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RV Contractility and Exercise-Induced Pulmonary Hypertension in Chronic Mountain Sickness

A Stress Echocardiographic and Tissue Doppler Imaging Study

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OBJECTIVES The aim of this study was to evaluate right ventricular (RV) and left ventricular function and pulmonary circulation in chronic mountain sickness (CMS) patients with rest and stress echocardiography compared with healthy high-altitude (HA) dwellers.

BACKGROUND CMS or Monge's disease is defined by excessive erythrocytosis (hemoglobin >21 g/dl in males, 19 g/dl in females) and severe hypoxemia. In some cases, a moderate or severe increase in pulmonary pressure is present, suggesting a similar pathogenesis of pulmonary hypertension.

METHODS In La Paz (Bolivia, 3,600 m sea level), 46 CMS patients and 40 HA dwellers of similar age were evaluated at rest and during semisupine bicycle exercise. Pulmonary artery pressure (PAP), pulmonary vascular resistance, and cardiac function were estimated by Doppler echocardiography.

RESULTS Compared with HA dwellers, CMS patients showed RV dilation at rest (RV mid diameter: 36 ± 5 mm vs. 32 ± 4 mm, CMS vs. HA, $p = 0.001$) and reduced RV fractional area change both at rest (35 ± 9% vs. 43 ± 9%, $p = 0.002$) and during exercise (36 ± 9% vs. 43 ± 8%, CMS vs. HA, $p = 0.005$). The RV systolic longitudinal function (RV-S′) decreased in CMS patients, whereas it increased in the control patients ($p < 0.0001$) at peak stress. The RV end-systolic pressure-area relationship, a load independent surrogate of RV contractility, was similar in CMS patients and HA dwellers with a significant increase in systolic PAP and pulmonary vascular resistance in CMS patients (systolic PAP: 50 ± 12 mm Hg vs. 38 ± 8 mm Hg, CMS vs. HA, $p < 0.0001$; pulmonary vascular resistance: 2.9 ± 1 mm Hg/min/l vs. 2.2 ± 1 mm Hg/min/l, $p = 0.03$). Both groups showed comparable systolic and diastolic left ventricular function both at rest and during stress.

CONCLUSIONS Comparable RV contractile reserve in CMS and HA suggests that the lower resting values of RV function in CMS may represent a physiological adaptation to chronic hypoxic conditions rather than impaired RV function. (Chronic Mountain Sickness, Systemic Vascular Function [CMS]; NCT01182792) (J Am Coll Cardiol Img 2013;6:1287–97) © 2013 by the American College of Cardiology Foundation

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Chronic mountain sickness (CMS), a syndrome that begins insidiously during adult life, is characterized by excessive erythrocytosis, severe hypoxemia, and, in some cases, moderate or severe pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive heart failure. The physiopathological mechanisms of CMS remain unsettled, but chronic alveolar hypoventilation is the likely initial mechanism of a series of events leading to progressive deterioration of adaptation and development of CMS (1). On rest echocardiography, CMS patients show normal left ventricular (LV) function, pulmonary arterial hypertension associated with right heart dilation, and an increased right ventricular (RV) Tei index (2). Mild exercise induces an exaggerated increase in pulmonary pressure, interstitial lung fluid accumulation, and hypoxemia in those with CMS compared with matched healthy high-altitude (HA) dwellers (3,4). The contribution of RV function to overall cardiac performance increases with exercise, which makes the study of RV function during exercise very interesting. However, the marked change in RV load may be a potential confounder of all echocardiographic measurements related to contractility. Therefore, the aim of this study was to evaluate noninvasive pulmonary vascular behavior and LV and RV function at rest and during mild exercise. Several echocardiographic Doppler measurements were used together with a surrogate of contractility as the end-systolic pressure-volume relationship (5,6) in subjects with CMS and in a control group of healthy HA dwellers.

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ABBREVIATIONS AND ACRONYMS

CMS = chronic mountain sickness

e′ = peak early diastolic tissue Doppler imaging velocity of the mitral annulus

E = peak velocity of early mitral inflow

E/e′ = ratio of peak velocity of early mitral inflow to mitral annular early diastolic peak velocity

HA = high altitude

Hb = hemoglobin

LV = left ventricular

PAP = pulmonary arterial pressure

RV = right ventricular

RV-ESPAR = right ventricular end-systolic pressure-area relationship

RV-S′ = tissue Doppler imaging peak systolic velocity of the lateral tricuspid valve annulus

TDI = tissue Doppler imaging

tric e′/a′ = ratio of early (e′) and late (a′) diastolic tissue Doppler imaging tricuspid peak annular velocities

METHODS

Study patients. The population consisted of 46 Bolivian male patients with CMS and 40 healthy male HA dwellers of similar age consecutively enrolled in the study. All study subjects were born and permanently living in or around La Paz, Bolivia (3,600 to 4,000 m sea level). They had typical Aymara surnames, identifying themselves as Aymaras, and had similar socioeconomic backgrounds. All the patients were initially referred to the Instituto Boliviano de Biologia de Altura, and the diagnosis of CMS was based on the consensus statement on chronic HA diseases (7). Inclusion criteria for CMS patients included erythrocytosis (hemoglobin [Hb] value ≥20 mg/dl), 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. All patients included in the study had Hb value ≥21 mg/dl at the time of CMS diagnosis. At study entry, however, some patients had Hb values below this threshold value because they had been treated with bloodletting. A complete clinical examination was performed on all subjects, and the CMS score was determined on the basis of the following signs and symptoms: breathlessness/palpitations, sleep disturbance, cyanosis, dilation of lower limb veins, paresthesia, headache, and tinnitus. A score between 0 and 3 was attributed, with 0 indicating an absence of CMS, 1 indicating mild, 2 indicating moderate, and 3 indicating severe signs and symptoms of CMS (5). A CMS score >5 is required for diagnosis, and the grading of the severity of CMS is as follows: mild (score of 6 to 10), moderate (score of 11 to 14), or severe (score >15).

Blood pressure and heart rate were measured at rest and at different stages of exercise. Pulse oximetry measurements were carried out at the fingertip after at least 10 min of rest, with warmed hands, and after 30 s of signal stabilization for an average of 3 consecutive measurements (Pulse-oximeter Model Tuff-Sat, Datex-Ohmeda, General Electric Healthcare Clinical System, Finland Oy, Helsinki, Finland). 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, Lausanne, Switzerland, and registered (NCT01182792). All studies were performed at the Instituto Boliviano de Biologia de Altura in La Paz, located at an altitude of 3,600 m sea level.

Echocardiographic examination and measurements. Echocardiography was performed using a portable fully equipped echocardiography unit (Vivid I, General Electric Healthcare Clinical System) with a

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cardiac probe (2.5 to 3.5 MHz). All recordings were stored on DVD for offline analysis by 2 operators (L.P., Y.A.) who were blinded to the patient's group assignment. All reported values represent the mean of at least 3 measurements. 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 4-chamber view, the inflow over the mitral valve (E and A velocities) was obtained, with the sample volume placed at the level of the tips of the opened mitral leaflets. Tissue Doppler imaging (TDI) was performed in 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 4-chamber view, a 5-mm sample volume was placed at the lateral and septal borders of the mitral annulus. Early diastolic velocities (peak early diastolic tissue Doppler imaging velocity of the mitral annulus [e′]) at the lateral and septal borders of the mitral annulus were measured together with the ratio of peak velocity of early mitral inflow to mitral annular early diastolic peak velocity (E/e′). The ratio between E wave and lateral TDI signal (lateral E/e′), and the mean values of lateral and septal borders (lateral-septal E/e′) have the best correlations with LV filling pressures and invasive indexes of LV stiffness in subjects with a normal LV ejection fraction (8,9). Cardiac output was determined by measuring the diameter of the LV outflow tract and the time-velocity integral of its Doppler signal. The LV 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 LV outflow tract time velocity integral by the cross-sectional area. Cardiac output was then obtained by multiplying stroke volume by heart rate (10). When a regurgitant tricuspid flow was sampled, the peak transtricuspidal jet velocity was obtained, and the systolic RV/right atrial gradient was calculated (11). Systolic pulmonary artery pressure (PAP) was estimated using the maximal velocity of the tricuspid regurgitation jet (V), assessed by continuous Doppler and transformed by the modified Bernoulli equation ($4 \times V^2$) to which an estimated central venous pressure of 5 mm Hg was added (12). The mean PAP was calculated as: $0.6 \times PAP + 2$ (13). Left atrial pressure was estimated from the ratio of the Doppler mitral E peak flow velocity-wave to the DTI mitral annulus early diastolic velocity e′ (i.e., left atrial pressure = 1.9 + 1.24 E/e′) (14). Pulmonary vascular resistance was calculated as: (mean PAP − left atrial pressure)/cardiac output (15). RV basal, mid-cavity dimension, RV end-diastolic area, and RV end-systolic area were obtained on an apical RV focused view. The RV function was evaluated by the percentage of RV fractional area change, defined as: (RV end-diastolic area − RV end-systolic area)/RV end-diastolic area × 100 (normal value >35%) (11). The RV systolic function was also assessed by TDI peak systolic velocity of the tricuspid annulus (RV S′, normal value: >10 cm/s) and RV-TDI myocardial acceleration during isovolumic contraction: peak isovolumic myocardial velocity divided by time to peak velocity (lower reference limit, 2.2 m/s^2) (11). TDI velocities were obtained 1 cm more apically than the tricuspid valve annulus within the RV lateral wall and adjusted to cover the longitudinal excursion both in 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 (11,16). The RV diastolic function was evaluated by TDI velocities on the tricuspid annulus. We measured early e′ and late a′ diastolic tricuspid annular velocities and computed the e′/a′ ratio (tric e′/a′) (normal value <1.9) (11). A composite RV myocardial performance index using the TDI method was also measured, as reported by Tei et al. (17). This parameter allowed a global estimation of both systolic and diastolic function of the right ventricle. All measurements were performed following the recommendations of the European Association and American Society of Echocardiography (10,11,16). The end-systolic pressure-volume relationship was calculated as for the left ventricle (5) but area was substituted as a surrogate of volume and the RV end-systolic area ratio (RV-ESPAR [mm Hg/cm^2]) was calculated (6). We measured the ratio of systolic PAP to cardiac output to normalize pulmonary pressure increases for increases in cardiac output (15).

Exercise stress echocardiography. Exercise stress echocardiography was conducted using a semisupine bicycle ergometer (Ergoline 900EL, Ergoline Company, Bitz, Germany) with an approximately 30° rotation to the left. After a warm-up phase of 2 to 3 min at 0 W, the exercise started at an initial workload of 25 W, which was maintained for 3 min and followed by a second workload of 50 W. All of the following were estimated during the last step of this mild exercise: LV ejection fraction, LV filling pressure (lateral E/e′ ratio and lateral-septal E/e′ ratio), RV middle dimensions, RV systolic and

diastolic function (RV fractional area change, RV-S′, RV-TDI myocardial acceleration during isovolumic contraction, tric e′/a′, RV Tei index), systolic PAP, mean PAP, pulmonary vascular resistance, mean PAP/cardiac output, and RV-ESPAR. Two-dimensional echocardiographic monitoring was performed throughout and up to 5 min after the end of the exercise test.

Statistical analysis. Statistical analyses were performed using the SPSS software package version 20 (SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD. Categorical variables are presented as count and percentage. Comparisons between groups were performed using an unpaired Student *t* test, when appropriate. Differences between rest and exercise results were assessed by a paired Student *t* test. For variables not normally distributed, the 2-sample Wilcoxon rank sum (Mann-Whitney) test was used for comparison, and the median and relative interquartile range were reported. Regression analysis with Pearson's test was also used to evaluate the relationship between the 2 continuous variables. Univariate comparisons between CMS patients with and without an exercise-induced increase in systolic PAP and pulmonary vascular resistance were made with a chi-square, 2-sample *t* test, or Mann-Whitney *U* test, as appropriate. The association of selected variables with the development of exercise-induced increase in systolic PAP and pulmonary vascular resistance was assessed by logistic regression analysis using univariate and stepwise multivariate procedures. The following variables were included into the analysis: age, oxygen saturation, resting echocardiographic parameters (LV ejection fraction, cardiac output, RV fractional area change, TDI systolic LV and RV waves, lateral-septal E/e′, RV tric e′/a′), stress echocardiographic parameters (peak ejection fraction, peak cardiac output, peak RV fractional area change, peak TDI systolic and diastolic LV and RV wave), peak workload, and peak oxygen saturation. These variables were selected according to their clinical relevance and potential impact on systolic PAP and/or pulmonary vascular resistance. Those variables significant on univariate analysis ($p \leq 0.1$) were entered into a multivariate analysis to determine independent predictors of the peak pulmonary vascular resistance. The odds ratio with the corresponding 95% confidence interval was estimated.

RESULTS

Clinical characteristics. The study population characteristics are shown in Table 1.

Table 1. Clinical and Hematological Characteristics

	CMS Patients	HA Dwellers	p Value
Age, yrs	51 ± 10	48 ± 8	0.06
O_2 saturation, %	85 (82–89)	90.6 (89–92)	<0.0001
HR, beats/min	66 ± 10	65 ± 7	0.8
SBP rest, mm Hg	132 ± 15	127 ± 12	0.2
DBP rest, mm Hg	83 ± 9	80 ± 8	0.8
CMS score	7.2 (5.0–9.7)	1.8 (0.0–3.0)	<0.0001
Hb, g/dl	21.5 (20.7–22.5)	17.2 (16.5–17.9)	<0.0001
Hct, %	63.3 (60–67)	49.7 (48–52)	<0.0001

Values are mean ± SD or median (relative interquartile range).
CMS = chronic mountain sickness; DBP = diastolic blood pressure; HA = high altitude; Hb = hemoglobin concentration; Hct = hematocrit; HR = heart rate; SBP = systolic blood pressure.

By definition, Hb and hematocrit levels and CMS scores were higher in CMS patients than in control subjects. However, according to the CMS score, the population under investigation had a mild form of the disease. All subjects at clinical evaluation before exercise were in hemodynamic balance with no signs of pulmonary congestion or water retention.

Resting echocardiography. In 3 CMS subjects, the peak transtricuspidal jet velocity was not feasible due to an insufficient acoustic window. The resting echocardiographic parameters are reported in Tables 2 and 3. LV ejection fraction and cardiac output were within normal limits and comparable in the 2 groups under investigation. LV filling pressures, assessed by lateral and lateral-septal E/e′ were within normal limits and not significantly different between CMS patients and control subjects (Table 2). Compared with the healthy HA dwellers, CMS patients had a larger RV cavity size in both diastole and systole. The longitudinal RV systolic function, assessed using different parameters (TDI [RV-S′] RV TDI myocardial acceleration during isovolumic contraction), was normal and comparable in both groups, whereas RV fractional area change was significantly lower in CMS patients. The RV diastolic function, identified as tric e′ and a′, was normal in both groups. The RV Tei index was at the upper reference limit in both CMS patients and HA dwellers. The CMS patients showed higher systolic PAP and mean PAP compared with HA dwellers; by contrast, pulmonary vascular resistance was not significantly different between CMS patients and HA dwellers (Table 3).

Exercise echocardiography. During exercise, at least 1 technically acceptable measurement of peak

Table 2. O_2 Saturation and Echocardiographic Parameters of Left Ventricular Systolic and Diastolic Function at Rest and During Mild Exercise in CMS Patients and HA Dwellers

	Rest			Exercise		
	CMS	HA	p Value	CMS	HA	p Value
O_2 saturation, %	85 (82–89)	90.6 (89–92)	<0.0001	83 (89–91)	90 (88–91)	<0.0001
EF, %	63 ± 7	65 ± 6	0.2	67 ± 5	66 ± 8	0.1
CO, l/min	5.0 ± 2	4.6 ± 1	0.1	7.5 ± 2	7.9 ± 2	0.4
E-wave, cm/s	61 ± 14	63 ± 12	0.4	81 ± 17	88 ± 18	0.1
A-wave, cm/s	62 ± 14	56 ± 11	0.03	80 ± 30	75 ± 23	0.5
Lateral e′, cm/s	12 ± 3	13 ± 3	0.1	15 ± 3	16 ± 3	0.05
Lateral-septal e′, cm/s	13 ± 5	14 ± 5	0.5	15 ± 4	16 ± 3	0.2
Lateral, E/e′	5.4 ± 1	5.2 ± 1	0.5	5.5 ± 1	5.5 ± 1	0.8
Lateral-septal, E/e′	5.9 ± 2	5.7 ± 1	0.5	6.3 ± 1	6.0 ± 1	0.5
LAP, mm Hg	8.6 ± 2	8.3 ± 2	0.5	9.2 ± 3	8.7 ± 2	0.5

Values are median (relative interquartile range) or mean ± SD.
A = mitral inflow late diastolic velocity; CO = cardiac output; E = mitral inflow early diastolic velocity; e′ = mitral annulus velocity by tissue Doppler imaging; EF = ejection fraction; LAP = left atrial pressure; other abbreviations as in Table 1.

velocity of the systolic tricuspid regurgitation jet (systolic PAP) was obtained in 89% of the subjects, and all of them had interpretable resting measurements. In the remaining subjects, thoracic and diaphragmatic movements made it impossible to locate the transtricuspidal regurgitation jet during exercise. The maximal double product reached during exercise testing was not different between the 2 groups (15.577 ± 3.699 mm Hg·beats/min vs. 15.627 ± 2.550 mm Hg·beats/min, CMS patients vs. HA dwellers, respectively, p = 0.9). As expected, arterial oxygen saturation just before the end of the exercise test (at 50 W) was lower in CMS patients than in HA dwellers (83% (range, 89% to 91%) vs. 90% (range, 88% to 91%), p < .0001). LV function increased during effort in a similar manner in the 2 groups (Δ ejection fraction: +4 ± 8% vs. +0.9 ± 10%, CMS patients vs. HA dwellers; p = 0.1) as

Table 3. Echocardiographic Measurements for RV Assessment at Rest and Peak of Exercise

	Rest			Exercise		
	CMS	HA	p Value	CMS	HA	p Value
RV bas, mm	36 ± 5	32 ± 4	0.001	36 ± 8	35 ± 3	0.6
RV mid, mm	33 ± 6	30 ± 5	0.02	33 ± 8	31 ± 5	0.3
RV EDA, cm^2	18 ± 4	17 ± 3	0.2	17 ± 5	16 ± 4	0.3
RV ESA, cm^2	12 ± 3	10 ± 2	0.01	12 ± 2	9 ± 2	0.02
RV FAC, %	35 ± 9	43 ± 9	0.002	36 ± 9	43 ± 8	0.005
RV-S′, cm/s	13 (11–14)	13 (10–14)	0.9	10 (8–12)	16 (14–17)	<0.0001
IVA, m/s^2	2.6 ± 0.6	2.9 ± 0.9	0.2	3.8 ± 1.4	3.7 ± 1.4	0.5
RV-ESPAR, mm Hg/cm^2	2.1 ± 0.5	2.3 ± 1	0.3	4.0 ± 1.6	3.7 ± 1.1	0.4
Tric e′/a′	0.8 (0.6–1.0)	0.9 (0.8–1.2)	0.07	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.6
RV Tei index	0.54 ± 0.1	0.58 ± 0.2	0.3	0.54 ± 0.2	0.57 ± 0.2	0.5
Systolic PAP, mm Hg	30 ± 6	27 ± 5	0.01	50 ± 12	38 ± 8	<0.0001
Mean PAP, mm Hg	20 ± 3	18 ± 3	0.01	31 ± 7	24 ± 5	<0.0001
PVR, mm Hg/min/l	2.3 ± 1	2.3 ± 1	0.7	2.9 ± 1	2.2 ± 1	0.03

Values are mean ± SD or median (relative interquartile range).
bas = basal part of the right ventricular lateral wall; EDA = end-diastolic area; ESA = end-systolic area; IVA = right ventricular tissue Doppler imaging myocardial acceleration during isovolumic contraction; mid = middle part of the right ventricular lateral wall; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RA FAC = fractional area changing; RV = right ventricular; RV-S′ = peak systolic velocity with tissue Doppler imaging at the tricuspid annulus; tric e′/a′ = tissue Doppler early and late diastolic tricuspid velocities ratio; other abbreviations as in Table 1.

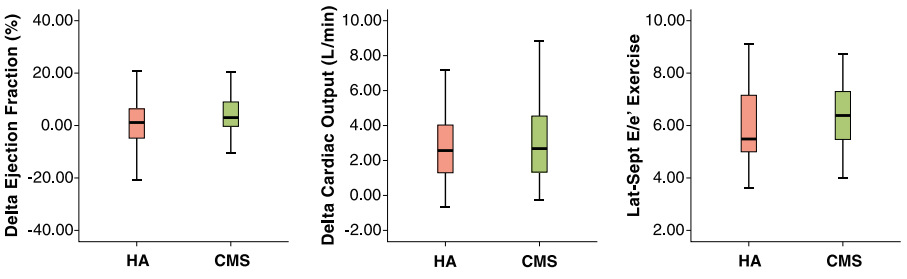

Figure 1. LV Systolic and Diastolic Function During Exercise in HA and CMS

Variation (exercise-rest) in left ventricle ejection fraction **(left)**, in cardiac output **(middle)**, and the mean value lateral-septal (lat-sept) of ratio of peak velocity of early mitral inflow to mitral annular early diastolic peak velocity (E/e′) **(right)** in chronic mountain sickness (CMS) and high-altitude (HA) dwellers. Horizontal lines represent the median; boxes, 25th to 75th percentiles; and T bars 95% confidence intervals.

did cardiac output (Δ cardiac output: +3 ± 2 l/min vs. + 3 ± 2 l/min; p = 0.8) (Fig. 1). The lateral e′ and the average lateral and septal e′ increased with exercise proportionally to E velocity of mitral inflow in both groups, so the E/e′ ratio remained unchanged (Table 2, Fig. 1). The significant differences observed at rest between CMS patients and HA dwellers in the RV end-systolic area and RV fractional area change remained during exercise (Table 3). RV-TDI myocardial acceleration during isovolumic contraction increased significantly in the 2 groups (CMS patients: rest, 2.6 ± 0.6 mm vs. exercise, 3.8 ± 1.4 mm, p = 0.001; HA dwellers: rest, 2.9 ± 0.9 mm vs. exercise, 3.7 ± 1.6 mm,

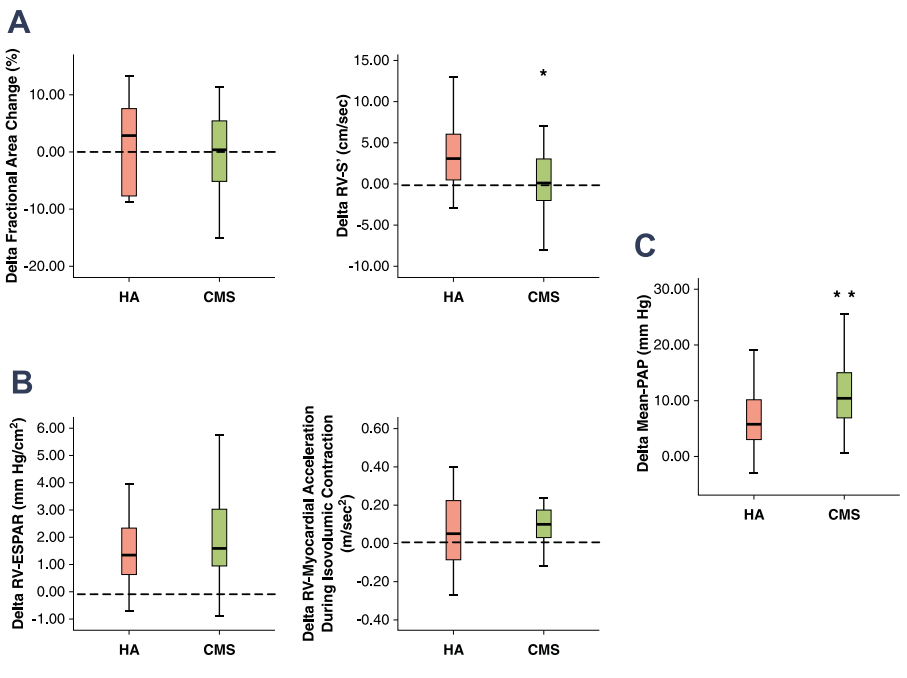

Figure 2. RV Systolic Function and Mean PAP During Exercise in HA and CMS

(A) Variation (exercise-rest) of fractional area change percentage **(left)** and tissue Doppler imaging peak systolic velocity of the lateral tricuspid valve annulus (RV-S′) cm/s **(right)** CMS and HA showed no variation in fractional area change and RV-S′. **(B)** Increased right ventricular end-systolic pressure-area relationship (RV-ESPAR) mm Hg/cm^2 **(left)** and right ventricular tissue Doppler imaging myocardial acceleration during isovolumic contraction (m/s^2) **(right)**. **(C)** In the presence of a significant increment of mean pulmonary arterial pressure (PAP) (mm Hg) compared with HA. *p = 0.001, **p < 0.0001 versus HA. Abbreviations as in Figure 1.

p = 0.06). In contrast, the TDI RV-S′ increased significantly only in HA dwellers (Δ RV-S′: HA +3 cm/s (+0.0 to +6 cm/s) vs. CMS +0.3 cm/s (−2.0 to +3 cm/s), p = 0.001) (Table 3, Fig. 2). With exercise, there was a significant increase in RV-ESPAR, a surrogate of RV contractility, in CMS patients and HA dwellers (HA dwellers: rest 2.3 ± 1 vs. exercise, 3.7 ± 1.1 mm Hg/cm^2, p < 0.0001; CMS patients: rest, 2.1 ± 0.5 vs. peak 4.0 ± 1.6 mm Hg/cm^2, p < 0.0001). Both CMS patients and HA dwellers presented a concomitant increase in tricuspid e′ and a′ velocity, so their ratio was not different in comparison with resting conditions as a physiological right atrial contribution to exercise (Table 3). Comparing the 2 surrogate measurements of contractility, there was a slight correlation between peak-rest (RV-ESPAR) and RV TDI myocardial acceleration during isovolumic contraction at peak exercise (r = 0.3, p = 0.03).

Pulmonary circulation during hypoxic exercise. As expected, the increase in mean PAP during exercise was 2-fold higher in CMS patients than in HA dwellers (Δ mean PAP: +11 ± 6 mm Hg vs. + 6 ± 4 mm Hg, p < 0.0001) (Fig. 3). In CMS patients, but not in HA dwellers, a significant inverse relationship between the exercise-induced increase in mean PAP (Δ mean-PAP) and O_2 saturation at the end of the exercise test (r = 0.35, p = 0.04) was observed.

Of the 77 subjects who had interpretable echocardiographic images during exercise, 46% of CMS patients and only 7.5% of HA dwellers showed a systolic PAP ≥50 mm Hg at peak exercise. There was no difference in age, Hb, hematocrit, CMS score, and rest and stress echocardiographic characteristics between CMS patients with peak systolic PAP <50 and ≥50 mm Hg. In the regression model, only rest systolic PAP was a predictor of peak systolic PAP ≥50 mm Hg (odds ratio: 1.2, 95% confidence interval: 1.0 to 1.4, p = 0.007). In the subgroup of 77 subjects, pulmonary vascular resistance was also assessed: feasibility was 89% at rest and 60% at peak stress. The pulmonary vascular resistance was significantly higher after exercise in CMS patients compared with HA dwellers (Table 3). Peak pulmonary vascular resistance ≥3 Wood units was present in 52% of CMS patients and 20% of HA dwellers, and in CMS patients, a peak pulmonary vascular resistance ≥3 was present in 75% of patients with peak systolic PAP ≥50 mm Hg. Univariate

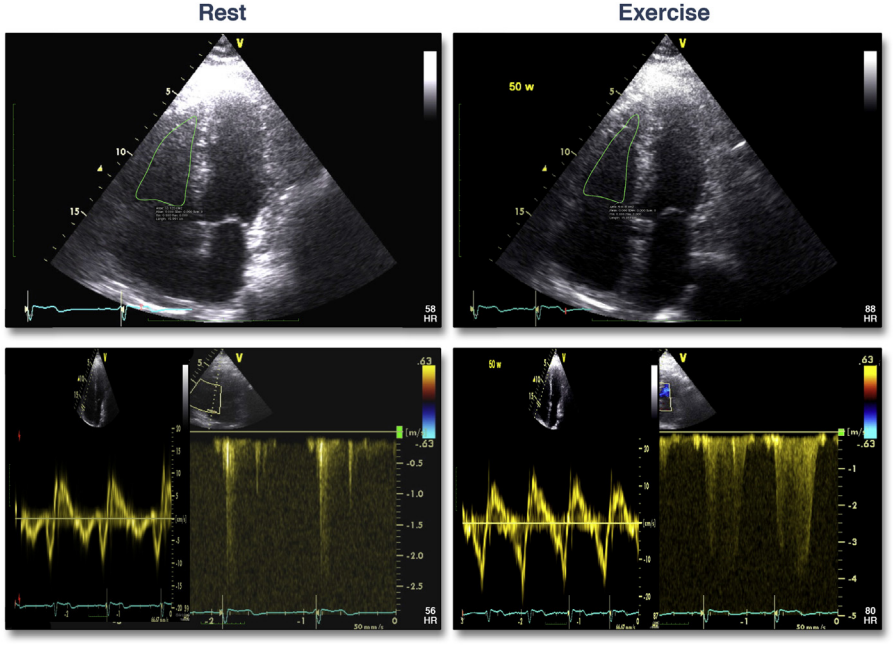

Figure 3. An Example of RV ESPAR in a CMS Patient

Echocardiographic measurement in a CMS patient: right ventricular end-systolic area (cm^2) at rest **(top left)** and at peak exercise **(top right)**. Tissue Doppler imaging of the tricuspid annulus and right ventricular-right atrial gradient at rest **(bottom left)** and during exercise **(bottom right)**. In this patient, we observed at peak exercise in a 4-chamber view a reduction of right ventricular end-systolic area associated with an increase in mean PAP, whereas the RV-S′ did not increase. Abbreviations as in Figures 1 and 2.

Table 4. Univariate Analysis to Predict Peak Pulmonary Vascular Resistance ≥3 Woods Units in CMS Patients

	OR (95% CI)	p Value
Resting O_2 saturation, %	0.9 (0.8–1.2)	0.9
Resting EF, %	1.0 (0.9–1.1)	0.6
Resting CO, l/min	0.7 (0.5–1.1)	0.18
Resting RV-S′, cm/s	1.2 (0.9–1.6)	0.17
Resting (lateral-septal), E/e′	0.9 (0.5–1.5)	0.7
Resting tricuspid e′/a′	0.3 (0.2–5.5)	0.4
Resting mitral S′, cm/s	1.0 (0.8–1.3)	0.7
Resting systolic PAP, mm Hg	1.1 (0.9–1.3)	0.1
DP, mm Hg·beats/min	1.0 (1.0–1.0)	0.6
Peak O_2 saturation, %	0.9 (0.8–1.0)	0.3
Peak EF, %	1.0 (0.9–1.2)	0.16
Peak RV FAC, %	1.0 (0.9–1.1)	0.2
Peak mitral S′, cm/s	0.7 (0.4–1.2)	0.2
Peak tric S′, cm/s	0.8 (0.6–1.1)	0.3
Peak (lateral-septal), E/e′	1.2 (0.6–2.4)	0.4
Peak tric, e/a′	0.3 (0.3–2.7)	0.3

CI = confidence interval; DP = double product; FAC = fractional area change; OR = odds ratio; Resting mitr S′ = peak systolic velocity with tissue Doppler imaging at the mitral annulus; other abbreviations as in Tables 1 to 3.

analysis showed that age and rest RV fractional area change were significant predictors of peak pulmonary vascular resistance ≥3 Woods units in CMS patients (Table 4). By stepwise analysis, the rest RV fractional area change was the most important predictors of peak pulmonary vascular resistance ≥3 mm Hg in CMS patients (Table 5).

The mean PAP/cardiac output ratio at the peak of exercise was higher in CMS patients (CMS patients: 4.5 ± 1.8 mm Hg/l^{-1} vs. HA dwellers: 3.4 ± 1.1 mm Hg/l^{-1}, p = 0.004). The mean PAP/cardiac output ratio at peak exercise in CMS patients was related to RV fractional area change at rest (r = 0.4, p = 0.04), RV TDI myocardial acceleration during isovolumic contraction at peak exercise (r = 0.4, p = 0.04), and RV Tei index at rest and peak exercise (rest: r = 0.3, p = 0.05; peak: r = 0.3, p = 0.05).

Table 5. Result After Stepwise Multivariate Procedure to Predict Peak Pulmonary Vascular Resistance ≥3 Woods Units in CMS Patients

	Multivariate OR (95% CI)	p Value
Resting RV FAC, %	1.1(1.0–1.4)	0.04

Abbreviations as in Tables 3 and 4.

DISCUSSION

This study shows the effect of mild exercise on pulmonary hemodynamics and RV and LV function, evaluated by echocardiography, in a selected population of CMS patients with a mild form of the disease. The results of this study showed that in CMS patients with mild disease the RV contractility is preserved, although RV remodeling was present in rest conditions. We also investigated the behavior of pulmonary circulation during exercise using a noninvasive method. In CMS patients, the exercised-induced increase in mean PAP was significantly higher compared with HA dwellers and the magnitude of the pressure response was related to the O_2 saturation at the peak of exercise. The mean PAP increased in association with cardiac output even in the presence of hypoxic conditions and the mean PAP/cardiac output relationship was steeper in CMS patients than in HA dwellers. The pulmonary vascular resistance increased during exercise in CMS patients, whereas in HA dwellers, it remained unchanged. We can speculate that in CMS patients the constitutional abnormality of pulmonary vasculature is somehow linked also to an increased pulmonary vasoreactivity. The vasoconstriction should be one of the possible contributing factors to increased pulmonary vascular resistance, a consequence of greater hypoxemia during exercise. In CMS patients, the exercise-induced increase in mean PAP ≥50 mm Hg was not related to age, Hb value, or LV and RV systolic and diastolic function. The majority of CMS patients with systolic PAP ≥50 mm Hg presented pulmonary vascular resistance ≥3 Woods units. The exercise-induced increase in pulmonary vascular resistance seems to be related to RV systolic function in rest conditions.

Comparison with previous studies. Previous studies have addressed the assessment of RV function in healthy HA dwellers and CMS patients, trying to identify whether right heart dysfunction was characteristic of this particular population (1,2,18). Maignan et al. (2) showed that CMS patients compared with healthy HA dwellers had normal LV function associated with RV dilation, increased RV Tei index, and higher PAP (2). The difference in PAP between the Maignan et al. (2) study and our study could be explained by differences in altitude (Cerro del Pasco being located higher at 4,350 m sea level, which possibly induces a stronger hypoxic stimulus in the pulmonary circulation), ethnicity, and degree of disease (distinctly higher CMS scores in the study of Maignan et al. [2]). Despite the higher PAP and more severe degree of disease

in the Peruvian CMS patients, they found results similar to those of our study in rest conditions. More recently, an echocardiographic study was performed in 15 healthy HA inhabitants of the Bolivian altiplano (4,000 m sea level) compared with acclimatized lowlanders (18). The healthy HA dwellers presented lower mean PAP and higher O_2 saturation, but more pronounced alteration in indexes of diastolic function of both ventricles, a lower LV ejection fraction, and decreased indexes of RV systolic function. This study attempted to clarify whether CMS patients and HA dwellers have RV dysfunction using load-independent parameters. It is well known that the evaluation of RV function by echocardiography has relevant flaws for different reasons: geometric assumptions (i.e., RV fractional area change), angle, and load dependence (i.e., RV fractional area change, RV-S′, Tei index) (11). To avoid these problems, we also measured load- and angle-independent indexes as RV TDI myocardial acceleration during isovolumic contraction and RV-ESPAR as a surrogate of contractility. RV TDI myocardial acceleration during isovolumic contraction was tested in an experimental study in comparison with the RV pressure-volume relationship and was shown to be unaffected by preload and afterload changes (19). The end-systolic pressure–end-systolic area of the left ventricle was assessed by echocardiography during exercise, dobutamine, and pacing (5,20,21). However, RV contractility was only assessed in 1 study with the end-systolic pressure-volume relationship using the echocardiographic method (6). La Gerche et al. (6) studied a particular subset of endurance athletes compared with nonendurance athletes. The endurance athletes showed lower resting values of RV function in rest conditions but a preserved contractility evaluated with RV-ESPAR (6). Interestingly, at rest, HA dwellers and CMS patients did not show pulmonary hypertension at the altitude of La Paz (3,800 m sea level). The finding is in line with previous data reported in healthy Aymara individuals studied in Oruro (4,000 m sea level) (18) but is inconsistent with the observation of a high incidence of pulmonary hypertension in Peruvian Quechua with CMS studied at an altitude of 4,350 m sea level (22). This difference may be explained by the difference in altitude where the studies were conducted and/or different regulatory mechanisms of PAP in the Aymara and Quechua populations. Healthy HA natives present anatomophysiological changes in distal pulmonary arteries and arterioles, with an increase in smooth muscle cells causing high pulmonary vascular resistance (23,24) and exercise-induced pulmonary hypertension (25). This vascular remodeling can be considered the main cause of the increase in pulmonary pressure described in HA dwellers. Other contributing secondary factors might be vasoconstriction, increased blood viscosity (1), and greater hypoxemia during exercise (24–26). In CMS patients, these findings are exaggerated and represent pathological adaptive mechanisms to high altitude. In the development of CMS, one of the early findings is excessive erythrocytosis, a consequence of exaggerated hypoxemia. The latter is due to differences in respiratory patterns characterizing CMS patients: alveolar hypoventilation, ventilation perfusion mismatch, and a widened alveolar-arterial pressure oxygen gradient (27). Considering the exercise response in the present study, in line with previous reports (1,3,4), we observed a significantly higher increase in mean PAP and in pulmonary vascular resistance in CMS patients associated with lower values of O_2 saturation compared with HA dwellers. This response could be associated with the relative hypoventilation usually present in CMS. This mechanism has recently been investigated in a study performed in CMS patients in Cerro Pasco (4,350 m sea level). Thirteen CMS patients underwent a cycloergometer cardiopulmonary exercise test and estimation of pulmonary arterial pressure by echocardiography and showed a preserved aerobic exercise capacity despite severe pulmonary hypertension and relative hypoventilation (22). These authors concluded that the aerobic exercise capacity of patients with CMS was preserved despite severe pulmonary hypertension and relative hypoventilation. They suggested that this was related to a combination of an increased oxygen-carrying capacity of the blood and lung diffusion, the latter being predominantly due to an increased capillary blood volume. On the basis of the present study, we can speculate that the exaggerated exercise-induced increase in mean PAP was not a consequence of compromised LV or RV diastolic or systolic functions. Moreover, in CMS patients, mean PAP increased significantly more during exercise than in healthy HA dwellers in the presence of cardiac output <8 to 10 l/min and a significant pulmonary vascular resistance increase. Consequently, we may conclude that the pulmonary vascular bed of CMS patients is unable to dilate and accommodate the exercise-induced increase in blood as normally happens in sea-level dwellers (1,28,29).

Study limitations. First, the number of patients investigated was relatively small. However, patients were selected on the basis of strict enrollment

criteria, which allowed discriminating different levels of RV dysfunction during exercise. Second, 2-dimensional echocardiography, like other tomographic imaging methods, has well-recognized inherent limitations precluding a good assessment of complex 3-dimensional anatomy, such as the right ventricle. For field studies, however, echocardiography remains the single possible tool. In this study, the same highly experienced operator, adopting strict reading criteria and blinded to the patient's group assignment, conducted all examinations. Such an approach can reduce the above-mentioned limitations (16,30). Third, the end-systolic pressure–end-systolic volume relationship is an approximation of contractility that can be determined by echocardiography during physical stress and has been shown to predict clinical outcome (31,32). It is obvious that echocardiographic quantification of RV volumes is challenging, especially during exercise. Other authors used the RV ESPAR as a surrogate of RV contractility, and in the same cohort of subjects, they found a strong correlation between RV area and RV volumes obtained by magnetic resonance imaging (6). Certainly this surrogate of contractility is based on assumptions, but, unfortunately, the RV pressure/volume index can only be performed invasively (33), so new studies are necessary to validate this echocardiographic method, which might approximate this gold standard.

CONCLUSIONS

The incidence of CMS is very high in the Andean population, and this pathology begins insidiously in adult life. Echocardiography is an available, low-cost, and nonionizing method that can also be applied in developing countries and in logistically demanding situations. Therefore, we designed a simple test to evaluate LV and RV function and mean PAP in CMS patients with mild disease submitted to mild exercise. The study showed that echocardiography is not only a feasible method for investigating RV function during exertion in CMS patients with a barrel-like thorax but also valuable for determining the true RV function in a disease characterized by pressure overload such as Monge's disease. To our knowledge, this study is the first to comprehensively assess RV and LV function and pulmonary circulation together in CMS patients at rest and during mild exercise. At rest, compared with healthy HA dwellers, patients with mild CMS have an already-dilated right ventricle and an impaired RV systolic function according to some RV parameters despite normal PAP and pulmonary vascular resistance. During mild exercise, CMS patients have an exaggerated increase in PAP and pulmonary vascular resistance compared with healthy HA natives but unchanged systolic and diastolic LV function. Compared with rest, RV diastolic function remained largely unchanged during exercise in CMS patients, and there was a normal RV contractile reserve as in HA dwellers. A preventive strategy to reduce the occurrence of pulmonary hypertension should be developed using noninvasive tools such as exercise echocardiography to identify the subset at higher risk and start appropriate drug therapy. It is conceivable that phosphodiesterase type 5 inhibitors maybe an attractive treatment for CMS patients. However, evidence is lacking and randomized trials are warranted to evaluate the effectiveness and outcome in this condition (34).

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