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Sleep-Disordered Breathing and Vascular Function in Patients With Chronic Mountain Sickness and Healthy High-Altitude Dwellers

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BACKGROUND: Chronic mountain sickness (CMS) is often associated with vascular dysfunction, but the underlying mechanism is unknown. Sleep-disordered breathing (SDB) frequently occurs at high altitude. At low altitude, SDB causes vascular dysfunction. Moreover, in SDB, transient elevations of right-sided cardiac pressure may cause right-to-left shunting in the presence of a patent foramen ovale (PFO) and, in turn, further aggravate hypoxemia and pulmonary hypertension. We speculated that SDB and nocturnal hypoxemia are more pronounced in patients with CMS compared with healthy high-altitude dwellers, and are related to vascular dysfunction.

METHODS: We performed overnight sleep recordings, and measured systemic and pulmonary artery pressure in 23 patients with CMS (mean ± SD age, 52.8 ± 9.8 y) and 12 healthy control subjects (47.8 ± 7.8 y) at 3,600 m. In a subgroup of 15 subjects with SDB, we assessed the presence of a PFO with transesophageal echocardiography.

RESULTS: The major new findings were that in patients with CMS, (1) SDB and nocturnal hypoxemia was more severe ($P < .01$) than in control subjects (apnea-hypopnea index [AHI], 38.9 ± 25.5 vs 14.3 ± 7.8 number of events per hour [nb/h]; arterial oxygen saturation, 80.2% ± 3.6% vs 86.8% ± 1.7%, CMS vs control group), and (2) AHI was directly correlated with systemic blood pressure ($r = 0.5216$; $P = .001$) and pulmonary artery pressure ($r = 0.4497$; $P = .024$). PFO was associated with more severe SDB (AHI, 48.8 ± 24.7 vs 14.8 ± 7.3 nb/h; $P = .013$, PFO vs no PFO) and hypoxemia.

CONCLUSIONS: SDB and nocturnal hypoxemia are more severe in patients with CMS than in control subjects and are associated with systemic and pulmonary vascular dysfunction. The presence of a PFO appeared to further aggravate SDB. Closure of the PFO may improve SDB, hypoxemia, and vascular dysfunction in patients with CMS.

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ABBREVIATIONS: AHI = apnea-hypopnea index; CMS = chronic mountain sickness; ODI = oxygen desaturation index; PFO = patent foramen ovale; Sa_{O_2} = arterial oxygen saturation; SDB = sleep-disordered breathing

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Chronic mountain sickness (CMS) is a major public health problem affecting several millions of people.[1-4] It is characterized by exaggerated erythrocytosis and hypoxemia[5] and is often associated with increased pulmonary artery pressure and systemic vascular dysfunction,[6-8] but the underlying mechanisms causing these alterations are incompletely understood. Sleep-disordered breathing (SDB), ie, an oscillatory pattern of waxing and waning ventilation with periods of hyperventilation with central apneas or hypopneas, frequently occurs during acclimatization at high altitude and is associated with exaggerated hypoxemia.[9,10] There is abundant evidence that at low altitude, SDB (ie, obstructive and central sleep apnea) is associated with increased sympathetic nerve activity[11-14] and oxidative stress,[15-17] two factors that may contribute to arterial hypertension and pulmonary and systemic vascular dysfunction in these patients.[3,7,8,18,19] Surprisingly, information on SDB in healthy high-altitude dwellers and patients with CMS is sparse and conflicting,[20-22] and there is no information on the relationship between SDB and pulmonary and systemic arterial pressure and vascular function.

We speculated that SDB and nocturnal hypoxemia are more pronounced in patients with CMS than in healthy high-altitude dwellers and that a relationship between the severity of this problem and vascular dysfunction exists. To test this hypothesis we performed overnight sleep recordings, assessed systemic vascular function, and measured systemic and pulmonary artery pressure in patients with CMS and healthy high-altitude dwellers at 3,600 m.

Patients with SDB exhibit transient elevations of right-sided cardiac pressure that in the presence of a patent foramen ovale (PFO) may result in right-to-left shunting and, in turn, further aggravate hypoxemia and pulmonary hypertension.[23,24] To test for this possibility, we evaluated the presence or absence of a PFO by transesophageal echocardiography in a subgroup of participants. Finally, added dead space through a nonvented mask has been used successfully to improve respiration in patients with Cheyne-Stokes breathing and idiopathic central apnea, which share some common pathophysiological features with altitude-induced SDB.[25,26] In line with this concept, increasing respiratory dead space improved altitude-induced SDB in healthy mountaineers.[27] Therefore, we tested the effects of added dead space on SDB in patients with CMS.

Materials and Methods

Between August 2008 and August 2010, 23 male patients with CMS (mean ± SD age, 52.8 ± 9.8 y) and 12 healthy high-altitude dwellers (47.8 ± 7.8 y) without traditional pulmonary and cardiovascular risk factors (smoking, arterial hypertension, hypercholesterolemia, or diabetes) or a family history of premature cardiovascular events, hypertension, or diabetes, who were born at and had been permanently living at high altitude (3,600-4,000 m), were included in the study. Inclusion criteria for patients with CMS were excessive erythrocytosis (hemoglobin concentration > 21 g/dL) in the presence of a normal pulmonary function study and no history of working in the mining industry. All participants had a typical Aymara surname, self-identified themselves as Aymaras, and had a similar socioeconomic background. Exclusion criteria were smoking, office blood pressure > 145/95 mm Hg, drug treatment, acute infection, cardiopulmonary or neurologic disease, and traveling to low altitude in the preceding 6 months. The experimental protocol was approved by the institutional review boards on human investigation of the Universities of San Andres, La Paz, Bolivia, and Lausanne, Switzerland (Commission d'Ethique de la recherche clinique, approval #203/09), and registered (Clinical Trials Gov Registration: NCT01182792). All participants provided written informed consent. All studies were performed at the Instituto Boliviano de Biologia de Altura (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 or palpitations, sleep disturbance, cyanosis, dilation of veins, paresthesia, headache, tinnitus. A score between 0 and 3 was attributed for each item, with 0 indicating the absence of the symptom, 1 mild, 2 moderate, and 3 severe symptoms. A score > 5 indicates CMS.[7]

Sleep Studies

Overnight sleep recordings were performed in individual rooms using portable Titanium acquisition systems (Embla Systems). Two electrooculogram electrodes (one to each outer cantus) and a standard polysomnography montage including occipital (O1,O2) as well as central electrodes (C3 C4) were applied to the scalp using the International 10-20 System,[28] and two surface electromyogram electrodes were placed over submental muscles. Electroencephalogram and electrooculogram electrodes were referenced to the linked earlobes (A1 + A2). Chest and abdominal movements, nasal air pressure (to assess nasal airflow), and body position were recorded simultaneously.

Investigation and Research in Sleep (Ms Andries and Drs Lovis and Heinzer) and the Department of Internal Medicine (Dr Sartori), Lausanne-CHUV, Switzerland; the Instituto Boliviano de Biologia de Altura (Drs Salinas and Villena and Ms Romero), La Paz, Bolivia; and the Facultad de Ciencias (Dr Scherrer), Departamento de Biología, Universidad de Tarapacá, Arica, Chile.

Drs Heinzer, Sartori, and Scherrer contributed equally to this manuscript.

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Oxyhemoglobin saturation was recorded using a Nonin pulse oximeter (Nonin Medical, Inc). Each patient with CMS had two night recordings in random order, one spent without and the other with added dead space. Added respiratory dead space was applied during sleep using a full-face nonvented mask with an open bottle made of polyethylene terephthalate connected to the mask outlet. The total volume of the dead space (mask + bottle) was 500 mL.[27] A coin toss determined whether dead space would be applied during the first or second night. Control subjects had only one night of sleep recordings without added dead space. As a result of technical problems, recordings could not obtained in one control subject.

Data were visually analyzed using Somnologica software version 5.1 (Embla Systems). An experienced investigator (D.A.) performed the electroencephalogram analysis for the whole night. Sleep stages and micro arousal (an abrupt shift in electroencephalogram frequency, including a theta-alpha pattern or a frequency higher than 16 Hz [but not spindles], lasting ≥ 3 s with ≥ 10 s of stable sleep preceding the change) were scored according to the American Academy of Sleep Medicine 2007 recommendations.[29] Sleep efficiency was calculated as the ratio between total sleep time and total recording time (ie, between lights off and lights on). Apnea was defined as ≥90% reduction in airflow signal amplitude for ≥10 seconds. Hypopnea was defined as ≥50% reduction in airflow signal amplitude for >10 seconds associated with ≥3% oxygen desaturation or arousal (American Academy of Sleep Medicine 2007 alternative criteria).[30] The apnea-hypopnea index (AHI) was calculated as the mean number of events per hour (nb/h) of night recording. The oxygen desaturation index (ODI) was defined as the number of desaturations (defined by an oxygen saturation fall of ≥3%) per hour (nb/h) of sleep.

Right Ventricular to Right Atrial Pressure Gradient Measurement

Right ventricular to right atrial pressure gradient was measured as described previously, using a portable, fully equipped echocardiography unit (Vivid I, General Electric Healthcare Clinical System) with a cardiac probe (2.5 to 3.5 MHz).[6,31-33] Noninvasive estimation of pulmonary artery pressure has been validated against invasive measurements at high altitude.[31] Recordings were stored on DVD for offline analysis by two operators (S. F. R., Y. A.) who were blinded to the subject's group assignment. Reported values represent the mean of at least three measurements. In two patients with CMS and one control subject, tricuspid regurgitation could not be detected and pulmonary artery pressure could not be estimated. For technical reasons, echocardiography could not be performed in three patients with CMS and three control subjects.

Transesophageal Echocardiography

To evaluate the presence of a PFO, in 11 patients with CMS and 4 control subjects, transesophageal echocardiography was performed as previously described,[24] in combination with injection of echocardiographic contrast medium.[34,35] The diagnosis of PFO required the crossing of bubbles from the right to the left atrium within four heart beats after the release of the strain.

Assessment of Systemic Vascular Function

Studies to assess brachial artery endothelial function and arterial stiffness were performed after 15 minutes of rest in the supine position in a temperature-controlled room (22°C) as previously described.[7] Systemic conduit artery endothelial function was assessed by determining the increase of the brachial artery diameter evoked by reactive hyperemia using high-resolution ultrasound and automatic wall tracking software.[36,37] Flow-mediated dilation was expressed as the maximal percentage change in vessel diameter from baseline. Assessment of arterial stiffness was performed according to international guidelines[38] by measuring carotid-femoral pulse wave velocity using the Complior device (Alam Medical).[38,39]

Statistical Analysis

Using the GraphPad Prism 5 software package (GraphPad Software Inc), we made group comparisons of continuous variables with unpaired and paired 2-tailed *t* tests. Relations between variables were analyzed by calculating the Pearson product-moment correlation coefficient.

Power calculation on the basis of our previous data on the effects of added dead space on SDB at this altitude[27] revealed that with a difference of 5 ± 5 events/h in AHI between sleep with and without added dead space (power > 0.90; $\alpha = .05$), 13 subjects were needed.

A value of $P < .05$ was considered to indicate statistical significance. Unless otherwise indicated, data are given as mean ± SD.

Results

The characteristics of the study participants are presented in Table 1. By definition, CMS score, hemoglobin, and hematocrit were markedly higher in patients with CMS compared with healthy high-altitude dwellers. BMI was higher in patients with CMS (29.5 ± 3.0 kg/m^2 vs 26.6 ± 3.1 kg/m^2; $P = .02$, CMS vs control group). Lung function and systemic blood pressure were normal and comparable in the two groups.

Sleep-Disordered Breathing and Nocturnal Hypoxemia

Figure 1 shows that SDB and nocturnal hypoxemia were more severe in patients with CMS than in healthy high-altitude dwellers, as evidenced by a more than 2-fold higher AHI (38.9 ± 25.5 nb/h vs 14.3 ± 7.8 nb/h; $P = .006$, CMS vs control group) (Fig 1A) and ODI (38.6 ± 23.6 nb/h vs 17.3 ± 9.4 nb/h; $P = .01$, CMS vs control group) (Fig 1B) These respiratory alterations during sleep in patients with CMS were reflected by a significantly lower nocturnal oxygen saturation (80.2% ± 3.6% vs 86.8% ± 1.7%; $P < .001$, CMS vs control group) (Fig 1C) than in healthy control subjects.

Figure 2 shows the inverse relationship that existed between AHI and nocturnal arterial oxygen saturation (Sa_{O_2}) ($r = -0.7522$; $P < .0001$) (Fig 2A). AHI was directly correlated with hemoglobin ($r = 0.5175$; $P = .002$) (Fig 2B), whereas nocturnal Sa_{O_2} was inversely related to this variable ($r = -0.7305$; $P < .001$).

Vascular Function

As expected,[8,19] estimated pulmonary artery pressure was higher (26.3 ± 6.5 mm Hg vs 20.9 ± 3.1 mm Hg; $P = .008$, CMS vs control group), and systemic vascular function was altered in patients with CMS, as

TABLE 1] Subject Characteristics

Characteristic	CMS (n = 23)	Control (n = 12)	*P* Value
Age, y	52.8 ± 9.8	47.8 ± 7.8	.11
CMS score	7.7 ± 2.9	1.3 ± 1.9	<.001
BMI, kg/m^2	29.5 ± 3.0	26.6 ± 3.1	.02
Nocturnal Sao_2, %	80.2 ± 3.6	86.8 ± 1.7	<.001
Hemoglobin, g/dL	21.7 ± 1.3	16.9 ± 0.7	<.001
Hematocrit, %	66.9 ± 5.1	49.8 ± 3.6	<.001
FEV_1/FVC	77.6 ± 4.7	78.8 ± 10.3	.81
Heart rate, beats/min	69.4 ± 10.0	65.8 ± 7.7	.26
SBP, mm Hg	125.0 ± 9.7	121.3 ± 9.1	.28
DBP, mm Hg	81.7 ± 9.1	79.3 ± 8.1	.42

Data are presented as mean ± SD. CMS = chronic mountain sickness; DBP = diastolic blood pressure; Sao_2 = arterial oxygen saturation; SBP = systolic blood pressure.

evidenced by impaired flow-mediated dilation (4.2% ± 1.1% vs 6.5% ± 2.7%; $P = .026$, CMS vs control group) and increased pulse wave velocity (10.1 ± 1.8 m/s vs 7.7 ± 1.3 m/s; $P = .003$, CMS vs control group) compared with healthy high-altitude dwellers.

Relationship Between Vascular Function and Sleep-Disordered Breathing

AHI was directly correlated with systolic ($r = 0.5216$; $P = .001$) (Fig 2C) and diastolic ($r = 0.3879$; $P = .02$) (Fig 2D) blood pressure, and the right ventricular to right atrial pressure gradient ($r = 0.4497$; $P = .024$) (Fig 2E). Accordingly, an inverse relationship existed between nocturnal Sao_2 and systolic ($r = -0.5373$; $P = .002$) and diastolic ($r = -0.4339$; $P = .015$) blood pressure and the right-ventricular-to-right-atrial pressure gradient ($r = -0.5532$; $P = .005$).

Patent Foramen Ovale, Sleep-Disordered Breathing, and Nocturnal Hypoxemia

PFO was present in 6 of 11 patients with CMS and in 2 of 4 control subjects. Its presence was associated with more severe SDB, as shown by an increased AHI (48.8 ± 24.7 nb/h vs 14.8 ± 7.3 nb/h; $P = .013$, PFO vs no PFO) (Fig 3A), and more severe nocturnal hypoxemia, as evidenced by a higher ODI (65.2 ± 25.5 nb/h vs 25.7 ± 22.7 nb/h; $P = .017$, PFO vs no PFO) (Fig 3B), a lower nadir nocturnal Sao_2 (66.9% ± 9.0% vs 76.0% ± 5.7%; $P = .047$, PFO vs no PFO) (Fig 3C), and a trend for lower nocturnal Sao_2 (80.7% ± 4.7% vs 83.9% ± 3.2%; $P = .18$, PFO vs no PFO) in comparison with high-altitude dwellers without PFO. Finally, as expected,[24] its presence was associated with an increased right ventricular to right atrial pressure gradient (28.5 ± 5.4 mm Hg vs 19.6 ± 4.6 mm Hg; $P = .014$, PFO vs no PFO).

Effects of Added Dead Space on Sleep-Disordered Breathing

Added dead space improved SDB in patients with CMS, as evidenced by a >30% decrease of AHI (from 38.9 ± 25.5 nb/h to 24.4 ± 20.3 nb/h; $P < .001$) (Fig 4A) and ODI (from 38.6% ± 23.6% to 24.9% ± 19.4 nb/h; $P < .001$) (Fig 4B). This improvement of SDB was reflected by significantly less severe nocturnal oxygen desaturation (81.4% ± 2.5% vs 80.2% ± 3.6%; $P = .015$)

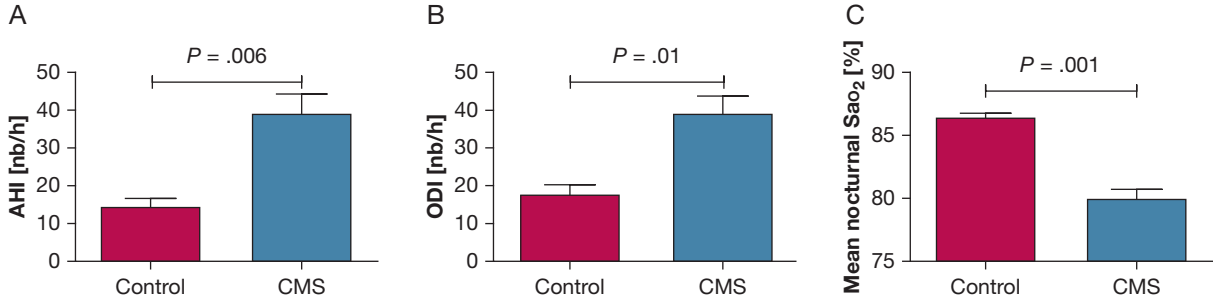

Figure 1 – *A-C, Sleep-disordered breathing (A, B) and Sao_2 (C) in healthy high-altitude dwellers and patients with CMS at 3,600 m. Data are mean ± SD. AHI = apnea/hypopnea index; CMS = chronic mountain sickness; ODI = oxygen desaturation index; Sao_2 = arterial oxygen saturation.*

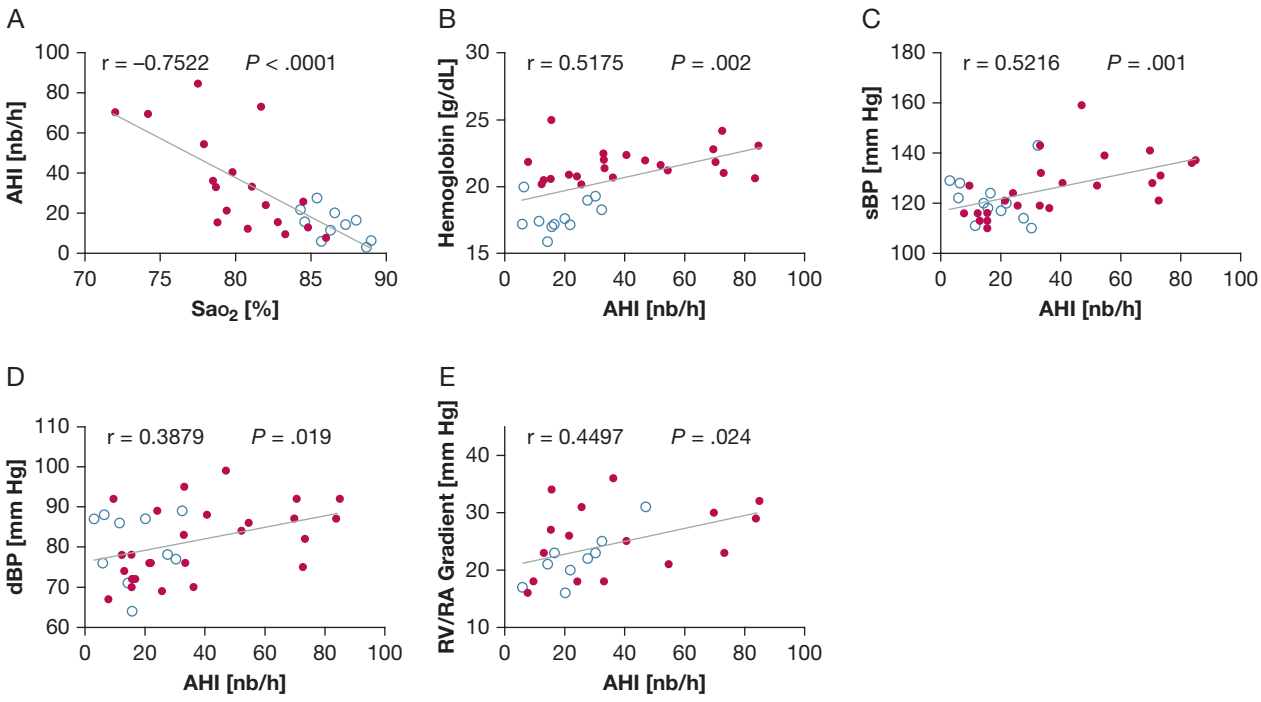

Figure 2 – *A-E, Relationship between AHI and Sao_2 (A), hemoglobin (B), sBP (C), dBP (D), and RV/RA (E) in patients with chronic mountain sickness (•) and in healthy high-altitude dwellers (◦) at 3,600 m. dBP = diastolic blood pressure; RV/RA = right-ventricular-to-right-atrial pressure gradient; sBP = systolic blood pressure. See Figure 1 legend for expansion of other abbreviations.*

(Fig 4C). Added dead space did not alter sleep quality, as evidenced by comparable micro arousal index (21.3 ± 17.1 nb/h vs 21.1 ± 16.0 nb/h; $P = .95$, baseline vs dead space) and sleep efficiency (88.0% ± 9.4% vs 83.9% ± 5.5%; $P = .14$, baseline vs dead space).

Discussion

CMS, a major health problem affecting several million people worldwide, is associated with vascular dysfunction,[7,18] but the underlying mechanism is incompletely understood. High altitude alters nocturnal breathing, and at low altitude, altered nocturnal respiration is associated with altered vascular function. We found that patients with CMS display more severe SDB and nocturnal oxygen desaturation compared with healthy high-altitude dwellers. These alterations of nocturnal breathing and oxygenation were associated with vascular dysfunction and increased pulmonary artery pressure. Collectively, these findings suggest that SDB may contribute to altered cardiovascular function in patients with CMS and in high-altitude dwellers.

SDB with central apnea or hypopnea frequently occurs during acute high-altitude exposure,[40,41] and its severity depends on absolute altitude[9] and the individual's predisposition.[27] In the present study, SDB was less severe in healthy, well-adapted high-altitude dwellers compared with a previous study in healthy lowlanders who were acutely exposed to a similar altitude,[27,42]

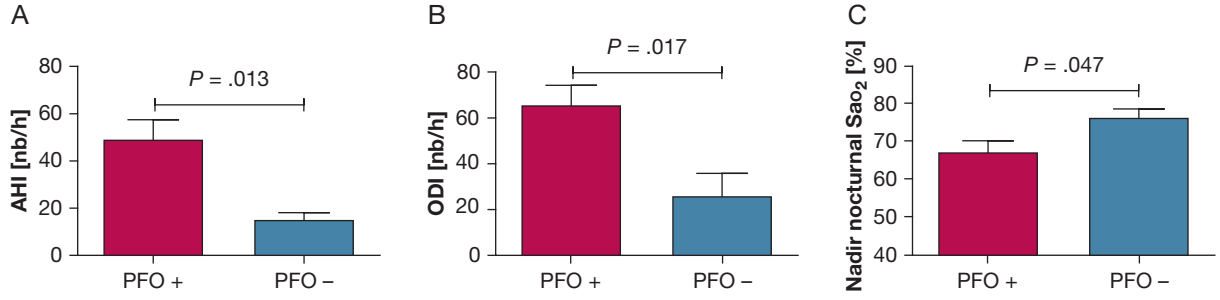

Figure 3 – *A-C, Sleep-disordered breathing (A, B) and nadir Sao_2 (C) in high-altitude dwellers with (PFO +) and without (PFO −) the presence of a PFO at 3,600 m. Data are mean ± SD. PFO = patent foramen ovale. See Figure 1 legend for expansion of other abbreviations.*

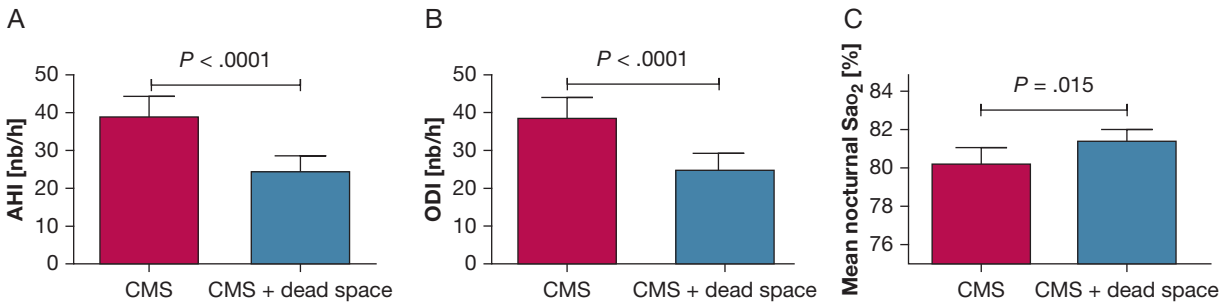

Figure 4 – *Effects of added dead space on sleep-disordered breathing (A, B) and mean Sao_2 (C) in patients with CMS at 3,600 m in La Paz, Bolivia. Data are mean ± SD. See Figure 1 legend for expansion of abbreviations.*

suggesting that in healthy high-altitude dwellers genetic or acquired adaptation results in improved regulation of ventilation during sleep.[41] Most importantly, such adaptation appears to be lacking in maladapted high-altitude dwellers who have CMS, as shown by a roughly 50% increase of AHI and ODI and more important nocturnal oxygen desaturation in comparison with healthy high-altitude dwellers. SDB in Andean patients with CMS in the present study was comparable to the one observed in lowlanders acutely exposed to high-altitude[27,42] and Han Chinese and Tibetan patients with CMS studied in Lhasa (3,658 m).[43] Interestingly, in young Andean high-altitude dwellers with excessive erythrocytosis (an early stage of CMS), AHI was reported to be roughly 4 times higher than in healthy control subjects,[20] highlighting the possibility that SDB may play an etiologic role in the development of CMS. The positive relationship, in the present study, between hemoglobin and AHI, and its inverse relationship with nocturnal Sao_2, are consistent with this hypothesis. Alternatively, obesity could contribute to SDB and CMS. In the present study, BMI was higher in patients than in control subjects, and obesity is frequently associated with SDB.[44] In line with this speculation, in a large population-based study of Peruvian high-altitude dwellers, among a series of clinical markers contributing to excessive erythrocytosis, the greatest attributable fraction was for being overweight.[1]

Desaturation-reoxygenation sequences are a typical pattern associated with SDB and have been suggested to increase sympathetic outflow[11,45] and oxidative stress.[46-48] Excess free radicals may cause cell membrane damage and vascular endothelial dysfunction and promote arteriosclerosis,[7,18] thereby contributing to pulmonary and systemic vascular dysfunction.[6,7,18] The positive relationship between AHI and systemic and pulmonary arterial pressure is consistent with this hypothesis and highlights the potential of SDB to increase cardiovascular risk in high-altitude dwellers.

At low altitude, a PFO is associated with more severe nocturnal oxygen desaturation[49] and pulmonary hypertension[50] in patients with SDB, but no such information exists in high-altitude dwellers. We found that a PFO was associated with more severe SDB and exaggerated pulmonary hypertension. The latter finding is consistent with a previous report[24] demonstrating that in high-altitude dwellers, a PFO facilitates exercise-induced pulmonary vasoconstriction and right ventricular dysfunction and could be consistent with the hypothesis that SDB may represent an additional mechanism contributing to pulmonary and right ventricular remodeling and dysfunction in high-altitude dwellers with a PFO.[24]

The mechanism leading to disordered breathing in high-altitude dwellers is not clear. High-altitude hypoxemia-induced stimulation of ventilation results in hypocapnia, which, if it decreases below a certain level (apnea threshold), will lead to apnea.[41,51] In patients with CMS, the apnea threshold was reported to be higher compared with healthy high-altitude natives, making the patients more likely to reach this threshold.[52] This may account, at least in part, for the difference in SDB we found between patients with CMS and control subjects. In line with this hypothesis, we found that added dead space improved SDB and nocturnal oxygen saturation in patients with CMS. This result is in accordance with (1) findings in healthy subjects demonstrating that administration of CO_2 (yielding an increase in $Paco_2$ of 1-2 mm Hg) at constant Sao_2 stabilizes nocturnal breathing and eliminates hypoxia-induced SDB during hypobaric hypoxia,[53] and (2) data in mountaineers with severe SDB at high altitude showing marked improvement with a 500-mL increase in dead space through a fitted face mask.[27,42] Alternatively, added dead

space may stabilize breathing by dampening the hypocarbia during postarousal hyperventilation.[42] Finally, increasing CO_2 reserve by acetazolamide administration to patients with CMS also increases ventilation and oxygenation during sleep.[54] Taken together, these data are consistent with the hypothesis that the positive effects of added dead space on nocturnal ventilation are mediated by CO_2.

Conclusions

We found that SDB and nocturnal oxygen desaturation are more severe in high-altitude dwellers with CMS than in healthy high-altitude dwellers. Most importantly, alterations in nocturnal breathing and oxygenation were associated with systemic and pulmonary vascular dysfunction. In the presence of a PFO, SDB and cardiovascular alterations were even more pronounced. This suggests, by analogy to recent observations in patients with sleep apnea syndrome at low altitude,[55,56] that PFO closure may improve systemic and pulmonary vascular function and SDB in patients with CMS. Finally, increasing the respiratory dead space improved SDB in patients with CMS. We speculate that in patients with CMS, manipulation of nocturnal CO_2 may not only improve SDB but also have favorable effects on the cardiovascular phenotype.

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Author contributions: U. S. is the guarantor of the content of the manuscript, including the data and analysis. E. R. was involved in the clinical examinations, study design, data analysis and interpretation, and wrote a first draft of the paper. S. F. R., L. P., R. B., D. A., R. S., C. Salinas, M. V., Y. A., and A. L. contributed substantially to the clinical examinations, data analysis and interpretation, and the writing of the manuscript. C. R. was involved in recruiting patients and control subjects. R. H., C. Sartori, and U. S. were involved in the design of the study, data analysis and interpretation, and final writing of the paper.

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References

1. De Ferrari A, Miranda JJ, Gilman RH, et al; CRONICAS Cohort Study Group. Prevalence, clinical profile, iron status, and subject-specific traits for excessive erythrocytosis in Andean adults living permanently at 3,825 meters above sea level. *Chest*. 2014;146(5):1327-1336.
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. Negi PC, Asotra S, Ravi Kumar V, et al. Epidemiological study of chronic mountain sickness in natives of Spiti Valley in the Greater Himalayas. *High Alt Med Biol*. 2013;14(3):220-229.
4. Sahota IS, Panwar NS. Prevalence of chronic mountain sickness in high altitude districts of Himachal Pradesh. *Indian J Occup Environ Med*. 2013;17(3):94-100.
5. León-Velarde F, Villafuerte FC, Richalet JP. Chronic mountain sickness and the heart. *Prog Cardiovasc Dis*. 2010;52(6):540-549.
6. Pratali L, Rimoldi SF, Rexhaj E, et al. Exercise induces rapid interstitial lung water accumulation in patients with chronic mountain sickness. *Chest*. 2012;141(4):953-958.
7. Rimoldi SF, Rexhaj E, Pratali L, et al. Systemic vascular dysfunction in patients with chronic mountain sickness. *Chest*. 2012;141(1):139-146.
8. Stuber T, Sartori C, Schwab M, et al. Exaggerated pulmonary hypertension during mild exercise in chronic mountain sickness. *Chest*. 2010;137(2):388-392.
9. Bloch KE, Latshang TD, Turk AJ, et al. Nocturnal periodic breathing during acclimatization at very high altitude at Mount Muztagh Ata (7,546 m). *Am J Respir Crit Care Med*. 2010;182(4):562-568.
10. Reite M, Jackson D, Cahoon RL, Weil JV. Sleep physiology at high altitude. *Electroencephalogr Clin Neurophysiol*. 1975;38(5):463-471.
11. Gilmartin GS, Lynch M, Tamisier R, Weiss JW. Chronic intermittent hypoxia in humans during 28 nights results in blood pressure elevation and increased muscle sympathetic nerve activity. *Am J Physiol Heart Circ Physiol*. 2010;299(3):H925-H931.
12. Imadojemu VA, Mawji Z, Kunselman A, Gray KS, Hogeman CS, Leuenberger UA. Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy. *Chest*. 2007;131(5):1406-1413.
13. Joho S, Oda Y, Ushijima R, Hirai T, Inoue H. Effect of adaptive servoventilation on muscle sympathetic nerve activity in patients with chronic heart failure and central sleep apnea. *J Card Fail*. 2012;18(10):769-775.
14. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96(4):1897-1904.
15. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. 8-Isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy. *Chest*. 2003;124(4):1386-1392.
16. Costanzo MR, Khayat R, Ponikowski P, et al. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. *J Am Coll Cardiol*. 2015;65(1):72-84.
17. Yamauchi M, Nakano H, Maekawa J, et al. Oxidative stress in obstructive sleep apnea. *Chest*. 2005;127(5):1674-1679.
18. Bailey DM, Rimoldi SF, Rexhaj E, et al. Oxidative-nitrosative stress and systemic vascular function in highlanders with and without exaggerated hypoxemia. *Chest*. 2013;143(2):444-451.
19. Pratali L, Allemann Y, Rimoldi SF, et al. RV contractility and exercise-induced pulmonary hypertension in chronic mountain sickness: a stress echocardiographic and tissue Doppler imaging study. *JACC Cardiovasc Imaging*. 2013;6(12):1287-1297.
20. Julian CG, Vargas E, Gonzales M, et al. Sleep-disordered breathing and oxidative stress in preclinical chronic mountain sickness (excessive erythrocytosis). *Respir Physiol Neurobiol*. 2013;186(2):188-196.
21. Monge-C C, Arregui A, León-Velarde F. Pathophysiology and epidemiology of chronic mountain sickness. *Int J Sports Med*. 1992;13(suppl 1):S79-S81.
22. Reeves JT, Leon-Velarde F. Chronic mountain sickness: recent studies of the relationship between hemoglobin concentration and oxygen transport. *High Alt Med Biol*. 2004;5(2):147-155.

23. Beelke M, Angeli S, Del Sette M, et al. Obstructive sleep apnea can be provocative for right-to-left shunting through a patent foramen ovale. *Sleep*. 2002;25(8):856-862.
24. Brenner R, Pratali L, Rimoldi SF, et al. Exaggerated pulmonary hypertension and right ventricular dysfunction in high-altitude dwellers with patent foramen ovale. *Chest*. 2015;147(4):1072-1079.
25. Khayat RN, Xie A, Patel AK, Kaminski A, Skatrud JB. Cardiorespiratory effects of added dead space in patients with heart failure and central sleep apnea. *Chest*. 2003;123(5):1551-1560.
26. Xie A, Rankin F, Rutherford R, Bradley TD. Effects of inhaled CO_2 and added dead space on idiopathic central sleep apnea. *J Appl Physiol*. 1997;82(3):918-926.
27. Lovis A, De Riedmatten M, Greiner D, et al. Effect of added dead space on sleep disordered breathing at high altitude. *Sleep Med*. 2012;13(6):663-667.
28. Klem GH, Lüders HO, Jasper HH, Elger C; The International Federation of Clinical Neurophysiology. The ten-twenty electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol Suppl*. 1999;52:3-6.
29. Iber C, Ancoli-Israel S, Chesson ALJ, Quan SF. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
30. Berry RB, Budhiraja R, Gottlieb DJ, et al; American Academy of Sleep Medicine; Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. *J Clin Sleep Med*. 2012;8(5):597-619.
31. 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.
32. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA; Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15(2):167-184.
33. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713.
34. Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol*. 2001;38(3):613-623.
35. Seiler C. How should we assess patent foramen ovale? *Heart*. 2004;90(11):1245-1247.
36. Faita F, Masi S, Loukogeorgakis S, et al. Comparison of two automatic methods for the assessment of brachial artery flow-mediated dilation. *J Hypertens*. 2011;29(1):85-90.
37. Gemignani V, Faita F, Ghiadoni L, Poggianti E, Demi M. A system for real-time measurement of the brachial artery diameter in B-mode ultrasound images. *IEEE Trans Med Imaging*. 2007;26(3):393-404.
38. Laurent S, Cockcroft J, Van Bortel L, et al; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27(21):2588-2605.
39. Asmar R, Benetos A, Topouchian J, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension*. 1995;26(3):485-490.
40. Fowler AC, Kalamangalam GP. Periodic breathing at high altitude. *IMA J Math Appl Med Biol*. 2002;19(4):293-313.
41. Weil JV. Sleep at high altitude. *High Alt Med Biol*. 2004;5(2):180-189.
42. Patz DS, Patz MD, Hackett PH. Dead space mask eliminates central apnea at altitude. *High Alt Med Biol*. 2013;14(2):168-174.
43. Sun S, Oliver-Pickett C, Ping Y, et al. Breathing and brain blood flow during sleep in patients with chronic mountain sickness. *J Appl Physiol*. 1996;81(2):611-618.
44. Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. *Can Respir J*. 2006;13(4):203-210.
45. Tamisier R, Pépin JL, Rémy J, et al. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. *Eur Respir J*. 2011;37(1):119-128.
46. Badran M, Ayas N, Laher I. Cardiovascular complications of sleep apnea: role of oxidative stress. *Oxid Med Cell Longev*. 2014;2014:985258. http://dx.doi.org10.1155/2014/985258.
47. Yamauchi M, Kimura H. Oxidative stress in obstructive sleep apnea: putative pathways to the cardiovascular complications. *Antioxid Redox Signal*. 2008;10(4):755-768.
48. Pialoux V, Hanly PJ, Foster GE, et al. Effects of exposure to intermittent hypoxia on oxidative stress and acute hypoxic ventilatory response in humans. *Am J Respir Crit Care Med*. 2009;180(10):1002-1009.
49. Shaikh ZF, Jaye J, Ward N, et al. Patent foramen ovale in severe obstructive sleep apnea: clinical features and effects of closure. *Chest*. 2013;143(1):56-63.
50. Rigatelli G, Sharma S. Patent foramen ovale-obstructive sleep apnea relationships: pro and cons. *Cardiovasc Revasc Med*. 2012;13(5):286-288.
51. Dempsey JA, Smith CA, Przybylowski T, et al. The ventilatory responsiveness to CO(2) below eupnoea as a determinant of ventilatory stability in sleep. *J Physiol*. 2004;560(Pt 1):1-11.
52. Fatemian M, Gamboa A, Leon-Velarde F, Rivera-Ch M, Palacios JA, Robbins PA. Selected contribution: ventilatory response to CO_2 in high-altitude natives and patients with chronic mountain sickness. *J Appl Physiol*. 2003;94(3):1279-1287.
53. Berssenbrugge A, Dempsey J, Iber C, Skatrud J, Wilson P. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. *J Physiol*. 1983;343(1):507-524.
54. Richalet JP, Rivera M, Bouchet P, et al. Acetazolamide: a treatment for chronic mountain sickness. *Am J Respir Crit Care Med*. 2005;172(11):1427-1433.
55. Rimoldi SF, Ott S, Rexhaj E, et al. Patent foramen ovale closure in obstructive sleep apnea improves blood pressure and cardiovascular function. *Hypertension*. 2015;66(5):1050-1057.
56. Rimoldi SF, Ott SR, Rexhaj E, et al. Effect of patent foramen ovale closure on obstructive sleep apnea. *J Am Coll Cardiol*. 2015;65(20):2257-2258.