinical examinations, including exercise testing, and helped recruit patients and control subjects.
Dr Salmòn: was involved in the clinical examinations, including echocardiography and exercise testing.
Dr Villena: was involved in the clinical examinations, including lung function testing, and was responsible for recruiting patients and control subjects.
Dr Scherrer: was involved in the design of the study, data analysis and interpretation, and final writing of the paper.
Dr Allemann: was involved in the design of the study, data analysis and interpretation, and final writing of the paper. He participated in the clinical examinations, including echocardiography.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Other contributions: We are indebted to Mrs Catherine Romero and to Dr Armando Rodriguez for invaluable help with these studies.

References

1. Maignan M, Rivera-Ch M, Privat C, León-Velarde F, Richalet JP, Pham I. Pulmonary pressure and cardiac function in chronic mountain sickness patients. *Chest*. 2009;135(2):499-504.
2. Peñaloza D, Sime F. Chronic cor pulmonale due to loss of altitude acclimatization (chronic mountain sickness). *Am J Med*. 1971;50(6):728-743.

3. Reeves JT, Weil JV. Chronic mountain sickness. A view from the crow's nest. *Adv Exp Med Biol*. 2001;502:419-437.
4. León-Velarde F, Richalet JP. Respiratory control in residents at high altitude: physiology and pathophysiology. *High Alt Med Biol*. 2006;7(2):125-137.
5. Himelman RB, Stulbarg M, Kircher B, et al. Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography in chronic pulmonary disease. *Circulation*. 1989;79(4):863-871.
6. Leavitt JI, Coats MH, Falk RH. Effects of exercise on transmitral gradient and pulmonary artery pressure in patients with mitral stenosis or a prosthetic mitral valve: a Doppler echocardiographic study. *J Am Coll Cardiol*. 1991;17(7):1520-1526.
7. Mininni S, Diricatti G, Vono MC, et al. Noninvasive evaluation of right ventricle systolic pressure during dynamic exercise by saline-enhanced Doppler echocardiography in progressive systemic sclerosis. *Angiology*. 1996;47(5):467-474.
8. Dehnert C, Grünig E, Mereles D, von Lennep N, Bärtsch P. Identification of individuals susceptible to high-altitude pulmonary oedema at low altitude. *Eur Respir J*. 2005;25(3):545-551.
9. León-Velarde F, Maggiorini M, Reeves JT, et al. Consensus statement on chronic and subacute high altitude diseases. *High Alt Med Biol*. 2005;6(2):147-157.
10. Allemann Y, Sartori C, Lepori M, et al. Echocardiographic and invasive measurements of pulmonary artery pressure correlate closely at high altitude. *Am J Physiol Heart Circ Physiol*. 2000;279(4):H2013-H2016.
11. Stevenson JG. Comparison of several noninvasive methods for estimation of pulmonary artery pressure. *J Am Soc Echocardiogr*. 1989;2(3):157-171.
12. Kaplan JD, Foster E, Redberg RF, Schiller NB. Exercise Doppler echocardiography identifies abnormal hemodynamics in adults with congenital heart disease. *Am Heart J*. 1994;127(6):1572-1580.
13. Oh JK, Seward JB, Taijk AJ. *The Echo Manual*. Philadelphia, PA: Lippincott-Raven; 1999:59-62.
14. Hughes JM. The single breath transfer factor (Tl,co) and the transfer coefficient (Kco): a window onto the pulmonary microcirculation. *Clin Physiol Funct Imaging*. 2003;23(2):63-71.
15. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26(4):720-735.
16. Schwab M, Jayet PY, Stuber T, et al. Pulmonary-artery pressure and exhaled nitric oxide in Bolivian and Caucasian high altitude dwellers. *High Alt Med Biol*. 2008;9(4):295-299.
17. Manier G, Guenard H, Castaing Y, Varene N, Vargas E. Pulmonary gas exchange in Andean natives with excessive polycythemia—effect of hemodilution. *J Appl Physiol*. 1988;65(5):2107-2117.
18. Pak O, Aldashev A, Welsh D, Peacock A. The effects of hypoxia on the cells of the pulmonary vasculature. *Eur Respir J*. 2007;30(2):364-372.
19. Kato M, Staub NC. Response of small pulmonary arteries to unilobar hypoxia and hypercapnia. *Circ Res*. 1966;19(2):426-440.