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RESEARCH ARTICLE

Possible strategies to reduce altitude-related excessive polycythemia

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Abstract

We sought to determine the effects of three treatments on hemoglobin (Hb) levels in patients with chronic mountain sickness (CMS): *1*) descent to lower altitude, *2*) nocturnal O_2 supply, *3*) administration of acetazolamide. Nineteen patients with CMS living at an altitude of 3,940 ± 130 m participated in the study, which consisted of a 3-wk intervention phase and a 4-wk postintervention phase. Six patients spent 3 wk at an altitude of 1,050 m (low altitude group, LAG), six received supplemental oxygen for 12 h overnight (oxygen group, OXG), and seven received 250 mg of acetazolamide daily (acetazolamide group, ACZG). Hemoglobin mass (Hbmass) was determined using an adapted carbon monoxide (CO) rebreathing method before, weekly during, and 4 wk postintervention. Hbmass decreased by 245 ± 116 g ($P < 0.01$) in the LAG and by 100 ± 38 g in OXG, and 99 ± 64 g in ACZG ($P < 0.05$, each), respectively. In LAG, hemoglobin concentration ([Hb]) decreased by 2.1 ± 0.8 g/dL and hematocrit by 7.4 ± 2.9% (both $P < 0.01$), whereas OXG and ACZG only trended toward lower values. Erythropoietin concentration ([EPO]) decreased between 81 ± 12% and 73 ± 21% in LAG at low altitude ($P < 0.01$) and increased by 161 ± 118% 5 days after return ($P < 0.01$). In OXG and ACZG, the [EPO] decrease was ∼75% and ∼50%, respectively, during the intervention ($P < 0.01$). Descent to low altitude (from 3,940 m to 1,050 m) is a fast-acting measure for the treatment of excessive erythrocytosis in patients with CMS, reducing Hbmass by 16% within 3 wk. Nighttime oxygen supplementation and daily acetazolamide administration are also effective, but reduce Hbmass by only 6%.

NEW & NOTEWORTHY To our knowledge, this is the first study examining the effect of three different treatments [descending to lower altitude (from 3,900 m to 1,050 m), nocturnal oxygen supply, and administration of acetazolamide] on changes in hemoglobin mass in patients experiencing chronic mountain sickness (CMS). We report that descent to low altitude is a fast-acting measure for the treatment of excessive erythrocytosis in patients with CMS, reducing Hbmass by 16% within 3 wk. Nighttime oxygen supplementation and daily acetazolamide administration are also effective, but reduce Hbmass by only 6%. In all three treatments, the underlying mechanism is a reduction in plasma erythropoietin concentration due to higher oxygen availability.

chronic mountain sickness; erythropoietin; hemoglobin concentration; hemoglobin mass; plasma volume

INTRODUCTION

Patients with chronic mountain sickness (CMS; 1, 2) develop severe polycythemia, in which a hemoglobin concentration ([Hb]) of >21 g/dL in men and >19 g/dL in women is considered typical (3–5). The disease occurs above an altitude of 2,500 m (4, 5) and affects ∼20 million people (particularly in the high altitude areas of the Andes, but also in Asia). Peripheral chemoreceptors are thought to be desensitized, causing altered respiratory stimulus and relative hypoventilation (6, 7). It is still unclear whether the lower sensitivity is the cause or the consequence of excessive erythropoiesis and whether the lower hypoxic ventilatory response (HVR) is primary or secondary (8). Hypoventilation causes a reduction in arterial O_2 partial pressure and Hb oxygen saturation. This leads to excessive erythropoiesis, which increases red blood cell count and blood viscosity (9). Characteristic symptoms include vascular dysfunction (10), decreased cerebral blood flow velocity (11), increased pulmonary blood pressure (12, 13), and heart failure, particularly in the right ventricle (4, 5).

Several studies demonstrated the magnitude of erythropoietic overregulation in patients with CMS by determination of hemoglobin mass (Hbmass; 14–18). Although [Hb] is an easy parameter to measure, it is less suitable for this study. Hemoglobin concentration is determined not only by the hemoglobin present in the circulation, but to a large extent by plasma volume (PV), which decreases in patients

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with severe CMS (15, 16, 18). In a recent study, we were able to demonstrate higher Hbmass on average by ~70%, in extreme cases by ~140%, compared with healthy altitude dwellers (18). Likewise, the blood volume (BV) was elevated on average by ~30% compared with healthy altitude dwellers despite lower PV by ~15% (18). Drastic changes in PV and BV in patients with CMS may cause [Hb] to be less reliable, while Hbmass can provide a more consistent measure.

Possible strategies to treat the disease consist in increasing the alveolar oxygen supply, which could prevent erythropoietic overcompensation. The most effective known therapy of the disease consists of descending to lower-altitude areas and staying there permanently (19). Currently, only experience reports exist, whereas extensive scientific studies on this subject are lacking. Just two case reports suggest rapid destruction of erythrocytes immediately after descent to low altitudes (20), which may be consistent with the theory of "neocytolysis" that hypothesized to occur when there is a sudden excess of erythrocytes as erythropoietin availability drops (21–23).

In patients with CMS, hypoxemia is more pronounced compared with healthy highlanders, especially during sleep, leading to increased erythropoietic activity that may be due to elevated plasma erythropoietin concentration ([EPO]) and decreased soluble EPO receptor (24). Therefore, it is conceivable that an increase in inspiratory O_2 supply at night leads to an effective reduction in the erythropoietic response, although this has not yet been investigated.

Another way to increase arterial O_2 in patients with CMS is to stimulate increased respiration, causing the normal physiological response to a hypoxic stimulus. Pharmacologically, this can be achieved by oral administration of acetazolamide (25). Acetazolamide dosing of 250 mg/day for 3 wk resulted in a decrease in hematocrit (Hct) of 7% (26), which was maintained at the same level for 6 wk (27) and 3 mo (28).

The aim of the present pilot study was to determine the hematologic effects of three different interventions in patients with polycythemia: *1*) descent to low altitude, *2*) nocturnal supplementation of O_2, and *3*) oral administration of acetazolamide. To date, the target variables determined in the treatment of patients with CMS have been [Hb] and/or Hct, which can provide important information as a first approximation, but does not allow accurate conclusions to be made about the magnitude of the hematologic treatment effects. In this study, therefore, Hbmass as well as PV and BV were determined.

METHODS

The present study is the third part of a larger three-phase project. In the first phase, the carbon monoxide (CO) rebreathing method was adapted to accommodate the special conditions of high-altitude residents and patients with polycythemia (29). In the second phase, representative data for Hbmass and BV were collected from a large number of patients to judge the extent of erythrocytosis. These data were used to differentiate between normal altitude adaptation and pathological reaction to chronic hypoxia (18). In the third phase, which is presented here, different therapeutic approaches for reducing Hbmass are evaluated.

Ethical Approval

Ethical approval was obtained from the Ethics Committee of the Universidad Mayor San Andres in La Paz, Bolivia (No. 846/2,014). The study met the standards of the Declaration of Helsinki. Written informed consent was obtained from all subjects. Subjects participated in the study voluntarily and could withdraw at any time without giving a reason.

Subjects

A total of 19 male subjects who were born at an altitude of ~3,900 m and continued to live at this altitude throughout their lives participated in the study (Table 1). Exclusion criteria for participants included chronic lung disease of various origins, phlebotomy (also known as sangria) within 3 mo before the start of the study, as well as short-term stays longer than 1 wk at lower altitudes during the year before study entry. All participants identified themselves as Aymara. For age, weight, and body mass index (BMI), see Table 1.

Before starting the study, all study participants were diagnosed with an [Hb] > 21.0 g/dL and a Hct > 63%. When the baseline values were determined Hct values of three patients were <63%, but in all cases >60%.

Study Design

Patients were divided into three groups. Group one participants were chosen according to their occupational and familial availability, whereas participants in groups two and three were assigned randomly. During the first week, basal values were collected at an altitude of 3,600 m for all patients. During the subsequent 3-wk intervention phase, participants of the first group (n = 6) lived for 3 wk continuously at an altitude of 1,050 m in the Yungas region, ~100 km from La Paz (low altitude group, LAG). Participants in the second group (n = 6) went about their normal occupation during the day and spent the nights (7:00 PM to 7:00 AM) over 3 wk in a hospital where they breathed an oxygen-enriched air mixture supplied through the nose (flow rate of 3 L/min) the entire time (oxygen group, OXG). One subject of this group was excluded from the calculation of mean values because of an apparent iron deficiency (initial ferritin: 6.9 ng/mL, initial [EPO]: 255 mU/mL) detected after the end of the study. Participants in the third group (n = 7) went about their normal occupation, taking a dosage of 250 mg of acetazolamide (EDEMOX, Chiesi, Barcelona, Spain) orally every morning for 3 wk (acetazolamide group, ACZG). Determinations of

Table 1. *Characteristics of patients*

	LAG	OXG	ACZG
Altitude of birth, m	3,642 ± 520	3,860 ± 192	3,896 ± 130
Altitude of residence, m	3,883 ± 129	3,950 ± 137	3,979 ± 122
Age, yr	63.3**†† ± 4.6	49.27 ± 0.0	54.0 ± 5.4
Body mass, kg	88.8 ± 10.9	81.3 ± 16.0	85.4 ± 5.8
BMI, kg/m^2	32.5 ± 3.5	29.1 ± 5.6	30.1 ± 3.6
[Hb], g/dL	21.5 ± 1.3	21.6 ± 1.5	21.8 ± 1.5
Hct, %	66.9 ± 4.5	67.0 ± 4.9	67.3 ± 4.6
Qinghai score	9.2 ± 2.2	9.2 ± 3.6	9.7 ± 3.8

Values are means ± SD. LAG, low-altitude group, n = 6; OXG, oxygen group, n = 6; ACZG, acetazolamide group, n = 7. BMI, body mass index; [Hb], hemoglobin concentration; Hct, hematocrit. Significance of differences between LAG and OXG: $^{**}P < 0.01$, between LAG and ACZG: $^{††}P < 0.01$.

all relevant parameters were made twice before the start of the intervention and at *day 7*, *14*, and *21* during each intervention. Subsequently, measurements were performed after 5 days and after 2 and 4 wk during the postintervention phase.

All three groups were supervised daily by research assistants throughout the intervention period, ensuring high compliance.

Anthropometric Determinations and Analytic Methods

All subjects completed a medical history survey before study initiation that included questions about previous life circumstances, pre-existing health conditions, and risk factors such as smoking and alcohol consumption. Before, and periodically after the interventions, the Qinghai score was recorded (4) as a total score and a clinical score without inclusion of [Hb] (30).

Body fat mass was determined using quadripolar impedance (Omron BF508 bioimpedance analyzer, Omron, Osaka, Japan). Subjects were weighed, and fat percentage and fat-free mass were determined in triplicate.

Two cubital venous blood samples (9 mL of heparinized blood and 5 mL for serum analysis) were collected for the determination of basic hematological parameters, erythropoietin (EPO), and ferritin levels. The entire procedure, including blood sample collection, transport, storage, and analysis, was performed under standardized conditions (31). Blood samples were collected after subjects had rested in a sitting position for at least 15 min. All samples were analyzed in the laboratory of the Instituto Boliviano de Biologia de la Altura (IBBA) at La Paz, and samples collected in the lowlands (Yungas) were transported to La Paz within 4 h under cool conditions.

Hemoglobin concentration ([Hb]) was determined in triplicate by the cyanmethemoglobin method, and Hct was determined by microcentrifugation. In serum, EPO and ferritin were measured with enzyme-labeled immuno-metric solid-phase chemiluminescence assays [both Immulite 1000 (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany)].

Before CO rebreathing and capillary blood sampling, patients spent at least 15 min in a sitting position, as they did before venous blood sampling. Capillary blood samples were collected from a hyperemic earlobe for analysis of blood gases and acid-base status. Partial O_2 pressure (P_{O_2}), partial CO_2 pressure (P_{CO_2}), peripheral O_2 saturation (Sp_{O_2}), and pH were measured (i-STAT 1 analyzer; Abbott, NJ; OSM3, Radiometer, Copenhagen, Denmark). Standard bicarbonate and base excess were calculated from these values. Actual and standard hemoglobin O_2 half-saturation pressure (P_{50}) from the hemoglobin-oxygen dissociation curve was calculated using the blood gas calculator from Radiometer (Copenhagen, Denmark) and established equations (31).

Hbmass and Blood Volume

The CO rebreathing method originally described by Schmidt and Prommer (32) and modified by Wachsmuth et al. (29) specifically for patients with polycythemia was performed to determine Hbmass and blood volume. In a sitting upright position, a bolus of CO was inhaled and rebreathed with pure oxygen for 2 min. Hbmass was then calculated from the difference in HbCO concentration before and after rebreathing. In healthy subjects residing at sea level, the increase in blood HbCO concentration 7 min after the start of rebreathing is used to calculate Hbmass. However, because the mixing time of CO after inhalation is prolonged in patients with altitude-related polycythemia (29), the HbCO concentration was averaged between the 14th and 20th minute after the start of inhalation and used for further calculation.

After this adjustment, valid and reliable results are obtained, reflected by a typical error (TE) of 1.6%. For a detailed description of the modified method, see the study by Wachsmuth et al. (29).

Calculation of Hbmass, Blood Volume, and Plasma Volume

Hbmass was calculated as described by Wachsmuth et al. (29). Red blood cell volume (RCV), BV, and PV were calculated according to formulae 1–3.

$$\mathrm{RCV(mL)} = \mathrm{Hbmass(g)}/[\mathrm{Hb}](\mathrm{g/dL}) \times \mathrm{Hct} \quad (1)$$

$$\mathrm{BV(mL)} = \mathrm{Hbmass(g)} \times 100/[\mathrm{Hb}](\mathrm{g/dL})/\mathrm{cf} \quad (2)$$

$$\mathrm{PV(mL)} = \mathrm{BV(mL)} - \mathrm{RCV(mL)} \quad (3)$$

where Hct is hematocrit (fraction), because peripheral Hct is usually higher than Hct in total blood volume, the ratio of body Hct/peripheral Hct, called cell factor (cf), is used to calculate blood volume (33). Because the cf changes with increasing Hct at increasing altitudes (34), we used the value of 0.96 for all groups instead of the value of 0.91 that is normally used at sea level (35).

Statistical Analysis

For statistical analysis, Statistical Product and Service Solutions (SPSS), RRID:SCR_002865 was used. Because this was a pilot study, a formal power calculation was not required. The α level was set to 0.05. The normality of the data distribution was assessed with the Kolmogorov–Smirnov test. All parameters except the EPO levels were normally distributed.

The following methods were used for the statistical analysis. *1*) To compare the mean anthropometric, hematological, and acid-base baseline data of the different groups, one-way ANOVA followed by the Bonferroni post hoc test was applied. *2*) In a second step, changes in the hematological and anthropometric variables over the course of the interventions were examined by a two-way ANOVA with repeated measurements and group and time as the independent variables. *3*) In addition, a one-way ANOVA with repeated measurements and time as a single independent factor was performed to show the development of hematological and anthropometric variables during and after each intervention. The significance of mean differences within one intervention protocol was tested using the paired *t* test with a correction for multiple measurements to minimize the risk for type I errors (36). The Wilcoxon signed-rank test was applied as a post hoc test to assess possible changes in EPO level during and after the intervention. *4*) Bivariate linear regression analyses were performed with *1*) [Hb] as the dependent variable and Hbmass and PV as the independent variable and *2*) Qinghai-score as the dependent and Hbmass as the independent variable.

RESULTS

Baseline Values

All subjects were born at an altitude of ~3,900 m. Since birth, subjects continuously resided at this high altitude. The three groups did not differ in terms of [Hb], Hct, and Qinghai score. Subjects who were engaged in regular work could not be chosen for the LAG, thus the age of the LAG was significantly higher than the other two groups. Body mass and BMI also tended to be higher in this group (Table 1).

No differences existed among the three groups with regard to blood gas and acid-base status, hematological values, and blood volumes.

Blood Gas and Acid-Base Status

P_{O_2} and Sp_{O_2} were significantly elevated during the stay at low altitude and tended toward lower values postintervention (Table 2). In the OXG, Sp_{O_2} increased to 93.9 ± 2.1% during the overnight intervention. However, during the daytime, there were no changes in Sp_{O_2} over the entire time course. In the ACZG, P_{O_2} increased only in the first week and was not statistically different from baseline level for the rest of the study.

The P_{50} of the oxygen dissociation curve remained unchanged under standard conditions in all three groups. However, under actual conditions, P_{50} increased in the ACZG by 3.2 ± 1.2 mmHg ($P < 0.01$) in the first week and remained elevated during the entire intervention period.

P_{CO_2} increased by ~5 mmHg during the stay at low altitude (LAG) and subsequently decreased back to baseline values. There were no changes in the OXG during the intervention, however P_{CO_2} dropped significantly by ~6 mmHg in the ACZG throughout the intervention. The pH did not change in LAG and OXG, whereas it decreased significantly in the first week after acetazolamide administration (from 7.40 ± 0.02 to 7.27 ± 0.03, $P < 0.001$) and remained decreased until the end of intervention. Actual HCO_3^- increased slightly in the LAG (23.3 ± 1.0 mmol/L to 26.3 ± 2.2 mmol/L, $P < 0.05$), remained unchanged in the OXG, and decreased markedly in the ACZG (from 23.6 ± 1.4 mmol/L to 14.6 ± 1.0 mmol/L, $P < 0.001$).

Hematological Data and Blood Volumes

In the LAG, Hbmass decreased continuously by 245 ± 116 g ($P < 0.01$) until the fifth day of postintervention and did not fully return to baseline values after the 4-wk postintervention (Fig. 1*A*; Table 3). In the OXG and ACZG, Hbmass decreased equally by 100 ± 38 g and 99 ± 64 g (both $P < 0.05$), respectively, during the intervention. The behavior of RCV corresponds to that of Hbmass with the strongest effect in the LAG (−804 ± 383 mL, $P < 0.01$, Fig. 1*B*). Blood volume decreased by 614 ± 367 mL ($P < 0.05$) 5 days after the end of the intervention at low altitude and tended toward lower values thereafter (Fig. 1*D*). There were no significant changes in BV in the OXG and ACZG. Plasma volume increased until the end of the intervention at low altitude (+445 ± 284 mL, $P < 0.05$) and returned to baseline values in the postintervention period (Fig. 1*C*). No changes were seen in the other two groups.

The [Hb] in the LAG dropped steadily from 21.5 ± 1.4 g/dL to 19.4 ± 1.1 g/dL ($P < 0.01$) by the third week of intervention and remained below baseline for two more weeks (Table 3). There was no significant change in [Hb] in the other two groups, except 5 days after the intervention in ACZG. Hematocrit and RBC responded similarly as [Hb] in all three groups. In the LAG, Hct dropped from 66.9 ± 4.6% to 59.5 ± 3.1% ($P < 0.01$). Reticulocyte count decreased significantly in the LAG after 2 wk ($P < 0.05$), reached the lowest value after 3 wk ($P < 0.01$), and remained lowered 5 days after reascension (Table 3). In the OXG, there was no significant change in reticulocyte count, however, the ACZG had the lowest values ($P < 0.05$) 5 days postintervention.

In both, the LAG and OXG, [EPO] decreased ~75% during the intervention period (Fig. 2, Table 3). On the fifth day of

Table 2. *Blood gas and acid-base status*

			Intervention Phase			Postintervention Phase			
	Group	Baseline	*Day 7*	*Day 14*	*Day 21*	*Day +5*	*Day +14*	*Day +28*	ANOVA
Sp_{O_2}, %	LAG***	80.8 ± 3.1	89.2** ± 3.0	88.5** ± 1.9	86.8* ± 4.0	77.3 ± 3.7	76.3 ± 5.2	78.7 ± 3.7	Time $P < 0.001$
	OXG	82.2 ± 2.9	81.6 ± 3.4	83.8 ± 1.6	82.8 ± 2.7	83.2 ± 3.8	82.0 ± 5.6	82.0 ± 4.4	group n.s.
	ACZG	81.9 ± 4.1	82.2 ± 5.2	78.8 ± 7.0	78.7 ± 6.6	79.2 ± 7.1	81.8 ± 3.8	79.2 ± 5.3	interaction $P < 0.001$
P_{O_2}, mmHg	LAG***	44.2 ± 2.9	58.0** ± 5.6	55.5** ± 3.2	53.0* ± 5.9	39.8 ± 2.4	41.0 ± 3.6	42.5 ± 2.6	Time $P < 0.001$
	OXG	45.7 ± 2.4	44.4 ± 2.3	47.2 ± 1.6	46.0 ± 1.9	47.0 ± 4.0	47.0 ± 4.2	48.3 ± 2.7	group n.s.
	ACZG**	46.5 ± 4.5	52.8** ± 6.0	48.0 ± 8.0	46.8 ± 7.3	44.7 ± 6.8	46.7 ± 4.2	44.3 ± 4.7	interaction $P < 0.001$
P_{CO_2}, mmHg	LAG***	35.7 ± 2.6	40.9** ± 3.7	41.7*** ± 2.8	41.2* ± 4.7	34.9 ± 2.7	34.7 ± 3.8	35.1 ± 3.6	Time $P < 0.05$
	OXG	38.5 ± 2.1	39.4 ± 2.0	37.1 ± 1.1	38.3 ± 2.4	35.7* ± 1.7	36.5 ± 2.2	38.1 ± 4.4	group n.s.
	ACZG***	37.8 ± 2.5	31.8*** ± 1.8	32.2** ± 2.8	31.9** ± 3.7	36.4 ± 2.2	37.2 ± 2.1	38.0 ± 2.0	interaction $P < 0.001$
pH	LAG*	7.42 ± 0.02	7.39 ± 0.04	7.41 ± 0.04	7.41 ± 0.03	7.44 ± 0.03	7.40 ± 0.04	7.40 ± 0.02	Time $P < 0.001$
	OXG*	7.42 ± 0.03	7.42 ± 0.03	7.43 ± 0.02	7.42 ± 0.03	7.41 ± 0.02	7.40 ± 0.05	7.37 ± 0.03	group $P < 0.001$
	ACZG***	7.40 ± 0.02	7.27*** ± 0.03	7.31*** ± 0.02	7.33*** ± 0.05	7.39 ± 0.03	7.40 ± 0.02	7.39 ± 0.03	interaction $P < 0.001$
$[HCO_3^-]$, mmol/L	LAG***	23.3 ± 1.0	24.6 ± 2.2	26.1* ± 1.8	26.3* ± 2.2	23.4 ± 1.9	21.4* ± 1.8	21.9 ± 2.0	Time $P < 0.01$
	OXG**	25.1 ± 2.3	25.8 ± 1.3	24.6 ± 0.9	25.1 ± 0.8	22.6* ± 2.0	22.5 ± 2.4	22.4 ± 1.4	group $P < 0.001$
	ACZG***	23.6 ± 1.4	14.6*** ± 1.0	16.2*** ± 2.0	16.9** ± 4.0	22.2 ± 1.9	23.0 ± 1.2	22.8 ± 1.0	interaction $P < 0.001$
P_{50}, mmHg	LAG**	25.9 ± 0.4	26.9* ± 1.1	26.6 ± 1.2	26.2 ± 0.6	24.9 ± 0.8	25.9 ± 0.9	25.9 ± 0.9	Time $P < 0.001$
	OXG	25.7 ± 0.5	25.5 ± 0.8	25.9 ± 0.6	25.6 ± 0.6	25.8 ± 0.5	26.6 ± 0.9	26.9 ± 1.2	group $P < 0.001$
	ACZG***	26.2 ± 0.4	29.4** ± 1.1	28.6*** ± 0.6	28.0* ± 1.4	26.2 ± 0.7	26.4 ± 0.6	26.6 ± 0.4	interaction $P < 0.001$

Values are means ± SD. LAG, low-altitude group, n = 6; OXG, oxygen group, n = 5; ACZG, acetazolamide group, n = 7. P_{CO_2}, capillary CO_2-pressure; P_{50}, O_2-half saturation pressure; P_{O_2}, capillary partial O_2-pressure; Sp_{O_2}, peripheral O_2-saturation. Significance of differences from baseline values or significances of time courses (column "group"): *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; n.s., not significant.

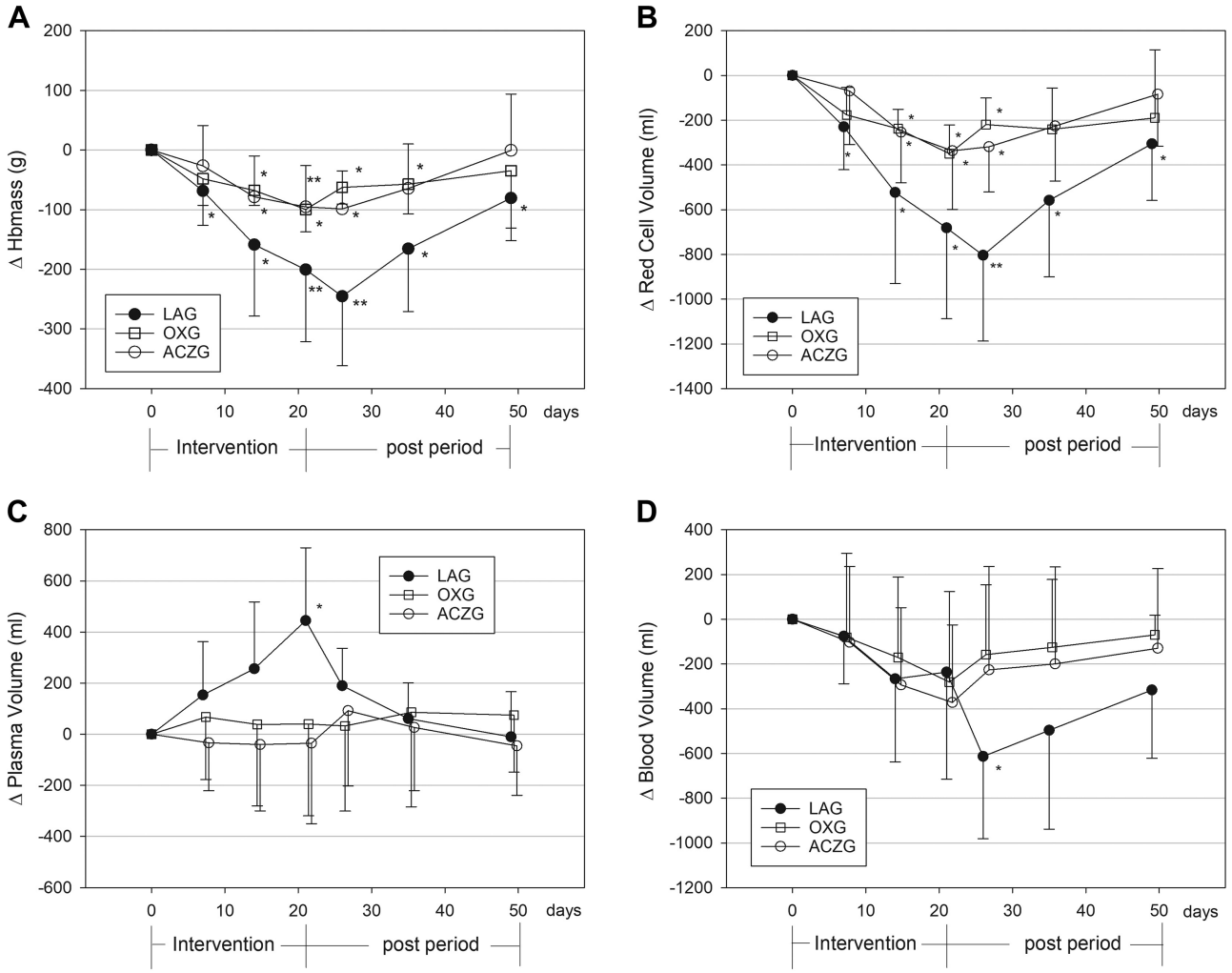

Figure 1. Changes in hemoglobin mass (*A*), red cell volume (*B*), plasma volume (*C*), and blood volume (*D*) during and after 3 wk at low altitude (LAG, $n = 6$), nocturnal O_2-supply (OXG, $n = 5$), and acetazolamide administration (ACZG, $n = 7$). Values are means ± SD. Significance of differences from baseline values (one-way ANOVA with repeated measurements and subsequent paired *t* test with a correction for multiple measurements) (36): $*P < 0.05$, $**P < 0.01$.

the postintervention phase, [EPO] increased by 161 ± 118% compared with baseline values in the LAG, whereas [EPO] had returned to baseline in the OXG. In the ACZG, [EPO] decreased by ~50% ($P < 0.01$) throughout the intervention period and returned to baseline during the postintervention period. The mean baseline [EPO] values, as well as the follow-up values showed high individual variability, but was clearly reduced during all three interventions.

Ferritin concentration increased significantly in all three groups during each intervention (Fig. 3, Table 3), which was most pronounced in the LAG (LAG: + 394 ± 191 ng/mL, $P < 0.001$; OXG: + 23 ± 12 ng/mL, $P < 0.05$; ACZG: + 118 ± 95 ng/mL, $P < 0.01$). In the postintervention phase, all groups almost reached the baseline ferritin values.

There was a significant relationship between the change in [Hb] over the entire observation period and the change in Hbmass and PV (Fig. 4, *A* and *B*).

Qinghai Score

The Qinghai score improved in all three groups at the end of the interventions and remained at a lower level for the following 4-wk postintervention phase (Table 3). There was a slight, but significant relationship between the reduction of Hbmass and the improvement of both the clinical and total score ($P < 0.05$ each).

DISCUSSION

To the best of our knowledge, the present study is the first to investigate the effects of different interventions to reduce Hbmass in altitude-associated excessive polycythemia. The most important result is an almost continuous reduction of Hbmass of ~16% after 3 wk of stay at low altitude, whereas nocturnal oxygen supply and the administration of acetazolamide both had an effect of 6%, over the same time course.

Stay at Low Altitude

For a long time it has been known that CMS is ameliorated or cured by descent to a low altitude (37), and even today this intervention is recommended (19). However, current scientific knowledge on this intervention is limited, furthermore, few data include observations about the reduction of excessive polycythemia.

Table 3. *Hematological data, blood volumes, and Qinghai score*

			Intervention Phase			Postintervention Phase			
	Group	Baseline	*Day 7*	*Day 14*	*Day 21*	*Day +5*	*Day +14*	*Day +28*	ANOVA
Hbmass, g	LAG***	1,559 ± 288	1,490* ± 240	1,400* ± 178	1,358* ± 182	1,313** ± 172	1,393* ± 193	1,478* ± 224	Time $P < 0.001$
	OXG**	1,568 ± 244	1,520* ± 222	1,501* ± 230	1,469** ± 250	1,506* ± 240	1,500* ± 258	1,525 ± 306	group n.s.
	ACZG***	1,614 ± 336	1,587 ± 314	1,535* ± 293	1,518* ± 303	1,515* ± 310	1,550 ± 309	1,589 ± 330	interaction $P < 0.05$
Red cell volume, mL	LAG***	4,851 ± 923	4,621* ± 754	4,328* ± 544	4,170* ± 578	4,047** ± 544	4,293* ± 610	4,545* ± 697	Time $P < 0.001$
	OXG*	4,873 ± 728	4,696 ± 692	4,634* ± 739	4,523* ± 782	4,653* ± 767	4,632 ± 803	4,683 ± 949	group n.s.
	ACZG**	5,223 ± 937	5,127 ± 864	4,931* ± 807	4,860* ± 803	4,893* ± 818	4,989 ± 786	5,149 ± 903	interaction $P < 0.01$
Blood volume, mL	LAG***	7,528 ± 1,076	7,452 ± 999	7,262 ± 895	7,292 ± 823	6,914* ± 797	7,032 ± 738	7,212 ± 842	Time $P < 0.01$
	OXG	7,548 ± 1,056	7,467 ± 806	7,377 ± 795	7,267 ± 877	7,390 ± 812	7,422 ± 783	7,478 ± 1,099	group n.s.
	ACZG	8,042 ± 1,020	7,878 ± 924	7,651 ± 1,025	7,608 ± 881	7,763 ± 830	7,826 ± 896	7,932 ± 1,014	interaction n.s.
Plasma volume, mL	LAG***	2,677 ± 393	2,831 ± 387	2,934 ± 454	3,122* ± 371	2,868 ± 429	2,738 ± 332	2,667 ± 294	Time $P = 0.07$
	OXG	2,703 ± 524	2,771 ± 426	2,742 ± 303	2,744 ± 383	2,736 ± 435	2,790 ± 484	2,779 ± 516	group n.s.
	ACZG	2,819 ± 303	2,750 ± 293	2,720 ± 396	2,748 ± 393	2,870 ± 249	2,837 ± 291	2,783 ± 328	interaction $P < 0.01$
[Hb], g/dL	LAG***	21.5 ± 1.4	20.8* ± 1.1	20.1** ± 1.0	19.4** ± 1.1	19.8** ± 1.3	20.6* ± 1.2	21.3 ± 1.0	Time $P < 0.001$
	OXG	21.6 ± 1.6	21.2 ± 1.7	21.1 ± 1.5	21.0 ± 1.8	21.2 ± 2.0	21.0 ± 2.4	21.1 ± 2.2	group n.s.
	ACZG	21.8 ± 1.5	21.8 ± 1.5	21.7 ± 1.3	21.7 ± 1.6	21.2* ± 1.6	21.6 ± 1.4	21.8 ± 1.4	interaction $P < 0.01$
[Hct], %	LAG***	66.9 ± 4.6	64.5* ± 3.6	62.2* ± 3.2	59.5** ± 3.1	61.0** ± 4.0	63.5* ± 3.9	65.5 ± 3.6	Time $P < 0.001$
	OXG	67.0 ± 5.1	65.4 ± 5.5	65.2 ± 5.0	64.6 ± 5.7	65.4 ± 6.4	64.8 ± 7.5	65.0 ± 7.1	group n.s.
	ACZG*	67.3 ± 4.6	67.5 ± 4.5	67.0 ± 3.9	66.3 ± 5.2	65.3* ± 4.8	66.2 ± 4.1	67.3 ± 4.5	interaction $P < 0.001$
RBC, 10^6/mL	LAG***	7.15 ± 0.41	6.97 ± 0.39	6.72* ± 0.34	6.43** ± 0.34	6.59** ± 0.43	6.86** ± 0.42	7.08 ± 0.38	Time $P < 0.001$
	OXG	7.32 ± 0.52	7.07 ± 0.59	7.06 ± 0.54	6.98 ± 0.61	7.07 ± 0.70	7.00 ± 0.81	7.08 ± 0.59	group n.s.
	ACZG	7.16 ± 0.54	7.16 ± 0.57	7.08 ± 0.56	7.02 ± 0.64	6.90* ± 0.64	7.02 ± 0.52	7.16 ± 0.53	interaction $P < 0.05$
Reticulocytes	LAG*	1.55 ± 0.55	1.28 ± 0.38	1.03* ± 0.35	0.76** ± 0.38	0.91** ± 0.46	1.20 ± 0.41	1.42 ± 0.36	Time n.s.
	OXG	1.65 ± 0.68	1.42 ± 0.20	1.68 ± 0.41	1.74 ± 0.46	1.77 ± 0.52	1.69 ± 0.63	1.71 ± 0.64	group $P < 0.001$
	ACZG	1.48 ± 0.51	1.47 ± 0.56	1.57 ± 0.39	1.35 ± 0.65	1.22* ± 0.65	1.37 ± 0.54	1.43 ± 4.41	interaction n.s.
[EPO], mU/mL	LAG**	43.0 ± 45.2	4.0*** ± 2.0	5.6*** ± 2.6	5.8*** ± 3.2	93.8** ±85.7	43.5 ± 40.2	37.1 ± 41.7	Time $P < 0.01$
	OXG**	19.6 ± 12.7	3.7** ± 2.5	3.1** ± 2.2	3.5** ± 2.0	18.0 ± 11.1	16.7 ± 14.6	18.3 ± 18.0	group n.s.
	ACZG**	20.3 ± 9.3	7.9*** ± 4.2	10.1** ± 6.2	9.1** ± 6.5	16.8 ± 6.3	21.3 ± 8.9	23.3 ± 12.4	interaction $P < 0.05$
Ferritin, ng/mL	LAG***	93 ± 73	264** ± 88	409** ± 166	487** ± 227	394* ± 206	211 ± 136	150 ± 120	Time $P < 0.001$
	OXG*	40 ± 50	60* ± 61	60* ± 60	63* ± 58	46 ± 64	49 ± 60	54 ± 71	group $P < 0.001$
	ACZG**	67 ± 73	121* ± 108	185* ± 145	170** ± 133	142** ± 112	121 ± 141	70 ± 75	interaction $P < 0.001$
Qinghai total score	LAG***	9.2 ± 2.2			2.5*** ± 0.5	4.7** ± 1.2	3.7** ± 1.8	5.3* ± 2.3	Time $P < 0.001$
	OXG*	9.2 ± 3.6			5.3* ± 2.5	4.5** ± 1.9	3.7* ± 2.2	5.3 ± 4.0	group n.s.
	ACZG**	9.7 ± 3.8			4.8* ± 1.8	4.3* ± 1.5	5.0* ± 2.3	4.8* ± 2.0	interaction n.s.
Qinghai clinical score	LAG**	6.7 ± 2.9			2.5* ± 0.5	3.7 ± 1.4	2.7* ± 1.5	2.8* ± 1.7	Time $P < 0.001$
	OXG*	6.2 ± 3.6			2.8* ± 1.9	2.0* ± 0.9	1.7* ± 0.8	2.8* ± 3.3	group n.s.
	ACZG**	7.2 ± 3.0			3.3* ± 0.8	2.3** ± 0.5	3.0* ± 2.0	2.3* ± 1.5	interaction n.s.

Values are means ± SD. LAG, low-altitude group, $n = 6$; OXG, oxygen group, $n = 5$; ACZG, acetazolamide group, $n = 7$. [EPO], erythropoietin concentration; [Hb], hemoglobin concentration; Hct, hematocrit, RBC, red blood cell count. Significance of differences from baseline values or significances of time courses (column "group"): *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; n.s., not significant.

When healthy high-altitude residents move to low altitudes, a rapid reduction in [Hb] occurs, with normal values being attained in an undetermined time period (38). In case reports, a reduction in [Hb] by up to 4 g/dL was observed in residents of Morococha (4,540 m) within 5 wk at sea level, with reticulocytes dropping to ~0.2% within 1 wk (20). According to Rice et al. (23), this decrease in hemoglobin occurs via the destruction of young erythrocytes (neocytolysis) as a result of a strong decrease in plasma [EPO]. Such destruction can be prevented by erythropoietin supplementation (39). The theory of neocytolysis seems to be confirmed by Ryan et al. (40), who recorded a complete deletion of the amount of erythrocytes formed at altitude in lowlanders 1 wk after return from a 2 wk stay at 5,300 m.

In contrast, a standardized study by Klein et al. (41) using labeled erythrocytes showed no signs of hemolysis upon return from 3,700 m, rather a slow decline in Hbmass explained entirely by a lower rate of red cell formation. Our data on young athletes from the same region as the patients with CMS studied here also showed no change in Hbmass values after 5 days at low altitude (42). These data together indicate that appreciable hemolysis after moving from high to low altitude remains questionable.

To the best of our knowledge, only experiential, individual case observations show changes in [Hb] in patients with CMS upon decent to low altitude and no data exist on Hbmass and blood volume. In this study, Hbmass decreases by an average of 245 g, corresponding to 15.7% of the initial volume, until the fifth day of postintervention (return to altitude). There is a mean daily decrease of 0.61% in the first week, 0.84% in the second week, and 0.46% in the third week until the fifth day after return to altitude, which argues against substantial hemolysis immediately after descent as assumed by Rice et al. (23) and supports the data of Klein et al. (41). The largest contribution to the observed reduction in Hbmass can be explained by low red cell formation, indicated by the reduction of reticulocyte counts during the stay at low altitude. Since it takes approximately 5 days for reticulocytes to appear in the bloodstream after a hypoxic stimulus, continued decreases in Hbmass at the fifth day after return to high altitude can also be explained through sustained lower production rate. The extent of the erythrocyte reduction is reflected in the ferritin concentration, which increases fivefold at low altitude. The cause of the reduced erythrocyte production is the 75%–80% reduction in [EPO] during the entire stay at low altitude due to increased arterial oxygen availability. This reduction is consistent with data

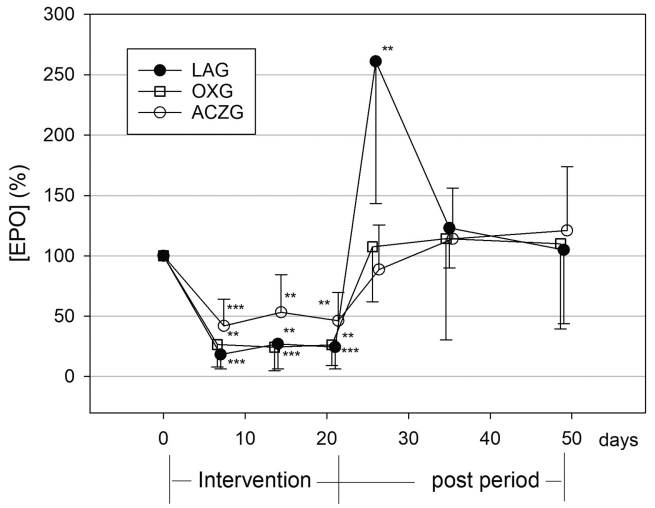

Figure 2. Serum erythropoietin (EPO) concentration (% from baseline value) during and after 3 wk at low altitude (LAG, n = 6), nocturnal O_2-supply (OXG, n = 5), and acetazolamide administration (ACZG, n = 7). Values are means ± SD. Significance of differences from baseline values (one-way ANOVA with repeated measurements and subsequent paired t test with a correction for multiple measurements) (34): $^{**}P < 0.01$, $^{***}P = 0.001$.

found in healthy high-altitude residents after descent to sea level (23).

However, the exclusion of hemolysis after descent from very high altitude cannot be inferred from this study. The altitude difference in this study was ~3,000 m, while the findings of hemolysis (23), or immediate decrease in Hbmass (40) were obtained at altitude differences of ~4,300 m. In addition, the marked reduction in Hbmass after 1 wk at low altitude (−9%) in one subject with highest initial Hbmass (2,106 g) may be due to partial hemolysis in addition to lower formation rate.

Using the kinetics the decrease in Hbmass to low altitude, the time for acclimation of Hbmass can be estimated. Assuming a linear or exponential decrease in Hbmass, the average value of healthy lowlanders [740 g (18)] would be reached after 85–110 days, which could be completely explained by reduced red cell formation.

Upon return to the high altitude, a transient but significant overcompensation of plasma [EPO] occurs, leading to an increase in reticulocyte counts, however, Hbmass did not reach baseline values within the postintervention observation period.

As expected, PV increased at low altitude, with the magnitude of change (~450 mL) corresponding to values we found in young healthy athletes from the same altitude region after descent to near sea level (42). We hypothesize that the cessation of hypoxia-induced suppression of the renin-aldosterone system (43), together with a decrease in atrial natriuretic peptide (44) and an increase in the antidiuretic hormone system (45), is responsible for the increase in PV. As a result of the increased PV, the decrease in RCV is almost completely offset, leaving BV close to baseline values. However, 5 days after return to altitude, the PV decreases, which may be due to the hypoxic hormonal influences, such that at this time point BV is significantly decreased by 610 mL.

The change in [Hb] and Hct during the stay at low altitude and after return to high altitude can be attributed to both the change in Hbmass and PV. Both factors act synergistically at low altitude, but immediately after return to high altitude, the decrease in PV overcompensates for the continued decrease in Hbmass, leading to increased [Hb] despite lowered Hbmass. Determination of [Hb] and Hct alone does therefore not allow accurate assessment of changes in the polycythemic status.

Oxygen Supply

Long-term oxygen therapy (LTOT) is well established for chronic hypoxemia in patients with chronic obstructive pulmonary disease (COPD) and chronic hypoxemic respiratory failure. Individuals are prescribed LTOT when $Pa_{O2} \leq 55$ mmHg (46). The goal of LTOT is to reduce lethality, improve quality of life, and exercise capacity.

In the present study, Pa_{O_2} determined in the morning was ~45 mmHg and thus met the criterion for use of LTOT. To complicate matters, sleep-disordered breathing is assumed to be central to the development of polycythemia at high altitude (47) and nocturnal hypoxemia is more severe in patients with CMS than in control subjects (48) leading to higher erythropoietic activity during the night than in healthy controls from identical altitude (24).

Therefore, we hypothesized that additional nocturnal oxygen supply could have a significant inhibiting effect on the rate of erythropoiesis. To the best of our knowledge, the effects of nocturnal oxygen therapy for patients with CMS have not been determined. However, in a different approach, Feng et al. (49) administered oxygen to polycythemic subjects from high altitude (mean [Hb] 19.1 g/dL) for 30 min daily via a nasal catheter at a flow rate of 2 L/min and found a slight decrease in [Hb] of 0.5 g/dL.

In our study, both [Hb] and hematocrit tended to be slightly lower values (−0.6 g/dL, and −2.4%, respectively),

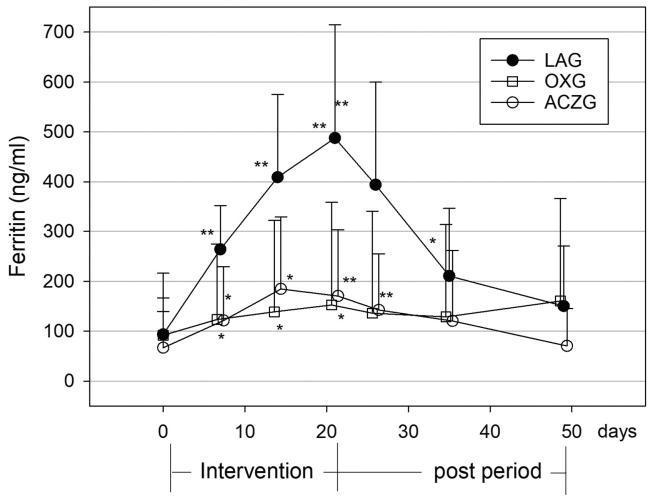

Figure 3. Serum ferritin concentration during and after 3 wk at low altitude (LAG, n = 6), nocturnal O_2-supply (OXG, n = 5), and acetazolamide administration (ACZG, n = 7). Values are means ± SD. Significance of differences from baseline values (one-way ANOVA with repeated measurements and subsequent paired t test with a correction for multiple measurements) (34): $^{*}P < 0.05$, $^{**}P < 0.01$.

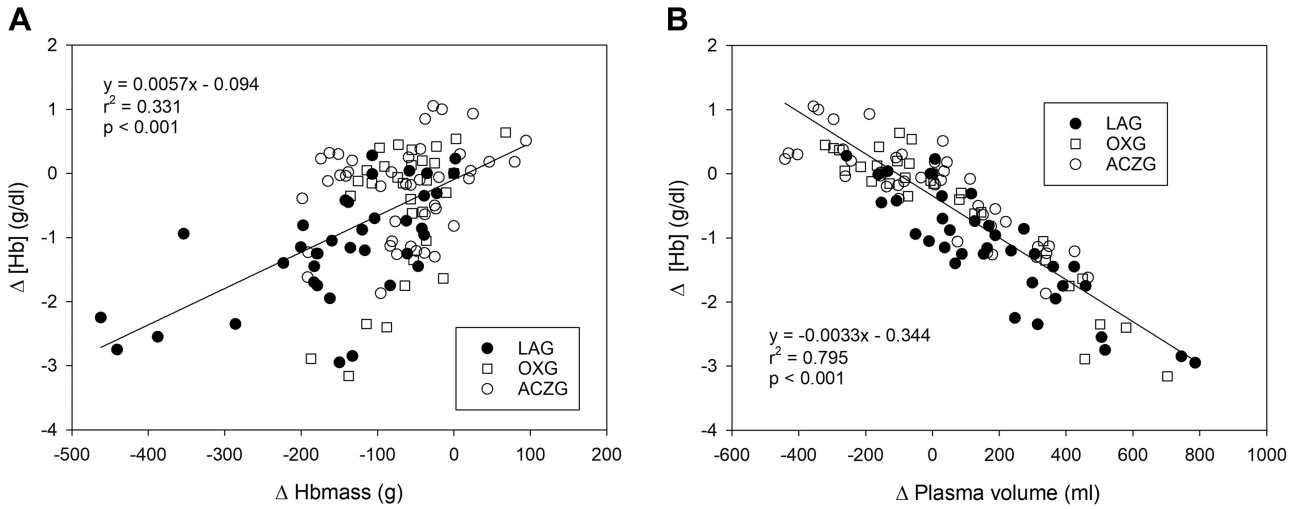

Figure 4. Relationship obtained by linear regression analysis between changes in hemoglobin concentration ([Hb]) and changes in hemoglobin mass (Hbmass; *A*) and changes in plasma volume (*B*) during and after 3 wk at low altitude (LAG, $n = 6$), nocturnal O_2-supply (OXG, $n = 5$), and acetazolamide administration (ACZG, $n = 7$). Regression equations for the subgroups: (*A*) LAG $y = 0.005x - 0.31$, $P < 0.001$; OXG $y = 0.010x + 0.08$, $P < 0.002$; ACZG $y = 0.003x - 0.07$, $P < 0.044$; (*B*) LAG $y = -0.003x - 0.48$; OXG $y = -0.004x - 0.29$; ACZG $y = -0.003x - 0.24$, in all cases $P < 0.001$.

although no significance was reached. However, Hbmass decreased continuously (up to 100 g) after 3 wk of O_2 administration, which is confirmed by an increase in ferritin concentration. These data indicate a moderate effect of LTOT on Hbmass, but also that relatively small changes in Hbmass cannot be clearly detected by either [Hb] or Hct as we have recently demonstrated (18).

The reduction in Hbmass is due to a significant decrease in [EPO] followed by a lower erythrocyte formation rate. However, it must be noted that EPO measurements were performed in the morning within 2 h after the end of the O_2 administration phase. Since EPO in plasma has a half-life of approximately 3 h, the low concentration after 12 h of almost normoxic conditions can be explained. However, since [EPO] increases as early as 2–3 h after the onset of a hypoxic stimulus, we assume that the EPO level had increased again substantially by the time of the next O_2 supplementation. Unfortunately, we did not perform further measurements in the diurnal cycle, so we cannot make any statements about the magnitude of the increase. Due to the likely circadian oscillation of [EPO] in the OXG, the effects on Hbmass are considerably smaller than in the LAG, which spent three continuous weeks under normoxic conditions.

Whereas the continuous stay of the LAG under normoxic conditions led to PV expansion of ~500 mL, the PV remained constant in the OXG. We postulated that the continuous alteration of normoxia and hypoxia may lead to oscillating concentrations of the volume-regulating hormones, however, this phenomenon was not reflected in a change of the PV.

Acetazolamide

Of the various drug therapy approaches, only the administration of acetazolamide (ACZ) has proven successful in the treatment of patients with CMS (19). To date, three studies have demonstrated the efficacy of ACZ. First Richalet et al. (26) showed a 7% decrease in Hct after three weeks of daily ACZ administration of 250 mg and 500 mg, which was confirmed in the same magnitude after administration of 250 mg for 6 wk (27), 3 mo, and with a short interruption also after 6 mo (28).

In our study, Hbmass was measured for the first time during treatment with ACZ and decreased by ~100 g until the fifth day postintervention (ascension to altitude). This proves that the decrease in Hct described earlier is due to a decrease in hemoglobin and not to dilution by a change in plasma volume as was suggested by Pichon et al. (50) in a hypoxic rat model. On the opposite, a mild diuretic effect could counteract the PV increase observed at low altitude with better oxygenation. However, the tendency toward a decrease in [Hb] and Hct observed in this study is much smaller than demonstrated by Richalet et al. (26) after 3 wk (−0.6 g/dL, and 2.0%, respectively). One possible explanation for this difference is the somewhat greater severity of the disease in Richalet's study, as seen in the significantly higher Qinghai score (22.8 vs. 9.2).

We postulated respiratory stimulation as the underlying mechanism of the decreased Hbmass. Acetazolamide is a carbonic anhydrase inhibitor that causes urinary bicarbonate loss, resulting in a metabolic acidosis that stimulates ventilation and increases arterial oxygenation (25). All three prior studies confirmed response to ACZ administration and showed a lowered pH with reactive decreased [HCO_3^-] as well as higher arterial P_{O_2} and lower P_{CO_2}. In our study, the greatest effects of ACZ were seen after 1 wk, and were similar in magnitude as the responses observed after 3 wk of treatment in previous studies (26–28). Interestingly, no data for Sp_{O_2} were previously reported. In this study, despite increased ventilation, there was no increase in Sp_{O_2}. This behavior is well explained by a rightward shift of the oxygen dissociation curve under in vivo conditions due to the Bohr effect (51), as evident from the increase in P_{50}. Consequently, the better tissue oxygenation resulting from ACZ administration seems to not be enabled by a higher arterial O_2 content, but rather by a higher P_{O_2} gradient between blood and tissues, thus better diffusion conditions. As a result of better O_2

availability and in agreement with Richalet et al. (26), [EPO] decreased by ~50% throughout the intervention in our study, resulting in a decrease in reticulocyte count. The magnitude of the ferritin increase was also consistent with the data in Richalet's study (26) and confirms the decrease in erythropoiesis.

Five days after cessation of ACZ treatment, no effects on acid-base status were detectable, so that Hbmass returned to baseline values by the end of the observation period.

Qinghai Score

The Qinghai score is the accepted specific clinical marker of the severity of CMS disease. When moving from lowland to high altitude, the score does not linearly or immediately respond to erythrocyte expansion, rather with a latency of several years, causing increased severity of CMS with time (29). Similarly, Oberholzer et al. (14) showed only a weak dependence of the disease on [Hb] and Hct, as both patients with CMS and control subjects without clinical diagnosis had [Hb] above 21 g/dL at an altitude of 5,050 m. In the present study, the significant relationship between reduction in Hbmass and improvement of the Qinghai score indicates a direct influence of hemoglobin on the expression of disease. However, the Qinghai score in all three groups also remained lowered throughout the follow-up period, although Hbmass in OXG and ACZG had returned to baseline, indicating that the health status is also improved independently of hematologic status and that not only low altitude but also LTOT and ACZ are temporarily effective at alleviating CMS severity.

Limitations

The greatest limitations of this study are the small sample size and the relatively short intervention period. To make generally valid statements on the success of the respective intervention, further studies are necessary. A larger number of subjects and longer intervention period must be performed, especially in the OXG and ACZG.

The subject population consisted predominantly of overweight patients, which may have contributed to the expression of erythrocytosis (52). Although age is not associated with Hbmass in healthy individuals to our knowledge, it may be a risk factor in patients with CMS (52) because of prolonged exposure to hypoxia (30) and concomitant diseases. In patients with obesity, adverse effects on respiratory physiology are likely to be one of the causative factors for excessive red cell production (52). However, whether these factors had an influence on the outcome of the therapies in this study cannot be assessed because of the small number of patients. To make a specific statement about the CMS originally described by Monge (1), the patient population would need to be further defined.

CMS disease is significantly more common in men than in women and increases significantly in women only after menopause. Since the present study was the first study to determine Hbmass with different treatment regimens and the number of participants was small, the measurements were to be made on as homogeneous a group of patients as possible, which is why male subjects were selected.

The response to interventions was highly individualized and dependent on the severity of disease, among other factors. For example, the patient with the greatest initial Hbmass in the LAG (2,106 g) showed the greatest decrease in [EPO], increase in ferritin, and decrease in Hbmass (Fig. 5). On the other hand, one patient in the OXG reacted normally during the intervention period, but continued to reduce Hbmass after cessation of the nocturnal O_2 supply. Therefore, it would be interesting to identify certain patterns of response in the respective treatments.

This study raises a number of other questions that remain to be answered. It would be interesting to investigate whether sleep behavior changes during each intervention, possibly eliminating a cause of excessive erythropoiesis (47).

Conclusions

Descent to low altitude (from 3,900 m to 1,050 m) is a fast-acting measure for the treatment of erythrocytosis in patients with CMS, reducing Hbmass by 16% within 3 wk. Nighttime oxygen supplementation and daily acetazolamide administration are also effective, but reduce Hbmass by only 6%.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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DISCLOSURES

W.F.J.S. is a managing partner of the company Blood tec GmbH, but he is unaware of any direct or indirect conflict of interest with the contents of this paper. The remaining authors declare that the research was conducted in the absence of any commercial or

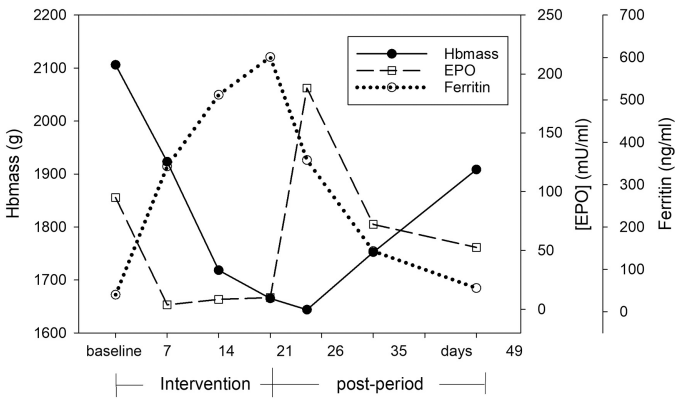

Figure 5. Hemoglobin mass (Hbmass), serum erythropoietin (EPO), and serum ferritin concentration in the patient with highest Hbmass (baseline 2,106 g) during and after 3 wk at low altitude.

financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

W.F.J.S., M.C.R.P., J.C.J.-C., and R.S. conceived and designed research; W.F.J.S., N.B.W., M.C.R.P., M.T.A.V., I.C.C.T., M.V., J.K., J.C.J.-C., and R.S. performed experiments; W.F.J.S., N.B.W., M.C.R.P., M.T.A.V., I.C.C.T., M.V., J.K., and R.S. analyzed data; W.F.J.S., M.V., J.K., J.C.J.-C., and R.S. interpreted results of experiments; W.F.J.S., N.B.W., M.C.R.P., M.T.A.V., I.C.C.T., and M.V. prepared figures; W.F.J.S., N.B.W., and J.C.J.-C. drafted manuscript; W.F.J.S., N.B.W., M.V., and J.C.J.-C. edited and revised manuscript; W.F.J.S., N.B.W., M.C.R.P., M.T.A.V., I.C.C.T., J.K., and J.C.J.-C. approved final version of manuscript.

REFERENCES

1. **Monge C.** Life in the Andes and chronic mpuntain sickness. *Science* 95: 79–84, 1942. doi:10.1126/science.95.2456.79.
2. **Monge CC**, **Whittembury J.** Chronic mountain sickness. *Johns Hopkins Med J* 139, Suppl: 87–89, 1976.
3. **Vásquez R**, **Villena M.** Normal hematological values for healthy persons living at 4000 meters in Bolivia. *High Alt Med Biol* 2: 361–367, 2001. doi:10.1089/15270290152608534.
4. **León-Velarde F**, **Maggiorini M**, **Reeves JT**, **Aldashev A**, **Asmus I**, **Bernardi L**, **Ge RL**, **Hackett P**, **Kobayashi T**, **Moore LG**, **Penaloza D**, **Richalet JP**, **Roach R**, **Wu T**, **Vargas E**, **Zubieta-Castillo G**, **Zubieta-Calleja G.** Consensus statement on chronic and subacute high altitude diseases. *High Alt Med Biol* 6: 147–157, 2005. doi:10.1089/ham.2005.6.147.
5. **Villafuerte FC**, **Corante N.** Chronic mountain sickness: clinical aspects, etiology, management, and treatment. *High Alt Med Biol* 17: 61–69, 2016. doi:10.1089/ham.2016.0031.
6. **Severinghaus JW**, **Bainton CR**, **Carcelen A.** Respiratory insensitivity to hypoxia in chronically hypoxic man. *Respir Physiol* 1: 308–334, 1966. doi:10.1016/0034-5687(66)90049-1.
7. **León-Velarde F**, **Richalet JP.** Respiratory control in residents at high altitude: physiology and pathophysiology. *High Alt Med Biol* 7: 125–137, 2006. doi:10.1089/ham.2006.7.125.
8. **Swenson ER.** Chronic mountain sickness evolving over time: new data from on high. *Chest* 161: 1136–1137, 2022. doi:10.1016/j.chest.2022.01.024.
9. **Kwaan HC**, **Wang J.** Hyperviscosity in polycythemia vera and other red cell abnormalities. *Semin Thromb Hemost* 29: 451–458, 2003. doi:10.1055/s-2003-44552.
10. **Rimoldi SF**, **Rexhaj E**, **Pratali L**, **Bailey DM**, **Hutter D**, **Faita F**, **Salinas SC**, **Villena M**, **Nicod P**, **Allemann Y**, **Scherrer U**, **Sartori C.** Systemic vascular dysfunction in patients with chronic mountain sickness. *Chest* 141: 139–146, 2012. doi:10.1378/chest.11-0342.
11. **Claydon VE**, **Norcliffe LJ**, **Moore JP**, **Rivera M**, **Leon-Velarde F**, **Appenzeller O**, **Hainsworth R.** Cardiovascular responses to orthostatic stress in healthy altitude dwellers, and altitude residents with chronic mountain sickness. *Exp Physiol* 90: 103–110, 2005. doi:10.1113/expphysiol.2004.028399.
12. **Maignan M**, **Rivera-Ch M**, **Privat C**, **Leòn-Velarde F**, **Richalet JP**, **Pham I.** Pulmonary pressure and cardiac function in chronic mountain sickness patients. *Chest* 135: 499–504, 2009. doi:10.1378/chest.08-1094.
13. **Soria R**, **Egger M**, **Scherrer U**, **Bender N**, **Rimoldi SF.** Pulmonary arterial pressure at rest and during exercise in chronic mountain sickness: a meta-analysis. *Eur Respir J* 53: 1802040, 2019. doi:10.1183/13993003.02040-2018.
14. **Oberholzer L**, **Lundby C**, **Stauffer E**, **Ulliel-Roche M**, **Hancco I**, **Pichon A**, **Lundby AKM**, **Villafuerte FC**, **Verges S**, **Robach P.** Reevaluation of excessive erythrocytosis in diagnosing chronic mountain sickness in men from the world's highest city. *Blood* 136: 1884–1888, 2020. doi:10.1182/BLOOD.2019004508.
15. **Lawrence JH**, **Huff RL**, **Siri W**, **Wasserman LR**, **Hennessy TG.** A physiological study in the Peruvian Andes. *Acta Med Scand* 142: 117–131, 1952. doi:10.1111/j.0954-6820.1952.tb13851.x.
16. **Hurtado A.** Some clinical aspects of life at high altitudes. *Ann Intern Med* 53: 247–258, 1960. doi:10.7326/0003-4819-53-2-247.
17. **Claydon VE**, **Norcliffe LJ**, **Moore JP**, **Rivera-Ch M**, **Leon-Velarde F**, **Appenzeller O**, **Hainsworth R.** Orthostatic tolerance and blood volumes in Andean high altitude dwellers. *Exp Physiol* 89: 565–571, 2004. doi:10.1113/expphysiol.2004.027698.
18. **Schmidt WFJ**, **Wachsmuth N**, **Jimenez J**, **Soria R.** Hemoglobin mass and blood volume in patients with altitude-related polycythemia. *Front Physiol* 13: 1–12, 2022. doi:10.3389/fphys.2022.867108.
19. **Villafuerte FC**, **Simonson TS**, **Bermudez D**, **León-Velarde F.** High-altitude erythrocytosis: mechanisms of adaptive and maladaptive responses. *Physiology (Bethesda)* 37: 175–186, 2022. doi:10.1152/physiol.00029.2021.
20. **Merino CF.** Studies on blood formation and destruction in the polycythemia of high altitude. *Blood* 5: 1–31, 1950. doi:10.1182/blood.v5.1.1.1.
21. **Trial J**, **Rice L**, **Alfrey CP.** Erythropoietin withdrawal alters interactions between young red blood cells, splenic endothelial cells, and macrophages: an in vitro model of neocytolysis. *J Investig Med* 49: 335–345, 2001. doi:10.2310/6650.2001.33899.
22. **Alfrey CP**, **Rice L**, **Udden MM**, **Driscoll TB.** Neocytolysis: physiological down-regulator of red-cell mass. *Lancet* 349: 1389–1390, 1997. doi:10.1016/S0140-6736(96)09208-2.
23. **Rice L**, **Ruiz W**, **Driscoll T**, **Whitley CE**, **Tapia R**, **Hachey DL**, **Gonzales GF**, **Alfrey CP.** Neocytolysis on descent from altitude: a newly recognized mechanism from the control of red cell mass. *Ann Intern Med* 134: 652–656, 2001. doi:10.7326/0003-4819-134-8-200104170-00010.
24. **Villafuerte FC**, **Corante N**, **Anza-Ramírez C**, **Figueroa-Mujíca R**, **Vizcardo-Galindo G**, **Mercado A**, **Macarlupú JL**, **León-Velarde F.** Plasma soluble erythropoietin receptor is decreased during sleep in Andean highlanders with chronic mountain sickness. *J Appl Physiol (1985)* 121: 53–58, 2016. doi:10.1152/japplphysiol.00107.2016.
25. **Swenson ER.** Carbonic anhydrase inhibitors and high altitude illnesses. *Subcell Biochem* 75: 361–386, 2014. doi:10.1007/978-94-007-7359-2_18.
26. **Richalet JP**, **Rivera M**, **Bouchet P**, **Chirinos E**, **Onnen I**, **Petitjean O**, **Bienvenu A**, **Lasne F**, **Moutereau S**, **León-Velarde F.** Acetazolamide: a treatment for chronic mountain sickness. *Am J Respir Crit Care Med* 172: 1427–1433, 2005. doi:10.1164/rccm.200505-807OC.
27. **Sharma S**, **Gralla J**, **Ordonez JG**, **Hurtado ME**, **Swenson ER**, **Schoene RB**, **Kelly JP**, **Callacondo D**, **Rivard C**, **Roncal-Jimenez C**, **Sirota J**, **Fuquay R**, **Jackson BP**, **Swenson KE**, **Johnson RJ**, **Hurtado A**, **Escudero E.** Acetazolamide and *N*-acetylcysteine in the treatment of chronic mountain sickness (Monge's disease). *Respir Physiol Neurobiol* 246: 1–8, 2017. doi:10.1016/J.RESP.2017.07.005.
28. **Richalet JP**, **Rivera-Ch M**, **Maignan M**, **Privat C**, **Pham I**, **Macarlupu JL**, **Petitjean O**, **León-Velarde F.** Acetazolamide for Monge's disease: efficiency and tolerance of 6-month treatment. *Am J Respir Crit Care Med* 177: 1370–1376, 2008. doi:10.1164/rccm.200802-196OC.
29. **Wachsmuth N**, **Soria R**, **Jimenez J**, **Schmidt W.** Modification of the CO-rebreathing method to determine haemoglobin mass and blood volume in patients suffering from chronic mountain sickness. *Exp Physiol* 104: 1819–1828, 2019. doi:10.1113/EP087870.
30. **Champigneulle B**, **Hancco I**, **Hamard E**, **Doutreleau S**, **Furian M**, **Brugniaux JV**, **Bailly S**, **Vergès S.** Excessive erythrocytosis and chronic mountain sickness in the highest city in the world: a longitudinal study. *Chest* 161: 1338–1342, 2022. doi:10.1016/j.chest.2021.11.030.
31. **World Anti-Doping Agency.** International Standard for Testing and Investigations (Online). https://www.wada-ama.org/sites/default/files/resources/files/isti_2019_en_new.pdf [2023 Feb 6].
32. **Schmidt W**, **Prommer N.** The optimised CO-rebreathing method: a new tool to determine total haemoglobin mass routinely. *Eur J Appl Physiol* 95: 486–495, 2005. doi:10.1007/s00421-005-0050-3.
33. **Wright RR**, **Tono M**, **Pollycove M.** Blood volume. *Semin Nucl Med* 5: 63–78, 1975. doi:10.1016/S0001-2998(75)80005-5.
34. **Sánchez C**, **Merino C**, **Figallo M.** Simultaneous measurement of plasma volume and cell mass in polycythemia of high altitude. *J Appl Physiol* 28: 775–778, 1970. doi:10.1152/jappl.1970.28.6.775.
35. **Chaplin H Jr**, **Mollison PL**, **Vetter H.** The body/venous hematocrit ratio: its constancy over a wide hematocrit range. *J Clin Invest* 32: 1309–1316, 1953. doi:10.1172/JCI102859.

36. **Benjamini Y**, **Hochberg Y.** Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B* 57: 289–300, 1995. doi:10.1111/j.2517-6161.1995.tb02031.x.
37. **Monge C.** Chronic mountain sickness. *Physiol Rev* 23: 166–184, 1943. doi:10.1152/physrev.1943.23.2.166.
38. **Hurtado A**, **Merino C**, **Delgado E.** Influence of anoxemia on the hematopoietic activity. *Arch Intern Med* 75: 284–323, 1945. doi:10.1001/archinte.1945.00210290007002.
39. **Trial J**, **Rice L.** Erythropoietin withdrawal leads to the destruction of young red cell at the endothelial-macrophage interface. *Curr Pharm Des* 10: 183–190, 2004. doi:10.2174/1381612043453423.
40. **Ryan BJ**, **Wachsmuth NB**, **Schmidt WF**, **Byrnes WC**, **Julian CG**, **Lovering AT**, **Subudhi AW**, **Roach RC.** AltitudeOmics: rapid hemoglobin mass alterations with early acclimatization to and de-acclimatization from 5260 m in healthy humans. *PLoS One* 9: e108788, 2014. doi:10.1371/journal.pone.0108788.
41. **Klein M**, **Kaestner L**, **Bogdanova AY**, **Minetti G**, **Rudloff S**, **Lundby C**, **Makhro A**, **Seiler E**, **van Cromvoirt A**, **Fenk S**, **Simionato G**, **Hertz L**, **Recktenwald S**, **Schäfer L**, **Haider T**, **Fried S**, **Borsch C**, **Marti HH**, **Sander A**, **Mairbäurl H.** Absence of neocytolysis in humans returning from a 3-week high-altitude sojourn. *Acta Physiol (Oxf)* 232: e13647, 2021. doi:10.1111/apha.13647.
42. **Wachsmuth N**, **Kley M**, **Spielvogel H**, **Aughey RJ**, **Gore CJ**, **Bourdon PC**, **Hammond K**, **Sargent C**, **Roach GD**, **Sanchez RS**, **Claros JC**, **Schmidt WF**, **Garvican-Lewis LA.** Changes in blood gas transport of altitude native soccer players near sea-level and sea-level native soccer players at altitude (ISA3600). *Br J Sports Med* 47, Suppl 1: i93–i99, 2013. doi:10.1136/bjsports-2013-092761.
43. **Steele AR**, **Tymko MM**, **Meah VL**, **Simpson LL**, **Gasho C**, **Dawkins TG**, **Williams AM**, **Villafuerte FC**, **Vizcardo-Galindo GA**, **Figueroa-Mujíca RJ**, **Ainslie PN**, **Stembridge M**, **Moore JP**, **Steinback CD.** Global REACH 2018: volume regulation in high-altitude Andeans with and without chronic mountain sickness. *Am J Physiol Regul Integr Comp Physiol* 321: R504–R512, 2021. doi:10.1152/ajpregu.00102.2021.
44. **Antezana A-M**, **Richalet J-P**, **Noriega I**, **Galarza M**, **Antezana G.** Hormonal changes in normal and polycythemic high-altitude natives. *J Appl Physiol (1985)* 79: 795–800, 1995. doi:10.1152/jappl.1995.79.3.795.
45. **De Lima J**, **Caillens H**, **Beaufils M**, **Ardaillou R.** Effects of furosemide-induced plasma volume reduction on plasma antidiuretic hormone in normal and hypertensive subjects. *Clin Nephrol* 15: 246–251, 1981.
46. **Haidl P**, **Jany B**, **Geiseler J**, **Andreas S**, **Arzt M**, **Dreher M**, **Frey M**, **Hauck RW**, **Herth F**, **Hämäläinen N**, **Jehser T**, **Kenn K**, **Lamprecht B**, **Magnet F**, **Oldenburg O**, **Schenk P**, **Schucher B**, **Studnicka M**, **Voshaar T**, **Windisch W**, **Woehrle H**, **Worth H**; **Weitere beteiligte wissenschaftliche Fachgesellschaften und Institutionen: Deutsche Atemwegsliga e. V; Deutsche Gesellschaft für Innere Medizin e. V. (DGIM); Deutsche Gesellschaft für Kardiologie—Herz- und Kreislaufforschung e. V. (DGK); Deutsche Gesellschaft für Palliativmedizin e. V. (DGP); Deutsche Interdisziplinäre Gesellschaft für Außerklinische Beatmung (DIGAB); Bun-desverband der Pneumologen, Schlaf- und Beatmungsmediziner (BdP); Schweizerische Gesellschaft für Pneumologie (SGP); Österreichische Gesellschaft für Pneumologie (ÖGP); Deutsche Sauerstoff- und BeatmungsLiga LOT e. V.** Guideline for long-term oxygen therapy. *Pneumologie* 74: 813–841, 2020. doi:10.1055/a-1252-1492.
47. **Julian CG**, **Vargas E**, **Gonzales M**, **Dávila RD**, **Ladenburger A**, **Reardon L**, **Schoo C**, **Powers RW**, **Lee-Chiong T**, **Moore LG.** Sleep-disordered breathing and oxidative stress in preclinical chronic mountain sickness (excessive erythrocytosis). *Respir Physiol Neurobiol* 186: 188–196, 2013. doi:10.1016/J.RESP.2013.01.016.
48. **Rexhaj E**, **Rimoldi SF**, **Pratali L**, **Brenner R**, **Andries D**, **Soria R**, **Salinas C**, **Villena M**, **Romero C**, **Allemann Y**, **Lovis A**, **Heinzer R**, **Sartori C**, **Scherrer U.** Sleep-disordered breathing and vascular function in patients with chronic mountain sickness and healthy high-altitude dwellers. *Chest* 149: 991–998, 2016. doi:10.1378/chest.15-1450.
49. **Feng B**, **Xu WH**, **Gao YQ**, **Liu FY**, **Li P**, **Zheng SJ**, **Gai LY**, **Zhang G.** Intermittent oxygen inhalation with proper frequency improves overall health conditions and alleviates symptoms in a population at high risk of chronic mountain sickness with severe symptoms. *Chin Med J (Engl)* 129: 1322–1329, 2016. doi:10.4103/0366-6999.182831.
50. **Pichon A**, **Connes P**, **Quidu P**, **Marchant D**, **Brunet J**, **Levy BI**, **Vilar J**, **Safeukui I**, **Cymbalista F**, **Maignan M**, **Richalet JP**, **Favret F.** Acetazolamide and chronic hypoxia: effects on haemorheology and pulmonary haemodynamics. *Eur Respir J* 40: 1401–1409, 2012. doi:10.1183/09031936.00216011.
51. **Berthelsen PG**, **Dich-Nielsen JO.** Respiratory function and carbonic anhydrase inhibition. *Intensive Care Med* 13: 323–327, 1987. doi:10.1007/BF00255787.
52. **De Ferrari A**, **Miranda JJ**, **Gilman RH**, **Dávila-Román VG**, **León-Velarde F**, **Rivera-Ch M**, **Huicho L**, **Bernabé-Ortiz A**, **Wise RA**, **Checkley W.** 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* 146: 1327–1336, 2014. doi:10.1378/chest.14-0298.