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Reduced exercise tolerance in Monge patients is associated with increased extravascular lung water: a stress echo study

Abstract

Chronic mountain sickness is characterized by exaggerated exercise-induced pulmonary hypertension. Evidence suggests that exercise may cause lung fluid accumulation at high altitude. We hypothesized that, in patients with chronic mountain sickness (CMS), exercise causes lung fluid accumulation.

Methods: In La Paz (Bolivia) 3600 m s.l. we evaluated 31 male CMS and 30 male healthy high-altitude dwellers (C) (CMS 54 ± 10 years vs. C 44 ± 11 years, p= .02) and we assessed systolic right-ventricular-right atrial pressure gradient, right and left systolic and ventricular function and ultrasound lung comets (ULCs, a marker of lung fluid accumulation) at rest and during mild bicycle exercise (up to 50W) and during oxygen inhalation (Fi O^2 100%).

Results: The CMS patients presented lower value of oxygen saturation at rest and peak of stress in comparison with C and an exaggerated systolic right-ventricular-right atrial pressure gradient response to exercise associated with a roughly 4-fold greater increase in UCLs in comparison with C (CMS +8±4 vs. C +2±5, p<.004). Right ventricular function (TDI on tricuspid annulus) decreased during exercise in CMS but increased in controls (CMS-1.8.±2.6 vs C +2.2±3.3, p=0.03). Left ventricular function remained unaltered in the 2 groups. During oxygen inhalation there were not significantly differences of left ventricular systolic and diastolic function, in the right-ventricular-right atrial pressure gradient and in terms of extravascular lung water.

Conclusions: we provide a direct evidence in CMS patients that exaggerated exercise-induced pulmonary hypertension causes rapid lung fluid accumulation and this response is related at least in part to hypoxemia.. We speculate that in patients with CMS these two phenomena contribute to reduced exercise performance.

Background

Chronic mountain sickness (CMS) is a disease that can develop in high altitude dwellers as a sign of loss of adaptation to hypoxia. It is also known as 'Monge's disease', after its first description in 1925 by Carlos Monge (1). CMS is a syndrome that begins insidiously in adult life and is characterized by erythrocytosis, hypoxemia and impaired mental function where in the end stage right heart failure associated to pulmonary hypertension (2). The most frequent symptoms and signs of CMS are headache, dizziness, tinnitus, breathlessness, palpitations, sleep disturbance, fatigue, anorexia, mental confusion, cyanosis, and dilation of veins (3). The actual mechanisms may cause this clinical syndrome remain unknown. Recently it was demonstrated that CMS patients have an exaggerated pulmonary hypertension response during a mild exercise in absence of lung anatomical and functional disease (4). Lung fluid accumulation and/or ventricular interdependence due to augmented pulmonary hypertension may play a role. Chest sonography has been shown to effectively detect pulmonary edema and quantify extravascular lung water through the sign of "ultrasound lung comets" (ULCs, 5). The technique requires basic 2D technology, and has been proved useful in hospitalized patients with heart failure (6-8), as well as in extreme physiology settings studied in logistically hostile environments, such as in a boat soon after apnoea diving (9) or at high altitude (10-11). The aim of this study was to assess the presence of extravascular lung water, right-ventricular-right atrial pressure gradient, right and left ventricular function, during mild bicycle exercise in CMS patients compared with a control group. Oxygen inhalation (Fi 0^2 100%) in rest condition and during a mild exercise was tested in the two groups to investigate the reversibility of pulmonary hypertension.

Patient population

31 male Bolivian patients with diagnosis of primary CMS (mean age 54±10 years) and 30 male healthy control subjects (mean age 46±11 years) born and permanently living in La Paz or around (3600-4000 ms.l.) were enrolled in the study. All the patients were initially referred to the Instituto Boliviano de Altura for CMS symptoms and the diagnosis was based on the consensus statement on

chronic high altitude disease (3). Inclusion criteria for CMS patients were: erythrocytosis (hemoglobin (hb) value > 20 Mg/dl), normal pulmonary function studies, and no history of lung injury from occupational exposure. The institutional review boards on human investigation of the University of San Andres, La Paz, Bolivia, University of Lausanne, Switzerland , had approved the experimental protocol and all subjects provided written informed consent. All studies were performed at Instituto Boliviano de Biologia de Altura in La Paz (3600 m). A complete clinical exam was performed and CMS score was determined (3) on the basis of the following signs and symptoms: breathless/palpitations, sleep disturbance, cyanosis, dilatation of veins, paresthesia, headache, tinnitus; a score between 0 and 3 was attributed, with 0 indicating the absence of symptoms, 1 mild, 2 moderate, 3 severe symptoms. The CMS score allowed us to determine the severity of CMS as mild (score 6-10), moderate (score 11-14) or severe (LLS > 15).

Blood pressure and heart rate were measured at rest and at different stages of exercise. Pulse oxymetry measurements were carried out with the subject at rest with hands warmed after 30 s of signal stabilization, for an average of three consecutive measurements (Pulse-oximeter Model Tuff-Sat, Datex-Ohmeda, General Electrics Healthcare Clinical System).

Transthoracic echocardiography

Echocardiography was performed using a portable echo machine (Vivid I, General Electric Healthcare Clinical System) with a cardiac probe (2.5-3.5 MHz). Left ventricular end-systolic, end-diastolic volumes were measured and ejection fraction was calculated by the modified biplane Simpson's method. The longitudinal function of the left ventricle was evaluated by mitral annular excursion on the lateral wall (MAPSE) (12) Using the pulsed wave Doppler technique from the apical four-chamber view, the inflow over the mitral valve was obtained, with the sample volume placed at the level of the tips of the mitral leaflets. The E- and A-wave velocities, the E/A ratio and the E wave deceleration time were calculated from the last three consecutive cardiac cycles. PW tissue Doppler imaging (DTI) was performed in the apical views to acquire the early diastolic annular velocity (e'). The mitral inflow E velocity to tissue Doppler e´ (E/e´) ratio was calculated

and this ratio plays an important role in the estimation of LV filling pressures (13). When a regurgitant tricuspid flow was sampled, we obtained peak trans-tricuspidal jet velocity and calculated the systolic right-ventricular to right-atrial gradient (14) Right ventricular function was evaluated with tricuspid annular plane excursion (TAPSE) and using peak systolic velocity with tissue Doppler imaging at the tricuspid annulus (RV-S') (15). Cardiac output was also determined by measuring the diameter of left-ventricular outflow tract and its time-velocity integral. The left ventricular outflow tract diameter was measured in 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 5-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 stroke volume by heart rate (14). All measurements were performed following the recommendations of the European Association of Echocardiography (16).

Chest echography

As described in (5), a lung comet is defined as an echogenic, coherent, wedge-shaped signal with a narrow origin from the hyperechoic pleural line. Examination with ultrasound consisted in scanning 28 chest sites on the anterior thorax and then summing up the number of ULCs found at each site. The total number of ULCs yielded the "comet score", integrating the number of ULCs in any intercostal space (the severity) with the number of intercostal spaces showing an abnormal signal (the extent). When a "white lung" pattern was observed in a given intercostal space, we assigned the arbitrary "plateau" value of 10 ULCs for quantification purposes. A number of ULCs ≤ 5 is a normal echographic chest pattern; healthy athletes may have a small number of ULCs, especially when confined laterally to the last intercostal spaces above the diaphragm (8). Ultrasound scanning was performed with subjects in the supine or near-supine position and the anterior and lateral chest was scanned on the right and left hemithorax. The chest exam was performed with the cardiac probe (2.5-3.5 MHz).

Echo-Exercise Test

Graded semi-supine exercise echo was performed on a bicycle ergometer (Ergoline 900EL, Ergoline Company, Bitz, Germany) with a 30° rotation to the left, starting at an initial workload of 25 watts lasting for 3 min; thereafter the workload was increased stepwise by 25 watts at 3-min intervals. Left ventricular ejection fraction, left ventricular filling pressure (E/e' ratio) (17), right ventricular function (TAPSE and RV-S'), right-ventricular to right-atrial gradient and cardiac output were estimated during mild exercise at 50 W. During exercise, at least one technically acceptable measurement of right-ventricular to right-atrial gradient could be obtained in 87 % of subjects with valuable baseline measurements. In the remaining subjects body and diaphragmatic movements made it impossible to locate the trans-tricuspidal regurgitation jet during exercise. Two-dimensional echocardiographic monitoring was performed throughout and up to 5 min after the end of stress.

All the recordings were stored on DVD for off-line analysis by two operators (LP, YA) who were unaware of the patient's group assignment. All reported values represent the mean of at least three measurements.

Oxygen inhalation

Eleven controls and 21 CMS patients were submitted to one-hour oxygen inhalation (Fi O^2 100%) through face mask with reservoir (Venturi mask) and the oxygen was administered in order to reach a saturation > 95%. All these subjects was underwent a rest and exercise echocardiogram (50 W) and a chest echo exam. The same measurements obtained without oxygen inhalation were measured after oxygen inhalation

Statistical analysis

Continuous variables are expressed as mean ± standard deviation values. Categorical variables are presented as counts and percentages. Patient characteristics were compared using ANOVA factorial analysis or the chi-square test for categorical data. All statistical analyses were performed using the SPSS software package version 13 (SPSS Inc, Chicago, Illinois).

Results

Clinical and echocardiographic evaluation

The study population characteristics are shown in Table 1. CMS patients had a higher CMS score than controls. None of the CMS patients complained for dyspnea at rest or presented heart failure symptoms and 20 patients were in NYHA class I and 11 in NYHA class II. By definition, hemoglobin and hematocrit levels were higher in CMS patients than controls. In rest condition the two groups were not significantly different as regard to left ventricular systolic and diastolic function and right ventricular function. As expected the right-ventricular-right atrial pressure gradient was higher in CMS patients than in controls (table1).

Echo-Exercise Test

During mild exercise (up to 50 w), the double product was not different in the two groups (controls 14941±4835 mmHg*bpm vs CMS pts 12589±8371 mmHg*bpm, p= n.s.) while the arterial oxygen saturation was lower in CMS patients than in controls (81.8±5 % vs 90±3 %, p<.0001) (fig 1). CMS subjects presented a significant increase in right-ventricular-right atrial pressure gradient, three time higher than in controls (+18.3±7 mmHg vs +5±12 mmHg, p=0.003) (fig 2), associated to a significant increase in ULCs (CMS +8± 4 vs. C +2 ± 5, p= .004) (fig 3). The ejection fraction (C: +1 ± 12%; CMS +5±6%; p=n.s.), and the cardiac output (C +3.3±3 l/min; CMS +3.3±3 l/min p= n.s.) increased similarly in the two groups. At the peak of the mild exercise, in the two groups, a slight increase in E/e' ratio (normal value < 15) was observed reflecting a mild but not pathological increase in the left ventricular filling pressure (C 7.3±1.8, CMS 9±5; p=n.s.). The right ventricular function, evaluated by TAPSE (normal value >17 cm/sec) and by RV-S' (normal value >10 cm/sec), was normal at the peak of stress in the two groups (TAPSE: C 27 ±5 mm, CMS 27±5 mm; RV-S': C 15±3 cm/s; CMS 12±2 cm/s). Although the RV-S' value was normal in the two groups we observed an increase of longitudinal velocity excursion in control subjects and a decrease in CMS patients (Delta RV-S') (C: + 2± 3 cm/s; CMS: - 1.7± 2 cm/s, p=.004).

Oxygen inhalation

In the subset undergoing oxygen inhalation (21 CMS and 11 C) no significant difference between the two groups as regards arterial oxygen saturation, left ventricular systolic and diastolic function, right-ventricular-right atrial pressure gradient and extravascular lung water was observed at rest and at peak stress (table 2)

Discussion

The results of this study are consistent with previous reports demonstrating that CMS patients show an abnormal increase in PAPS with respect to healthy highlander dwellers (4) but, at the best of our knowledge it is demonstrated, for the first time a rapid lung fluid accumulation associated to decrease in oxygen saturation, increase in PASP, with normal left ventricular function and normal left ventricular filling pressure here identify by the ratio E/e'.

Comparison with preview studies

Earlier studies on cardiopulmonary response to exercise in Andean population demonstrated an abnormal increase in pulmonary pressure invasively assessed in CMS patients in comparison with healthy high altitude dwellers during a mild (50 w) supine exercise (18-19). Recently Stuber reported high value of PAPS in CMS patients in comparison with controls highlanders evaluated by Doppler echocardiography both in rest conditions and during mild exercise (up to 50 w) (4). The authors showed a decrease in PAPS after nitric oxide inhalation similarly in CMS patients and in the control group even if the PAPS in CMS patients remained higher than in controls. These results confirm that pulmonary vascular remodelling causes PASP increase in CMS patients (20). Maignan evaluated CMS patients without overt cardiac heart failure symptoms at rest with echocardiography and showed high PAPS values and right ventricle dilatation without impairment in right and left ventricle function (21). Recently, chest sonography has been shown to effectively detect pulmonary edema and quantify extravascular lung water through the sign of (ULCs) originating from water-thickened interlobular septa (5-9) and this method was used in high altitude setting to evaluate patients with clinical diagnosis of high altitude pulmonary edema (10). In this

study the patients with clinical diagnosis of high altitude pulmonary edema presented a higher ULC Score and lower oxygen saturation than control subjects (10).

Hypotheses of pathophysiological mechanisms

In patients with left ventricular dysfunction, the exercise may increase left ventricular end-diastolic filling pressure, pulmonary artery and wedge pressure causing ultrastructural changes in the walls of pulmonary capillaries resulting in high permeability type of alveolar edema (22-25). But interstitial lung edema is observed during ascent at medium-high altitudes even in completely asymptomatic subjects in presence of normal left ventricular function (26-27). On the basis of the presents results we can speculate that the exaggerated exercise induced interstitial fluid accumulation and pulmonary hypertension in CMS patients could be caused by a more severe hypoxemia during a mild exercise. In CMS subjects we observed also a significant decrease in right ventricular function evaluated by peak systolic tissue Doppler velocity on tricuspid annulus where in control subjects we observed a increase of the basal value at peak of stress. The decreasing in right ventricular dysfunction induced with exercise should be caused by an exaggerated increase in PASP present in CMS patients (4).

Study limitations

In our study, ULC assessment was performed by an independent reader blinded to subject identity and study conditions (before and after exercise with or without oxygen inhalation). Therefore, the information obtained can be considered methodologically robust, especially if we take into account that the technique was evaluated in a particularly favourable experimental setting, with each subject acting as his/her own control. As always, ultrasound is ideal as a “delta” technique (difference between peak and basal condition), especially when core lab, single-reader, strict standardization of acquisition by a trained certified sonographer, pre-specified interpretation criteria, and blinding to study conditions are implemented, as recommended by the American Society of Echocardiography for use of echocardiography in research protocols (28). The ULCs score is derived summing each comet sign in each intercostals space. During breathing a comet sign can move from one position to

another in the same intercostals space with the result that the same comet sign is summed several times in the ULC score calculation. This phenomenon can be accentuated in the post exercise phase. To eliminate this mistake, we evaluate the presence of ULC while patients breath holding.

Conclusions

This study provides the first direct evidence in humans that exaggerated exercise-induced pulmonary hypertension is associated to rapid lung fluid accumulation and this problem is related at least in part to hypoxemia. We speculate that in patients with CMS these two phenomena contribute to reduced exercise performance.

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Table 1 Patients characteristics and echocardiogram, thorax echo measurements at rest

	CMS	Controls	p value
N subjects	31	30	
Age (years)	54±10	45±10	**.02**
Hb (g/dl)	16±1	21±1	<.0001
Hematocrit (%)	65±5	50±9	<.0001
CMS score	7±2	2±2	<.0001
Sat O2 (%)	83±4	91±3	**.001**
SBP rest (mmHg)	128±11	130±16	n.s.
HR rest (bpm)	68±9	63±8	n.s.
EF (%)	63±6	66±6	n.s.
E/e'septal	6.7±2	6.5±1	n.s.
TAPSE (mm)	23±4	22±4	n.s.
RV-S' (cms^{-1})	13±2	13±3	n.s.
Cardiac output (l/min)	5.3±2	4.6±1	n.s.
Systolic RV-RA pressure gradient (mmHg)	28.2±6	24.3±5	**.02**
ULCs	3.3±3.6	1.9±3	n.s.

Hb: hemoglobin; CMS: chronic mountain sickness; Sat O2: oxygen saturation; SBP: systolic blood pressure; HR: heart rate; EF: ejection fraction; E/e' septal: mitral inflow early diastolic velocity/ mitral annulus velocity by TDI ; TAPSE: tricuspid annular plane excursion; RV-S': peak systolic velocity with tissue Doppler imaging at the tricuspid annulus; RA-RV: right-ventricular to right-atrial; ULCs: ultrasound lung comets.

Table 2
Results of echocardiogram and thorax echo studies at rest and peak of exercise during oxygen inhalation

	CMS rest	Controls rest	p value	CMS exercise	Controls exercise	p value
N subjects	21	11				
Age (years)	55±9	47±7	**.01**			.
Sat O2 (%)	97±1	99±1,4	**.001**	95±1,6	97±1,3	**.001**
HR (bpm)	59.5±10	54.5±7	n.s	91±11	90±7	n.s.
SBP rest (mmHg)	134±14	131±6	n.s.	165±23	156±11	n.s.
EF (%)	61±9	67±4	n.s.	65±8	64±5	n.s.
E/e'septal	4.8±2	5.5±2	n.s.	7.7±2	7±1	n.s.
TAPSE (mm)	24±4	25.7±4	n.s.	24±2	27±4	n.s.
RV-S' (cms^{-1})	11±1	11±1	n.s.	12±2	14±2	**.007**
Cardiac output (l/min)	4.8±1	4.2±1	n.s.	9.4±2	9.8±1	n.s.
RA-RV pressure gradient (mmHg)	20±6	22±4	n.s.	32 ±7	37±8	n.s.
ULCs				5.4±2.6	2.3±2.2	n.s.

CMS: chronic mountain sickness; Sat O2: oxygen saturation; SBP: systolic blood pressure; HR: heart rate; EF: ejection fraction; E/e' septal: mitral inflow early diastolic velocity/ mitral annulus velocity by TDI ; TAPSE: tricuspid annular plane excursion; RV-S': peak systolic velocity with tissue Doppler imaging at the tricuspid annulus; RA-RV: right-ventricular to right-atrial; ULCs: ultrasound lung comets.