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Autonomic cardiovascular function in high-altitude Andean natives with chronic mountain sickness

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Keyl, C., A. Schneider, A. Gamboa, L. Spicuzza, N. Casiraghi, A. Mori, R. Tapia Ramirez, F. León-Velarde, and L. Bernardi. Autonomic cardiovascular function in high-altitude Andean natives with chronic mountain sickness. *J Appl Physiol* 94: 213–219, 2003. First published September 13, 2002; 10.1152/japplphysiol.01258.2001.—We evaluated autonomic cardiovascular regulation in subjects with polycythemia and chronic mountain sickness (CMS) and tested the hypothesis that an increase in arterial oxygen saturation has a beneficial effect on arterial baroreflex sensitivity in these subjects. Ten Andean natives with a Hct >65% and 10 natives with a Hct <60%, all living permanently at an altitude of 4,300 m, were included in the study. Cardiovascular autonomic regulation was evaluated by spectral analysis of hemodynamic parameters, while subjects breathed spontaneously or frequency controlled at 0.1 and 0.25 Hz, respectively. The recordings were repeated after a 1-h administration of supplemental oxygen and after frequency-controlled breathing at 6 breaths/min for 1 h, respectively. Subjects with Hct >65% showed an increased incidence of CMS compared with subjects with Hct <60%. Spontaneous baroreflex sensitivity was significantly lower in subjects with high Hct compared with the control group. The effects of supplemental oxygen or modification of the breathing pattern on autonomic function were as follows: *1*) heart rate decreased significantly after both maneuvers in both groups, and *2*) spontaneous baroreflex sensitivity increased significantly in subjects with high Hct and did not differ from subjects with low Hct. Temporary slow-frequency breathing may provide a beneficial effect on the autonomic cardiovascular function in high-altitude natives with CMS.

autonomic nervous system; hypoxia; baroreflex

CHRONIC HYPOBARIC HYPOXIA is known to be related to an increase in hemoglobin and Hct. The combination of polycythemia and a variety of clinical symptoms, such as decreased physical performance, pulmonary hypertension, and an impairment in cerebral function, has been defined as chronic mountain sickness (CMS) (13, 24). This syndrome has primarily been observed in Andean natives living at altitudes >3,000 m (24) but also occurs in geographic regions outside South America (43, 44). The amount of polycythemia seems to be related to arterial oxygen saturation (Sa_{O_2}), regardless of the population investigated (32).

The typical cerebral symptoms of CMS, such as fatigue and mental disorders, may be caused by cerebral hypoxia because of factors such as decreased cerebral blood flow and an impairment of cerebral autoregulation (2, 24, 39, 43). It is not known whether CMS is also associated with a disturbed function of the autonomic nervous system. However, an impairment in cardiovascular autonomic regulation has been shown to be related to a disturbed control of cerebral circulation and thus may interfere with symptoms of CMS (8, 41).

The aim of the present study was to test the hypothesis that subjects living at high altitude and showing the clinical signs of CMS have an impaired arterial baroreflex sensitivity as a measure of autonomic cardiovascular regulation compared with otherwise healthy subjects living in the same environment. Furthermore, we investigated the impact of maneuvers that increase Sa_{O_2} on measures of autonomic cardiovascular function. In previous studies, our laboratory found that breathing at a slow rate not only has a beneficial effect on Sa_{O_2} in patients with heart failure or during simulated altitude (5, 6) but similarly increases the arterial baroreflex sensitivity (3). In view of these results, we evaluated the hypothesis that temporary slow-frequency breathing may improve both the Sa_{O_2} and the arterial cardiac baroreflex in patients with CMS.

METHODS

The study was performed in Cerro de Pasco, Peru, at an altitude of 4,300 m. The study was approved by the Human Subject Research Committee of the Universities of Pavia and Lima, and all participants gave their informed consent. The investigation conforms to the principles outlined in the Declaration of Helsinki.

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Twenty male subjects living in Cerro de Pasco were investigated. These subjects were recruited from a cohort of 30 men, all not employed as miners, who were born and lived in Cerro de Pasco, with the last stay at lower altitudes being at least 6 mo before the study. The subjects underwent a clinical evaluation including spirometry (Sensomedics, Milano, Italy) and the determination of hemoglobin and Hct. Ten subjects with the highest Hct values (Hct >65%) and 10 subjects with low Hct values (Hct <60%) were included in the study. The subjects were evaluated by using the CMS score published by León-Velarde et al. (20). This scoring system includes clinical symptoms typical for CMS (dizziness; physical weakness; mental fatigue; anorexia; paresthesia of hands and feet; cyanosis of lips, face, or fingers; prominent capillaries of conjunctives, or prominent veins of hands and feet; sleep disturbance; breathlessness or palpitations; tinnitus; headache) and classifies a value of hemoglobin or Hct >2 SD of the mean of the population as pathological, as well as Sa_{O_2} <82% (calculated for the population of Cerro de Pasco) (20). A value <12 points is regarded as indicative of the absence of CMS, a value between 12 and 18 points indicates light symptoms, between 19 and 24 points moderate symptoms, and >24 points severe symptoms of CMS.

The study protocol included registration of ECG and continuous noninvasive recording of the blood pressure curve of the radial artery by arterial tonometry (CBM 7000, Colin, San Antonio, TX). Additionally, pulse oximetry and inspiratory and expiratory CO_2 (CO2SMO, Novametrix Medical Systems, Wallingford, CA), tidal volume (pneumotachography), and abdominal-thoracic breathing movements (induction plethysmography) were recorded. The registrations were performed with the subjects in a sitting position between 9:00 and 12:00 AM on 2 subsequent days.

Arterial blood pressure, heart rate, Sa_{O_2}, and carbon dioxide were continuously monitored after instrumentation for at least 30 min of familiarization with the laboratory setting. Measurements were performed during steady-state conditions of hemodynamic variables.

The measurements consisted of two sequences, which were randomly assigned (in equal proportions) to 1 of 2 subsequent days. One sequence consisted of a 5-min baseline registration while subjects breathed spontaneously (*control A*) and of two 3-min recordings with breathing frequency controlled at 6 and 15 breaths/min, respectively. These registrations were followed by the administration of 4 l/min supplemental oxygen by face mask for 1 h. The recordings during spontaneous breathing were repeated after a break of 15 min without oxygen supplementation. The other sequence consisted of a 5-min baseline registration while subjects breathed spontaneously (*control B*), followed by a 1-h episode of frequency-controlled breathing at 6 breaths/min. The recordings during spontaneous breathing were repeated after a break of 15 min.

Data were sampled by using a 12-bit analog-to-digital converter via the serial RS-232 interface at 300 Hz on a Macintosh laptop computer. The single breaths were identified, and end-expiratory CO_2 was determined. After identification of the R peaks, the time series of R-wave-R-wave (R-R) interval, systolic and diastolic blood pressure, Sa_{O_2}, respiration, and CO_2 were created and visually inspected, and artifacts were removed by interpolation with the use of interactive software. Spectral analysis of R-R interval and systolic and diastolic blood pressure was performed after linear detrending by an autoregressive algorithm (4, 37). The area under the distinct components of the curve was determined by a decomposition algorithm. Spectral power was calculated as absolute power (variance of the time series), low-frequency (LF) power (0.03–0.15 Hz), and high-frequency (HF) power (0.15–0.4 Hz).

Following previous studies, which showed that the LF fluctuation in R-R interval might be influenced by baroreflex activity (9–11, 38), spontaneous baroreflex sensitivity was estimated as the square root of the relation between LF power of the R-R interval and systolic blood pressure (15, 27, 31, 33, 34). The accuracy of the relationship between fluctuations in R-R interval and systolic blood pressure at a specific frequency was measured by the coherence function (37). A value >0.5 was regarded as statistically significant and interpreted as a sign of stable phase shift.

Statistical analysis was performed by using the software SPSS 9.0 (SPSS, Chicago, IL). Data were tested for normal distribution by using the Kolmogorov-Smirnov test. Because results of spectral power analysis were left-skewed, logarithmic transformation was necessary to obtain normal distribution. Data are presented as means ± SD. Differences between groups are reported as mean difference and 95% confidence interval (95% CI). The mean values of R-R interval, blood pressure, tidal volume, end-expiratory CO_2, and Sa_{O_2}, obtained during each registration, as well as the results of power spectral analysis and spontaneous baroreflex sensitivity, were compared between the groups by using a general linear model procedure (repeated-measures analysis of variance; the within-subjects factors were tested by simple contrasts taking the first measure as the reference) and Student's *t*-test for unpaired data with adjustment for the α-error. The degree of severity of CMS was compared between groups with high and low Hct by using the χ^2 test. A P value <0.05 was regarded as statistically significant.

RESULTS

One subject from the high-Hct group (Hct 75%) was excluded from the study because of atrial fibrillation. Clinical characteristics of the subjects are presented in Table 1. The results are comprehensively presented in Tables 2 and 3.

Subjects with high Hct had a significantly higher CMS score than subjects with low Hct (mean difference: 11.0; 95% CI: 1.2–20.7%). Spirometry did not reveal significant differences between groups. Sa_{O_2} was slightly lower in subjects with high Hct compared with subjects with low Hct without statistical significance.

Table 1. *Characteristics and clinical data of subjects with low Hct and high Hct*

	Age, yr	Weight, kg	Height, cm	Hct, %	CMS Score, points	SBP, mmHg	DBP, mmHg	HR, beats/min	FVC, liters	FEV_1, liters	PEF, 1/s
Low Hct	38.5 ± 4.6	60.5 ± 7.9	160 ± 4.4	54.4 ± 2.7	11.6 ± 9.7	106.6 ± 9.8	59.1 ± 13.0	72.0 ± 4.9	4.55 ± 0.54	3.80 ± 0.44	9.29 ± 1.16
High Hct	38.9 ± 8.0	65.5 ± 6.5	165 ± 4.4*	72.6 ± 4.1‡	22.6 ± 10.3*	119.1 ± 8.7†	71.2 ± 13.6	76.2 ± 9.8	4.43 ± 0.80	3.52 ± 0.65	9.05 ± 1.39

Values are means ± SD. Low Hct, hematocrit <60%; high Hct, hematocrit >65%; CMS, chronic mountain sickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; FVC, forced vital capacity; FEV_1, forced expiratory volume over 1 s; PEF, peak expiratory flow. Significant difference vs. low Hct: *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$.

Table 2. *Results of registration sequence A in subjects with low Hct and high Hct*

	Control A		15 Breaths/Min		6 Breaths/Min		After O_2	
	Low Hct	High Hct	Low Hct	High Hct	Low Hct	High Hct	Low Hct	High Hct
f, breaths/min	17.9 ± 4.2	19.1 ± 2.8	14.9 ± 0.1*	15.1 ± 0.4*	6.1 ± 0.2*	6.1 ± 0.1*	19.2 ± 4.7	18.4 ± 2.8
V_T, ml	694 ± 95	695 ± 93	1,344 ± 558*	1,449 ± 431*	1,948 ± 520*	2,463 ± 610*	644 ± 92	695 ± 187
$\dot{V}_E$, 1/min	12.1 ± 1.6	13.2 ± 1.2	20.0 ± 8.4*	21.7 ± 6.4*	12.0 ± 3.4	15.0 ± 3.9	11.8 ± 1.6	14.3 ± 8.0
CO_2, mmHg	38.0 ± 2.8	39.5 ± 3.4	28.8 ± 4.7*	28.8 ± 2.7*	36.2 ± 3.8*	36.3 ± 2.9*	36.1 ± 3.1*	37.8 ± 4.5*
Sa_{O2}, %	88.8 ± 1.8	87.4 ± 1.5	94.7 ± 2.0*	93.6 ± 1.7*	92.4 ± 2.3*	91.9 ± 1.9*	90.7 ± 1.9*	90.0 ± 3.3*
R-R interval								
Mean, ms	837 ± 70	767 ± 91	897 ± 109*	810 ± 104*	871 ± 88*	804 ± 98*	914 ± 97*	852 ± 139*
SD, ms	38.1 ± 15.4	24.5 ± 11.1	36.4 ± 17.8	28.1 ± 13.6	57.8 ± 16.8*	55.5 ± 26.2*	52.1 ± 20.2*	30.8 ± 12.1*
CV	4.6 ± 1.8	3.2 ± 1.4	4.0 ± 1.8	3.5 ± 1.7	4.0 ± 1.9	3.5 ± 1.7	5.7 ± 2.1	3.6 ± 1.3
ln LF, ln ms^2	5.73 ± 1.15	3.73 ± 1.88‡	5.52 ± 0.97	4.95 ± 1.50	7.51 ± 0.86*	7.59 ± 1.31*†	4.77 ± 1.97	4.70 ± 1.31†
ln HF, ln ms^2	5.53 ± 0.97	4.52 ± 1.23	6.21 ± 1.14*	5.84 ± 0.87*	5.33 ± 1.04	4.76 ± 1.21	4.62 ± 2.54	5.11 ± 1.56
SBP, mmHg	118.4 ± 16.3	126.4 ± 13.2	111.0 ± 14.5	122.1 ± 8.6	109.9 ± 14.9	124.9 ± 9.2‡	104.6 ± 14.4*	117.9 ± 11.5*‡
DBP, mmHg	63.0 ± 17.2	74.0 ± 13.0	62.2 ± 9.7	69.9 ± 12.9	61.8 ± 10.6	70.8 ± 12.9	62.2 ± 10.8	72.6 ± 10.4
BRS, ms/mmHg	11.2 ± 8.5	3.9 ± 2.1‡	10.4 ± 5.9	6.8 ± 3.3	11.9 ± 7.8	9.3 ± 4.7*	11.1 ± 5.1	9.8 ± 6.1*

Values are means ± SD. Measurements were performed during spontaneous breathing (*control A*) and frequency-controlled breathing (15 breaths/min; 6 breaths/min) and during spontaneous breathing after a 1-h period of oxygen administration (after O_2). f, Respiratory frequency; V_T, tidal volume; $\dot{V}_E$, minute ventilation; Sa_{O_2}, arterial oxygen saturation; R-R interval, R-wave-R-wave interval; CV, coefficient of variation (SD/mean × 100); LF, low-frequency component; HF, high-frequency component; BRS, baroreflex sensitivity. *$P < 0.05$ vs. *control A.* †Significant interaction between groups compared with *control A,* $P < 0.05$. ‡$P < 0.05$ vs. low Hct.

Sa_{O_2} increased significantly in both groups during controlled breathing at 15 or at 6 breaths/min and after the temporary administration of supplemental oxygen (Table 2). Frequency-controlled breathing did not significantly influence the absolute difference in Sa_{O_2} between subjects with high and low Hct.

The subjects showed a marked hyperventilation when breathing at 15 breaths/min. At a breathing rate of 6 breaths/min, end-expiratory CO_2 was not significantly different from the values recorded during spontaneous breathing.

Systolic blood pressure was significantly higher in subjects with high Hct than in subjects with low Hct (mean difference: 12.5 mmHg; 95% CI: 3.5–21.5 mmHg; Table 1 reports the oscillometric measurement at the start of the recordings). Similarly, the mean R-R interval was shorter in subjects with high Hct compared with the control group. This difference between groups reached statistical significance at the registration point *control B* (mean difference: 80.9 ms; 95% CI: 21.4–140.3 ms; Table 3).

The HF component of R-R interval variability, which is mediated predominantly by vagal activity, was decreased in subjects with high Hct. Tidal volume was similar in subjects with low and high Hct; breathing frequency and minute ventilation were not significantly increased in subjects with high Hct. LF power showed a more marked variation between *control A* and *control B* than did HF power.

Exemplary power spectra of systolic blood pressure and R-R interval and coherence and phase spectra are demonstrated in Fig. 1. The spontaneous baroreflex sensitivity was markedly impaired in subjects with high Hct compared with subjects with low Hct (mean difference and 95% CI: *control A*, 7.3 and 0.15–14.4 ms/mmHg; *control B*, 5.1 and 0.92–9.3 ms/mmHg, respectively) and

Table 3. *Results of registration sequence B in subjects with low Hct and high Hct*

	Control B		After Slow Breathing	
	Low Hct	High Hct	Low Hct	High Hct
f, breaths/min	17.6 ± 4.1	19.2 ± 4.0	17.9 ± 4.5	19.1 ± 2.8
V_T, ml	716 ± 121	694 ± 125	657 ± 107	634 ± 159
$\dot{V}_E$, 1/min	12.2 ± 1.2	13.0 ± 2.4	11.3 ± 2.1*	11.9 ± 3.8*
CO_2, mmHg	39.8 ± 3.1	39.0 ± 3.7	37.3 ± 3.3*	34.3 ± 7.7*
Sa_{O2}, %	88.7 ± 1.6	87.2 ± 1.8	89.2 ± 3.6	85.8 ± 5.9
R-R interval				
Mean, ms	853 ± 44	772 ± 76‡	898 ± 68*	830 ± 116*
SD, ms	40.8 ± 11.2	28.9 ± 9.1	47.9 ± 10.8*	34.0 ± 15.3*‡
CV	4.8 ± 1.2	3.8 ± 1.2	5.4 ± 1.4	4.1 ± 1.7
ln LF, ln ms^2	5.05 ± 1.95	5.15 ± 1.41	5.77 ± 1.24	5.56 ± 1.06
ln HF, ln ms^2	5.86 ± 1.05	4.94 ± 1.27	5.84 ± 0.53	4.73 ± 1.13‡
SBP, mmHg	114.5 ± 12.9	120.0 ± 16.5	105.0 ± 9.2	113.8 ± 13.1
DBP, mmHg	63.1 ± 12.0	60.9 ± 14.7	59.0 ± 10.0	71.9 ± 12.3†
BRS, ms/mmHg	11.1 ± 5.5	5.9 ± 2.2‡	11.9 ± 7.8	9.3 ± 4.7*

Values are means ± SD. Measurements were performed during spontaneous breathing before (*control B*) and after (after slow breathing) a 1-h period of breathing at 6 breaths/min. *$P < 0.05$ vs. *control B.* †Significant interaction between groups compared with *control B,* $P < 0.05$. ‡$P < 0.05$ vs. low Hct.

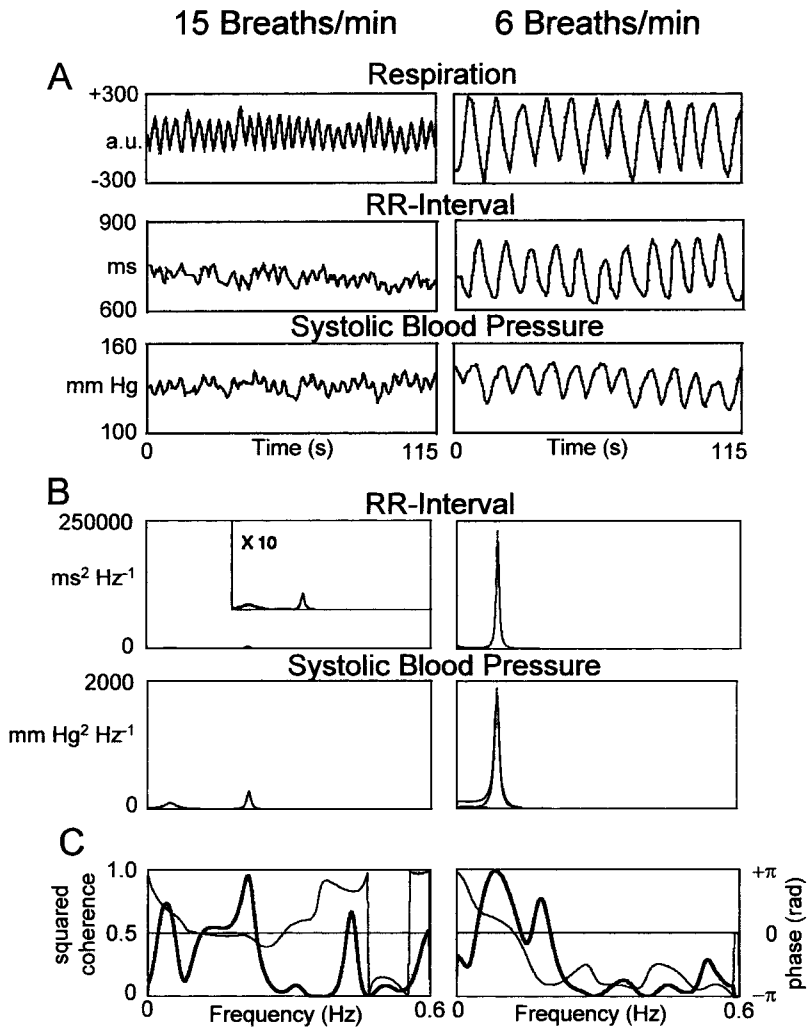

Fig. 1. *A*: exemplary registration of respiratory signal (*top*), R-wave-R-wave (R-R) interval (*middle*), and systolic blood pressure (*bottom*) in a subject with chronic mountain sickness during breathing at 15 breaths/min (*left*) and 6 breaths/min (*right*). *B*: power spectra of R-R interval (*top*) and systolic blood pressure (*bottom*). *Inset* in the left R-R interval power spectrum: ×10 magnification of amplitude. *C*: coherence (thick line, *left y*-axis) and phase spectra (thin line, *right y*-axis) of systolic blood pressure and R-R interval, indicating a significant relationship between signals at the respiratory frequency. A positive phase shift indicates that systolic blood pressure precedes the output signal (R-R interval) in this presentation. au, Arbitrary units.

did not differ between the two control registrations. Baroreflex sensitivity improved in subjects with high Hct during breathing at 6 breaths/min but not during breathing at 15 breaths/min (Tables 2 and 3).

The temporary administration of oxygen and the performance of a slow-frequency breathing pattern for 1 h had a persisting effect on the autonomic activity. After both maneuvers, mean R-R interval increased significantly in both groups with high and low Hct (mean difference and 95% CI after oxygen: high-Hct group, 84.4 and 29.7–140.0 ms; low-Hct group, 76.1 and 20.5–131.7 ms; mean difference and 95% CI after slow breathing: high-Hct group, 80.0 and 2.8–120.1 ms; low-Hct group, 83.1 and 14.0–104.9 ms, respectively). Systolic blood pressure decreased after oxygen administration but remained significantly higher in subjects with high Hct compared with subjects with low Hct (mean difference: 13.4 mmHg; 95% CI: 6.6–26.1 mmHg). Systolic blood pressure decreased to a somewhat lesser extent after slow-frequency breathing. With the exception of baseline *registration B*, diastolic pressure was higher, although not statistically significant, in patients with CMS compared with the control group.

Baroreflex sensitivity increased significantly in subjects with high Hct after the administration of supplemental oxygen (mean difference: 6.3 ms/mmHg; 95% CI: 0.35 to 12.3 ms/mmHg) or after the 1-h episode with LF breathing (mean difference: 4.8 ms/mmHg; 95% CI: 0.18–9.4 ms/mmHg). In subjects with low Hct, these maneuvers did not have a significant impact on baroreflex sensitivity. Phase shift between fluctuation in systolic blood pressure and R-R interval around 0.1 Hz did not differ between subjects with low and high Hct. Fluctuations in systolic blood pressure preceded those in R-R interval by 1.76 ± 0.23 rad (*control A*, low Hct) and 1.62 ± 0.23 rad (*control A*, high Hct) or 1.76 ± 0.25 rad (*control B*, low Hct) and 1.50 ± 0.41 rad (*control B*, high Hct). This phase relationship did not change significantly after oxygen administration (low Hct: 1.64 ± 0.31 rad; high Hct: 1.54 ± 0.16 rad) or after LF breathing (low Hct: 1.64 ± 0.33 rad; high Hct: 1.47 ± 0.34 rad).

DISCUSSION

The present study reveals that the arterial cardiac baroreflex is impaired in high-altitude natives with high Hct and a high CMS score, compared with a

control group with normal Hct and a significantly lower CMS score. Temporary maneuvers, such as the administration of oxygen or slow-frequency breathing, are sufficient to improve autonomic function in subjects with CMS.

Differences between subjects with high and low Hct during baseline measurements. We defined an Hct >65% as a significant sign of polycythemia. This value was chosen with regard to the studies of León-Velarde et al. (19), who measured hemoglobin in the population of Cerro de Pasco and found a 95th percentile of 21.3 g/dl, which may roughly correspond to an Hct of ~64% (32). The score defines a value of Sa_{O_2} <82% as pathological in accordance with the results of previous studies (20). It should be emphasized that these values are characteristic for the population of Cerro de Pasco and cannot be simply transferred to populations in other geographical regions. Furthermore, the incorporation of values of Hct may have created a selection bias as subjects were stratified by Hct. Whereas the scoring system indicated the absence of severe symptoms of CMS in subjects with low Hct, it suggested moderate-to-severe signs of CMS in subjects with high Hct. This finding supports previous studies, which demonstrated a relationship between polycythemia at altitude and CMS, although this relationship may vary among different geographic regions (25, 44), and severity of CMS may not strictly parallel Hct.

Sa_{O_2} was slightly decreased in subjects with high Hct compared with subjects with low Hct. This phenomenon has already been reported and may support the hypothesis that subjects with CMS suffer more frequently from lung disease than subjects without CMS (20, 40, 43). León-Velarde and co-workers (20) observed a decreased peak expiratory flow in patients with CMS as a sign of chronic pulmonary disease. Our subjects with high Hct showed a decrease in forced expiratory volume in 1 s compared with subjects with low Hct. This phenomenon is compatible with the presence of chronic lower respiratory disease in subjects with CMS. However, peak expiratory flow was comparable between groups. The combination of slightly increased minute ventilation and decreased Sa_{O_2} may be interpreted in accordance with other authors as a sign of increased dead space ventilation in subjects with CMS (18). However, our results are also in agreement with the hypothesis that the more pronounced hypoxia may be related additionally to a ventilation-perfusion mismatch (23) or a reduced diffusing capacity (42) in patients with CMS.

Systolic blood pressure was higher and R-R interval shorter in subjects with high Hct compared with the control group, thus suggesting increased sympathetic activity in subjects with CMS. Additionally, the HF component of the R-R interval spectrum was slightly lower in subjects with high Hct during spontaneous breathing, despite breathing frequency and tidal volume being similar in both groups. This finding may be interpreted as a sign of lower vagal activity in subjects with high Hct, according to the phenomenon that fluctuations in R-R interval >0.15 Hz are nearly entirely mediated by vagal activity (1, 35). Spontaneous baroreflex sensitivity was lower in subjects with high Hct compared with the control group, thus indicating impairment in autonomic cardiovascular regulation in subjects with high Hct and clinical symptoms of CMS. The differences in baroreflex sensitivity had no effect on the temporal coupling between blood pressure and R-R interval in the LF range: the phase shift between these signals was comparable between groups.

Effects of oxygen administration. Even more than 15 min after termination of the administration of oxygen, both subjects with low and those with high Hct showed an improvement in ventilation during spontaneous breathing, indicated by an increase in Sa_{O_2} and a decrease in end-expiratory P_{CO_2}.

It is well known that a permanent increase in Sa_{O_2} improves the symptoms of CMS (42). Additionally, an increase in the P_{O_2} reverses the depressant effect of hypoxia on ventilation (36), which has been interpreted as a reversal of the centrally depressed ventilatory response (18, 36). Our data indicate that the improvement of ventilation outlasts the maneuvers that increase Sa_{O_2}.

We observed that the temporary administration of oxygen was associated with a persistent, significant decrease in systolic blood pressure, an increase in mean R-R interval, and an increase in heart rate variability, in both subjects with low and those with high Hct. Regarding the results of power spectral analysis and spontaneous baroreflex sensitivity, this improvement in autonomic function was more pronounced in subjects with high Hct. Baroreflex sensitivity did not change significantly in subjects with low Hct, whose values were within the range of those of healthy controls at sea level (15). Thus our findings suggest a normalization of a previously impaired autonomic nervous function after improved oxygenation in patients with CMS that lasted at least for the subsequent registrations after the administration of supplemental oxygen.

Effects of frequency-controlled breathing. Sa_{O_2} increased significantly in both subjects with low and those with high Hct during frequency-controlled breathing, whereas the difference in Sa_{O_2} between the two groups did not change. During breathing at 15 breaths/min, the improvement in Sa_{O_2} was related to a marked hyperventilation and thus to an increase in the alveolar P_{O_2}. During breathing at 6 breaths/min, the subjects showed less hyperventilation, and P_{CO_2} was only slightly and not significantly different from the values obtained during spontaneous breathing. Thus the increase in Sa_{O_2} during LF breathing may have been caused by reduced dead space ventilation and by an improvement of ventilation-perfusion mismatch. This effect of LF breathing has already been demonstrated in a previous study, which showed that intermittent training of a LF breathing pattern resulted in a more efficient ventilation in patients with impaired myocardial function (6).

The effect of frequency-controlled breathing at 6 breaths/min on autonomic cardiac control was similar

to that of temporary oxygen administration: baroreflex sensitivity increased in subjects with high Hct to values that were not significantly different from those of the control group with low Hct.

Beside these direct effects of breathing at 6 breaths/min on autonomic activity, normalization of cardiovascular autonomic activity persisted even after termination of the actively controlled training period of LF breathing in patients with high Hct.

These effects of breathing at 6 breaths/min may depend on two phenomena: a previous study demonstrated that Sa_{O_2} and autonomic cardiovascular regulation were maintained better during hypobaric hypoxia in Western yoga trainees who regularly performed LF breathing than in a control group, even when breathing frequency was not deliberately controlled (5). This phenomenon may have been caused by a more efficient breathing pattern in yogis, which improved cerebral oxygenation and, therefore, might have been similar to the supplementation of oxygen. On the other hand, it is known that spontaneous fluctuations in blood pressure and R-R interval of ~6 cycles/min (equivalent to the LF oscillations at ~0.1 Hz) are markedly enhanced by breathing or stimulation of baroreceptors at this frequency (4, 11, 26, 35). These maneuvers were associated with an increase in heart rate variability (35), as well as in baroreflex sensitivity (3, 7, 37). Our data suggest that this effect was more pronounced in subjects with CMS. Unlike the control group, subjects with CMS showed an increase in LF power, as well as in spontaneous baroreflex sensitivity, after oxygen administration. This effect was less marked after the slow-breathing period. The beneficial effect of improved oxygenation on the ventilatory response might have been counteracted by acute changes in P_{CO_2}. Subjects showed hypocapnia and a decrease in ventilation without significant changes in Sa_{O_2}, even 15 min after the slow-breathing episode. Slow-frequency breathing, as well as oxygen supplementation, was not able to decrease diastolic blood pressure, which was, except for *control B*, constantly higher in subjects with CMS compared with subjects with low Hct.

Limitations. In the present study, we used "spontaneous" baroreflex sensitivity as a marker of autonomic cardiovascular regulation. Several studies demonstrated that this parameter was a sensitive marker to detect autonomic dysfunction (12, 22, 27, 28). However, it should be pointed out that the different methods for assessing baroreflex sensitivity are not interchangeable (21, 30). The computation of spontaneous baroreflex sensitivity reveals information about the dynamic autonomic regulation at the actual baroreflex operating point and does not provide information about the sigmoid curve describing the relationship between static changes in blood pressure and the heart rate response (29).

Previous investigations found a high reproducibility and a lack of placebo effect when assessing hemodynamic regulation by spectral analytic methods and measures of spontaneous baroreflex sensitivity (14, 16, 17). However, a period effect could have theoretically influenced the results of our study, i.e., spontaneous baroreflex improved regardless of the maneuvers performed. Because measurements were carried out in resting subjects after at least 0.5 h of adaptation to the measurement procedure on 2 days, and diurnal changes in baroreflex sensitivity should not be of importance within this period of time, this effect is unlikely but cannot be strictly excluded.

In conclusion, we found in high-altitude natives with Hct >65% and significant signs of CMS an impaired cardiovascular regulation, expressed as reduced spontaneous baroreflex sensitivity, compared with subjects with Hct <60%. Spontaneous baroreflex sensitivity normalized after the temporary administration of oxygen as well as after slow-frequency breathing. Our results indicate that this beneficial effect outlasts the actively controlled training period of slow-frequency breathing; however, the long-term efficiency of this maneuver as a therapeutic option in patients with CMS should be investigated in further studies.

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