CHEST

Original Research

PULMONARY VASCULAR DISEASE

Exercise Induces Rapid Interstitial Lung Water Accumulation in Patients With Chronic Mountain Sickness

Lorenza Pratali, MD, PhD; Stefano F. Rimoldi, MD; Emrush Rexhaj, MD; Damian Hutter, MD; Francesco Faita, PhD; Carlos Salinas Salmòn, MD; Mercedes Villena, MD; Rosa Sicari, MD, PhD; Eugenio Picano, MD, PhD; Yves Allemann, MD; Urs Scherrer, MD; and Claudio Sartori, MD

Background: **Chronic mountain sickness (CMS) is a major public health problem in mountainous regions of the world. In its more advanced stages, exercise intolerance is often found, but the underlying mechanism is not known. Recent evidence indicates that exercise-induced pulmonary hypertension is markedly exaggerated in CMS. We speculated that this problem may cause pulmonary fluid accumulation and aggravate hypoxemia during exercise.**

Methods: **We assessed extravascular lung water (chest ultrasonography), pulmonary artery pressure, and left ventricular function in 15 patients with CMS and 20 control subjects at rest and during exercise at 3,600 m.**

Results: **Exercise at high altitude rapidly induced pulmonary interstitial fluid accumulation in all patients but one (14 of 15) with CMS and further aggravated the preexisting hypoxemia. In contrast, in healthy high-altitude dwellers exercise did not induce fluid accumulation in the majority of subjects (16 of 20) ($P = .002$ vs CMS) and did not alter arterial oxygenation. Exercise-induced pulmonary interstitial fluid accumulation and hypoxemia in patients with CMS was accompanied by a more than two times larger increase of pulmonary artery pressure than in control subjects ($P < .001$), but no evidence of left ventricular dysfunction. Oxygen inhalation markedly attenuated the exercise-induced pulmonary hypertension ($P < .01$) and interstitial fluid accumulation ($P < .05$) in patients with CMS but had no detectable effects in control subjects.**

Conclusions: **To our knowledge, these findings provide the first direct evidence that exercise induces rapid interstitial lung fluid accumulation and hypoxemia in patients with CMS that appear to be related to exaggerated pulmonary hypertension. We suggest that this problem contributes to exercise intolerance in patients with CMS.**

Trial registry: **ClinicalTrials.gov; No.: NCT01182792; URL: www.clinicaltrials.gov**

CHEST 2012; 141(4):953–958

Abbreviations: CMS = chronic mountain sickness; NS = not significant; ULC = ultrasound lung comet

Chronic mountain sickness (CMS) is a major public health problem in mountainous regions of the world.[1,2] Although erythrocytosis and hypoxemia are its most prominent signs, in its more advanced stages exercise intolerance is often found,[3] but the underlying mechanism is not known.

We recently found that in patients with CMS, exercise induces markedly exaggerated pulmonary hypertension.[4] Circumstantial evidence suggests that in healthy subjects, exaggerated pulmonary hypertension may cause lung fluid accumulation.[5-7] Chest sonography allows quantifying extravascular lung water by assessing ultrasound lung comets (ULCs) originating from water-thickened interlobular septa.[8-10] We speculated that in patients with CMS, exercise intolerance is caused by pulmonary fluid accumulation related to pulmonary hypertension-induced capillary stress failure in the absence of left ventricular dysfunction. To test this hypothesis, we assessed ULCs, pulmonary artery pressure, and left ventricular function in patients with CMS and control subjects at rest and during exercise at 3,600 m. To evaluate the role of hypoxemia in this setting we repeated these measurements during a 1-h inhalation of 100% oxygen.

Materials and Methods

Patient Population

Twenty-five male Bolivian patients with CMS and 26 male healthy control subjects born and permanently living in La Paz or its surroundings (3,600-4,000 m) were enrolled in the study. All patients were initially referred to the Instituto Boliviano de Biologia de Altura for CMS symptoms, and the diagnosis was based on the consensus statement on chronic high altitude disease.[2] Inclusion criteria for patients with CMS were excessive erythrocytosis (hemoglobin concentration > 20 g/dL) in the presence of a normal pulmonary function and no history of smoking or working in the mining industry. All subjects had a typical Aymara surname, self-identified as Aymaras (the major indigenous population living in this region), and had a similar socioeconomic background. 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, Switzerland. All studies were performed at the Instituto Boliviano de Biologia de Altura in La Paz (3,600 m).

A complete clinical examination was performed, and the CMS score was determined on the basis of the following signs and symptoms: breathlessness/palpitations, sleep disturbance, cyanosis, dilatation of veins, paresthesia, headache, and tinnitus. A score between 0 and 3 was attributed, with 0 indicating the absence of the symptom, 1 mild, 2 moderate, and 3 severe symptoms. A score > 5 indicates CMS.[2]

Transthoracic Echocardiography

Transthoracic Doppler echocardiography was performed in all participants to rule out structural heart disease. To estimate systolic pulmonary artery pressure, echocardiographic recordings were obtained after 15 min of supine rest with a real-time, phased array sector scanner (Vivid I; General Electric Healthcare Clinical System) equipped with a 2.5 to 3.5 MHz transducer. The recordings were stored on DVD for off-line analysis by two of the investigators (L. P., Y. A.) who were unaware of the subject's identity. All reported values represent the mean of at least three measurements. After tricuspid regurgitation had been localized with Doppler color flow imaging, the peak flow velocity of the transtricuspid jet was measured with the use of continuous-wave Doppler, and the pressure gradient between the right ventricle and the right atrium was calculated using the modified Bernoulli equation.[11,12] Right ventricular to right atrial pressure gradient measurements are the standard method for the noninvasive estimation of pulmonary artery pressure[13] and have been validated against invasive measurements at high altitude.[14] We found that the intraobserver and interobserver variability for the right ventricular to right atrial pressure gradient measurements at this high-altitude location were 5.1% ± 4.6% and 6.0% ± 8.6%, respectively.[4]

Cardiac output was determined by measuring the diameter of the left ventricular outflow tract and the time-velocity integral of its Doppler signal. The left ventricular outflow tract diameter was measured in the parasternal long axis view, and its surface was calculated assuming circular geometry. 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 stroke volume with heart rate. We have previously found that the intraobserver and interobserver variability for cardiac output measurements at this altitude was 10.7% ± 10.2% and 7.2% ± 4.0%, respectively.[4] Left ventricular end-systolic and end-diastolic volumes were measured and ejection fraction was calculated by the modified biplane Simpson method.

Chest Echography

Ultrasound scanning was performed with the subject in the supine or near-supine position by an investigator who was unaware of the subject's group assignment. Using the cardiac probe (2.5-3.5 MHz), 14 sites on each anterior and lateral hemithorax were scanned with the patient holding his breath to prevent respiration-induced movement and double-counting of lung comets. A lung comet was defined as an echogenic, coherent, wedge-shaped signal with a narrow origin from the hyperechogenic pleural line.[10] When a "white lung" pattern was observed in an intercostal space, an arbitrary value of 10 ULCs was assigned for this space. The sum of the number of ULCs measured at each of the 28 sites was calculated. A total number of ≤ 5 ULCs is considered normal.[15]

Exercise Test

Graded semisupine 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 stepwise increases of 25 W every 3 min up to a maximum of 100 W. Left ventricular ejection fraction, right ventricular to right atrial pressure gradient, and cardiac output were assessed at 50 W; ULCs were assessed immediately after cessation of the 100-W effort. In 10 of the 25 patients with CMS and six of the 26 control subjects, body and diaphragmatic movements made it impossible to locate the trans-tricuspidal regurgitation jet and/or assess ULCs during exercise. Thus, in 15 patients with CMS and 20 control subjects complete data at rest and during exercise could be obtained. Heart rate reserve was calculated as predicted maximum heart rate (220 − age) minus heart rate at maximum exercise divided by predicted maximum heart rate × 100. The double product was calculated as heart rate times systolic BP. In representative subgroups of 10 patients with CMS and 12 control subjects, exercise was repeated at the end of a 1-h oxygen inhalation (F_{IO_2} 100%) through a face mask.

Arterial Oxygen Saturation and Carbon Monoxide Diffusing Capacity

Transcutaneous arterial oxygen saturation and heart rate were measured at a fingertip with a pulse oximeter (OxiMax N-595; Nellcor). Carbon monoxide diffusing capacity was measured with the single-breath technique following standard guidelines, as previously described.[4]

Manuscript received January 11, 2011; revision accepted August 3, 2011.

Affiliations: From the Institute of Clinical Physiology (Drs Pratali, Faita, Sicari, and Picano), Pisa, Italy; the Department of Cardiology (Drs Rimoldi, Hutter, Allemann, and Scherrer), University Hospital of Bern, Bern, Switzerland; the Department of Internal Medicine and Botnar Center for Clinical Research (Drs Rimoldi, Rexhaj, and Sartori), Lausanne, Switzerland; the Instituto Boliviano de Biologia de Altura (Drs Salinas Salmòn and Villena), La Paz, Bolivia; and the Facultad de Ciencias (Dr Scherrer), Departamento de Biología, Universidad de Tarapacá, Arica, Chile.

Funding/Support: This work was supported by grants from the Swiss National Science Foundation, the Placide Nicod Foundation, and the Leenards Foundation.

Correspondence to: Claudio Sartori, MD, University Hospital Lausanne, BH 10.640, 1011 Lausanne-CHUV, Switzerland; e-mail: claudio.sartori@chuv.ch

DOI: 10.1378/chest.11-0084

Statistical Analysis

Data were analyzed using the SPSS software package, version 13 (SPSS Inc). Comparisons were made with the paired and unpaired two-tailed Student *t* test as appropriate. Unless otherwise indicated, data are given as mean ± SD. A value of $P < .05$ was considered to indicate statistical significance.

Results

By definition, hemoglobin, hematocrit, and CMS score were significantly higher in patients with CMS than in control subjects (Table 1).

Hemodynamic Function and Extravascular Lung Fluid at Rest

As expected, the arterial oxygen saturation was significantly lower in patients with CMS than in control subjects (Table 1). Pulmonary artery pressure, left ventricular ejection fraction, cardiac output, and the number of ULCs were not different between the two groups.

Hemodynamic Function and Extravascular Lung Fluid During Exercise

During mild exercise at 50 W, the double product and the percentage of estimated maximal heart rate during exercise (58% ± 4% vs 60% ± 7%, patients vs control subjects, $P = .24$) were similar, and left ventricular function remained normal in the two groups, whereas, as expected, the exercise-induced increase in pulmonary artery pressure was more than twofold larger in patients with CMS than in control subjects (19.0 ± 9.8 mm Hg vs 8.4 ± 6.7 mm Hg, $P < .002$) (Table 1). This exaggerated pulmonary artery pressure response to exercise was associated to a roughly threefold greater pulmonary interstitial fluid accumulation in patients with CMS than in control subjects (7.7 ± 4.6 ULCs vs 2.2 ± 4.6 ULCs, $P < .002$) (Fig 1). At the end of exercise, all but one of the 15 patients with CMS, but only four of the 20 control subjects, had an abnormal number (> 5) of ULCs ($P = .002$, patients vs control subjects). Moreover, there existed a significant direct relationship between pulmonary artery pressure and ULCs during exercise ($r = 0.43$, $P = .009$). Heart rate (116 ± 7 beats/min vs 122 ± 7 beats/min, patients vs control subjects, P = not significant [NS]), heart rate reserve (30% ± 6% vs 31% ± 4%, P = NS), and percentage of estimated maximum heart rate (70% ± 6% vs 69% ± 4%, patients vs control subjects, P = NS) during exercise at 100 W were not different between patients and control subjects. There was no relationship between the percentage of estimated maximum heart rate and the number of ULCs ($r = 0.08$, P = NS).

Effects of Oxygen Inhalation on Hemodynamic Function and Extravascular Lung Fluid During Exercise

Oxygen inhalation markedly attenuated the exercise-induced pulmonary hypertension in the patients by 11.6 ± 9.4 mm Hg ($P = .02$), but pulmonary artery pressure during exercise remained significantly higher in patients than in control subjects ($P = .04$) (Fig 2, Table 2). Attenuation of exaggerated pulmonary hypertension markedly decreased exercise-induced

Table 1—*Patient Characteristics, Hemodynamic and Pulmonary Fluid Data in Patients With CMS and Control Subjects at Rest and During Mild Exercise at High Altitude (3,600 m)*

	Rest			Exercise (50 W)		
Characteristic	CMS (n = 15)	Control Subjects (n = 20)	*P* Value	CMS (n = 15)	Control Subjects (n = 20)	*P* Value
Age, y	54 (9)	48 (7)	.07	…	…	…
Hemoglobin, g/L	21.7 (1.3)	16.4 (0.9)	< .0001	…	…	…
Hematocrit, %	66 (5)	50 (3)	< .0001	…	…	…
CMS score	8.0 (2.3)	2.2 (1.9)	< .0001	…	…	…
Systolic BP, mm Hg	131 (14)	129 (13)	.62	170 (24)	163 (20)	.29
Diastolic BP, mm Hg	84 (9)	82 (10)	.58	95 (10)	102 (16)	.24
Heart rate, beats/min	66 (11)	63 (8)	.32	100 (14)	99 (7)	.83
SaO_2, %	83.6 (2.7)	91.0 (3.1)	< .0001	80.3 (5.8)	90.3 (3.2)	< .0001
LVEF, %	63 (8)	66 (6)	.22	68 (7)	67 (9)	.75
Cardiac output, L/min	5.3 (2.1)	4.7 (0.8)	.26	10.1 (2.9)	10.2 (2.2)	.94
RV-RA, mm Hg	27.9 (6.2)	25.0 (5.1)	.14	46.9 (12.4)	33.4 (7.0)	< .001
ULCs	3.6 (4.5)	1.9 (2.8)	.21	11.3 (7.4)[a]	4.1 (3.6)[a]	.002
Double product				17,120 (4,290)	16,260 (2,450)	.49
DLCO/VA, l/min/mmHg/L	6.2 (1.5)	5.7 (1.0)	.37			

Data are expressed as mean (SD). CMS = chronic mountain sickness; DLCO = diffusing capacity of lung for carbon monoxide; LVEF = left ventricular ejection fraction; RV-RA = right ventricular to right atrial pressure gradient; SaO_2 = arterial oxygen saturation; ULC = ultrasound lung comet; VA = alveolar volume.

[a]Measured immediately after cessation of 100-W exercise.

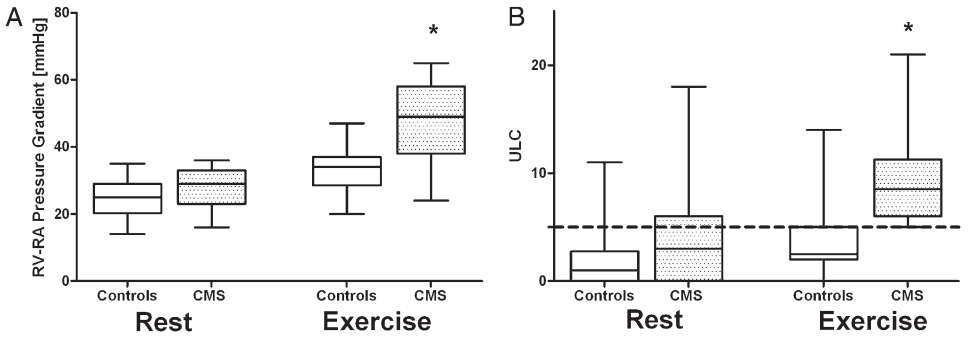

FIGURE 1. Systolic RV-RA pressure gradient and ULCs in 15 patients with CMS and 20 control subjects at rest and during mild exercise at high altitude (3,600 m). A, Systolic RV-RA pressure gradient. B, ULCs. *$P < .01$ vs control subjects. Horizontal lines represent the median; boxes, 25th to 75th percentiles; and T bars, 95% CIs. CMS = chronic mountain sickness; RV-RA = right ventricular to right atrial; ULC = ultrasound lung comet.

interstitial pulmonary fluid accumulation (by 2.7 ± 3.4 ULCs, $P < .05$) in patients with CMS. Oxygen inhalation had no detectable effect on pulmonary artery pressure and interstitial fluid responses to exercise in control subjects.

DISCUSSION

Patients with CMS often suffer from exercise intolerance, but the underlying mechanism is poorly understood.[2] Here, we show that exercise at high altitude rapidly induced pulmonary interstitial fluid accumulation in all patients but one (14 of 15) with CMS and further aggravated the preexisting hypoxemia. In contrast, in healthy high-altitude dwellers exercise did not induce fluid accumulation in the vast majority (16 of 20) of subjects and did not alter arterial oxygenation. Exercise-induced pulmonary interstitial fluid accumulation and hypoxemia in patients with CMS was accompanied by a more than two times larger increase of pulmonary artery pressure than in control subjects, but no evidence of left ventricular dysfunction, suggesting that rapid interstitial lung fluid accumulation during exercise is caused by exaggerated exercise-induced pulmonary hypertension. These findings suggest that exercise intolerance in patients with CMS is caused, at least in part, by exaggerated pulmonary hypertension-induced pulmonary fluid accumulation and hypoxemia.

These data represent the first simultaneous measurements of pulmonary artery pressure, arterial oxygen saturation, and pulmonary interstitial fluid accumulation during exercise at high altitude, to our knowledge. Consistent with previous findings, the exercise-induced increase in pulmonary artery pressure was much larger in patients with CMS than in control subjects.[4] Several studies have shown that

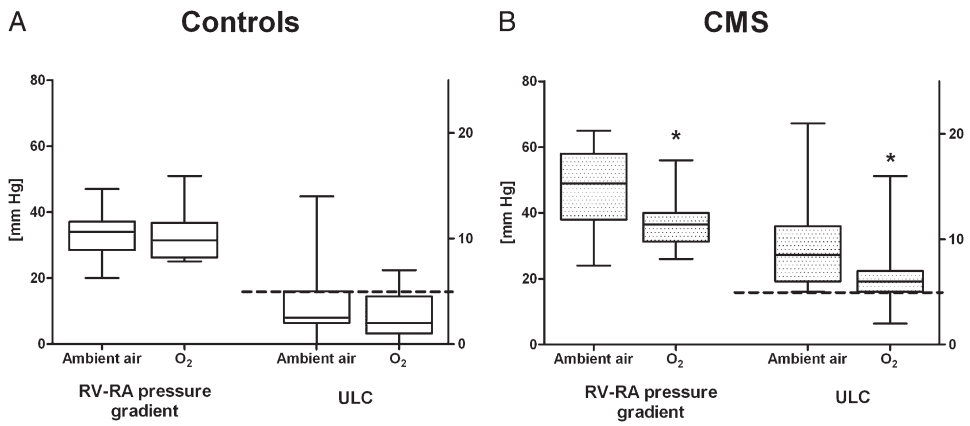

FIGURE 2. Systolic RV-RA pressure gradient and ULCs during mild exercise performed at room air or during 100% oxygen inhalation at high altitude (3,600 m). A, In 10 control subjects. B, In 12 patients with CMS. *$P < .05$ vs ambient air. Horizontal lines represent the median; boxes, 25th to 75th percentiles; and T bars, 95% CIs. The dotted line indicates the upper limit of normal comet occurrence. O_2 = oxygen. See Figure 1 legend for expansion of other abbreviations.

Table 2—*Patient Characteristics and Responses to Exercise (50 W) at Room Air or During Oxygen Inhalation at High Altitude (3,600 m)*

	Exercise at Room Air			Exercise During 100% Oxygen Inhalation		
Characteristic	CMS (n = 10)	Control Subjects (n = 12)	*P* Value	CMS (n = 10)	Control Subjects (n = 12)	*P* Value
Age, y	53 (9)	47 (7)	.06	…	…	…
Hemoglobin, g/L	22.1 (1.2)	16.5 (0.7)	< .0001	…	…	…
Hematocrit, %	68 (4)	50 (2)	< .0001	…	…	…
CMS score	7.8 (2.1)	2.0 (1.8)	.002	…	…	…
Heart rate, beats/min	98 (7)	101 (4)	.24	89 (13)	92 (7)	.57
Sa_{O_2}	82.1 (5.7)	90.6 (2.7)	< .0001	94.6 (1.6)	97.5 (1.3)	.001
LVEF, %	68 (8)	66 (8)	.65	67 (9)	65 (6)	.54
Cardiac output, L/min	10.2 (2.7)	10.2 (2.4)	.99	9.4 (2.5)	9.8 (1.6)	.68
RV-RA, mm Hg	51.5 (8.5)	35.2 (6.0)	< .001	39.9 (7.5)	32.7 (7.6)	.04
ULCs	9.3 (4.0)[a]	3.8 (3.5)[a]	< .01	7.0 (4.3)[a]	2.6 (2.3)[a]	.02
Double product	16,690 (3,620)	16,200 (1,860)	.70	14,500 (4,130)	14,140 (1,210)	.80

Data are expressed as mean (SD). See Table 1 legend for expansion of abbreviations.
[a]Measured immediately after cessation of 100-W exercise.

chest sonography allows quantifying extravascular lung water and that this technique is particularly robust for assessing changes in interstitial fluid.[8-10,16] Here, we found exaggerated exercise-induced hypoxemia and interstitial pulmonary fluid accumulation in patients with CMS. Several lines of evidence suggest that exaggerated pulmonary hypertension contributed to pulmonary interstitial fluid accumulation in patients with CMS. First, left ventricular function was normal and comparable in patients and control subjects. Second, there existed a direct relationship between pulmonary artery pressure and ULCs during exercise. Finally, and most importantly, attenuation by oxygen inhalation of the exaggerated pulmonary hypertension during exercise markedly attenuated pulmonary fluid accumulation in patients with CMS. In line with this concept, exaggerated exercise-induced pulmonary hypertension at simulated high altitude induces ventilation-perfusion inequalities in healthy humans that have been attributed to interstitial edema.[7] In addition to exaggerated pulmonary hypertension, other factors such as increased endothelial permeability are also known to induce interstitial fluid accumulation in the lung.[17] However, it appears unlikely that this mechanism played a role in patients with CMS, since increased vascular permeability would have been expected, resulting in increased interstitial fluid accumulation already under resting conditions.

Although oxygen inhalation markedly attenuated the exercise-induced pulmonary hypertension in patients with CMS, pulmonary artery pressure during exercise still was significantly higher in patients than in control subjects. Together with the previous observation that nitric oxide inhalation did not normalize pulmonary artery pressure in patients with CMS,[4] this finding suggests that in addition to exaggerated hypoxemia, a structural vascular defect contributes to exaggerated exercise-induced pulmonary hypertension in patients with CMS.

Limitations

We used the same absolute workload in all participants and did not use a subjective assessment of exercise intensity (Borg scale) in these studies. Patients with CMS tended to be slightly older and were more hypoxemic than control subjects. Even though the percentage of the maximal heart rate during exercise was similar in the two groups, we cannot exclude the possibility that differences in relative workload may have contributed to the large differences of exercise-induced pulmonary hypertension and pulmonary interstitial fluid accumulation between the two groups.

Conclusions

These findings provide the first direct evidence that exercise induces rapid interstitial lung fluid accumulation and hypoxemia in patients with CMS that appear to be at least in part related to exaggerated pulmonary hypertension. We suggest that this problem contributes to exercise intolerance in patients with CMS.

Acknowledgments

Author contributions: *Dr Pratali:* contributed to the clinical examinations, including echocardiography, and exercise testing, and wrote a draft of the paper.
Dr Rimoldi: contributed to the study design, data analysis and interpretation, and final writing of the paper. He also participated in the clinical examinations.
Dr Rexhaj: contributed to the clinical examinations and revising the manuscript.
Dr Hutter: contributed to the clinical examinations, echocardiography, and exercise testing and revising the manuscript.
Dr Faita: contributed to the clinical examinations and revising the manuscript.

Dr Salinas Salmòn: contributed to the clinical examinations and revising the manuscript.
Dr Villena: contributed to the clinical examinations, recruiting patients and control subjects, and revising the manuscript.
Dr Sicari: contributed to the funding of the study and drafting of the manuscript.
Dr Picano: contributed to the funding of the study and drafting of the manuscript.
Dr Allemann: contributed to the clinical examinations, including echocardiography, and revising the manuscript.
Dr Scherrer: contributed to the design of the study, data analysis and interpretation, and final writing of the manuscript.
Dr Sartori: contributed to the design of the study, data analysis and interpretation, and final writing of the manuscript.
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.
Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.
Other contributions: We thank Catherine Romero for invaluable help with these studies.

References

1. Peñaloza D, Sime F. Chronic cor pulmonale due to loss of altitude acclimatization (chronic mountain sickness). *Am J Med*. 1971;50(6):728-743.
2. 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.
3. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. *Circulation*. 2007;115(9):1132-1146.
4. Stuber T, Sartori C, Schwab M, et al. Exaggerated pulmonary hypertension during mild exercise in chronic mountain sickness. *Chest*. 2010;137(2):388-392.
5. Cremona G, Asnaghi R, Baderna P, et al. Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study. *Lancet*. 2002;359(9303):303-309.
6. Maggiorini M, Mélot C, Pierre S, et al. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. *Circulation*. 2001;103(16):2078-2083.
7. West JB. Left ventricular filling pressures during exercise: a cardiological blind spot? *Chest*. 1998;113(6):1695-1697.
8. Agricola E, Bove T, Oppizzi M, et al. "Ultrasound comet-tail images": a marker of pulmonary edema: a comparative study with wedge pressure and extravascular lung water. *Chest*. 2005;127(5):1690-1695.
9. Jambrik Z, Monti S, Coppola V, et al. Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. *Am J Cardiol*. 2004;93(10):1265-1270.
10. Picano E, Frassi F, Agricola E, Gligorova S, Gargani L, Mottola G. Ultrasound lung comets: a clinically useful sign of extravascular lung water. *J Am Soc Echocardiogr*. 2006; 19(3):356-363.
11. Scherrer U, Vollenweider L, Delabays A, et al. Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med*. 1996;334(10):624-629.
12. Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med*. 2002;346(21):1631-1636.
13. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*. 2001;104(23):2797-2802.
14. 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.
15. Lichtenstein D, Mézière G, Biderman P, Gepner A, Barré O. The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. *Am J Respir Crit Care Med*. 1997;156(5): 1640-1646.
16. Fagenholz PJ, Gutman JA, Murray AF, Noble VE, Thomas SH, Harris NS. Chest ultrasonography for the diagnosis and monitoring of high-altitude pulmonary edema. *Chest*. 2007; 131(4):1013-1018.
17. Sartori C, Rimoldi SF, Scherrer U. Lung fluid movements in hypoxia. *Prog Cardiovasc Dis*. 2010;52(6):493-499.