

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

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Abstract

Background: Oxygen inhalation therapy is essential for the treatment of patients with chronic mountain sickness (CMS), but the efficacy of oxygen inhalation for populations at high risk of CMS remains unknown. This research investigated whether oxygen inhalation therapy benefits populations at high risk of CMS.

Methods: A total of 296 local residents living at an altitude of 3658 m were included; of which these were 25 diagnosed cases of CMS, 8 cases dropped out of the study, and 263 cases were included in the analysis. The subjects were divided into high-risk ($180 \leq$ hemoglobin (Hb) <210 g/L, $n = 161$) and low-risk (Hb <180 g/L, $n = 102$) groups, and the cases in each group were divided into severe symptom (CMS score ≥ 6) and mild symptom (CMS score 0-5) subgroups. Severe symptomatic population of either high- or low-risk CMS was randomly assigned to no oxygen intake group (A group) or oxygen intake 7 times/week group (D group); mild symptomatic population of either high- or low-risk CMS was randomly assigned to no oxygen intake group (A group), oxygen intake 2 times/week group (B group), and 4 times/week group (C group). The courses for oxygen intake were all 30 days. The CMS symptoms, sleep quality, physiological biomarkers, biochemical markers, etc., were recorded on the day before oxygen intake, on the 15th and 30th days of oxygen intake, and on the 15th day after terminating oxygen intake therapy.

Results: A total of 263 residents were finally included in the analysis. Among these high-altitude residents, CMS symptom scores decreased for oxygen inhalation methods B, C, and D at 15 and 30 days after oxygen intake and 15 days after termination, including dyspnea, palpitation, and headache index, compared to those before oxygen intake (B group: $Z = 5.604, 5.092, 5.741$; C group: $Z = 4.155, 4.068, 4.809$; D group: $Z = 6.021, 6.196, 5.331$, at the 3 time points respectively; all $P < 0.05/3$ vs. before intake). However, dyspnea/palpitation (A group: $Z = 5.003, 5.428, 5.493$, both $P < 0.05/3$ vs. before intake) and headache (A group: $Z = 4.263, 3.890, 4.040$, both $P < 0.05/3$ vs. before intake) index decreased significantly also for oxygen inhalation method A at all the 3 time points. Cyanosis index decreased significantly 30 days after oxygen intake only in the group of participants administered the D method ($Z = 2.701, P = 0.007$). Tinnitus index decreased significantly in group A and D at 15 days (A group: $Z = 3.377, P = 0.001$, D group: $Z = 3.150, P = 0.002$), 30 days after oxygen intake (A group: $Z = 2.836, P = 0.005$, D group: $Z = 5.963, P < 0.0001$) and 15 days after termination (A group: $Z = 2.734, P = 0.006$, D group: $Z = 4.049, P = 0.0001$), and decreased significantly in the group B and C at 15 days after termination (B group: $Z = 2.611, P = 0.009$; C group: $Z = 3.302, P = 0.001$). In the population at high risk of CMS with severe symptoms, oxygen intake 7 times/week significantly improved total symptom scores of severe symptoms at 15 days (4 [2, 5] vs. 5.5 [4, 7], $Z = 2.890, P = 0.005$) and 30 days (3 [1, 5] vs. 5.5 [2, 7], $Z = 3.270, P = 0.001$) after oxygen intake compared to no oxygen intake. In the population at high risk of CMS with mild symptoms, compared to no oxygen intake, oxygen intake 2 or 4 times/week did not improve the total symptom scores at 15 days (2 [1, 3], 3 [1, 4] vs. 3 [1.5, 5]; $\chi^2 = 2.490, P = 0.288$), and at 30 days (2 [0, 4], 2 [1, 4.5] vs. 3 [2, 5]; $\chi^2 = 3.730, P = 0.155$) after oxygen intake. In the population at low risk of

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CMS, oxygen intake did not significantly change the white cell count and red cell count compared to no oxygen intake, neither in the severe symptomatic population nor in the mild symptomatic population.

Conclusions: Intermittent oxygen inhalation with proper frequency might alleviate symptoms in residents at high altitude by improving their overall health conditions. Administration of oxygen inhalation therapy 2–4 times/week might not benefit populations at high risk of CMS with mild CMS symptoms while administration of therapy 7 times/week might benefit those with severe symptoms. Oxygen inhalation therapy is not recommended for low-risk CMS populations.

Key words: Chronic Mountain Sickness; Efficacy; Hypoxia; Individualized Therapy; Oxygen Inhalation

INTRODUCTION

Oxygen is essential for normal functioning of the human body. Lack of oxygen may lead to organ dysfunction that may impair normal homeostasis.^[1] However, hypoxia is common in many areas, especially those at high altitudes; hypoxia is one of the major factors associated with poor health and mortality in those areas. Thus, oxygen plays a very important role for people living on elevated plateaus, especially among those with chronic mountain sickness (CMS).

CMS frequently occurs in people who have been living at a high altitude for an extended period. External oxygen intake can alleviate hypoxic symptoms in patients with CMS. However, once the oxygen intake ends, blood oxygen saturation decreases dramatically within <1 min due to the constant consumption of oxygen, indicating that the primary goal of oxygen-intake therapy should be not only alleviation of hypoxic symptoms but also improvement of oxygen partial pressure in human organs, tissues, and certain cells. For example, after a night sleep in an oxygen-enriched environment, the human body might change either the reactivity of respiratory center or the carotid body response to hypoxia.^[2] Brain cells in the human body, the most sensitive tissue to hypoxia, are key for regulation of plateau acclimatization.^[3,4]

In clinical practice, oxygen intake therapy is usually used to increase patient arterial oxygen pressure and oxygen saturation and to alleviate hypoxic symptoms among populations living at high altitudes.^[5,6] Individuals may exhibit various responses to oxygen intake.^[7,8] People living on high-altitude plateaus (i.e., 3000–4000 m above sea level) for long periods of time may demonstrate obvious symptoms while other people may adapt well and show fewer symptoms.^[9] However, optimization of oxygen inhalation strategies in specific populations living at high altitudes remains a challenge, and research on this topic is scarce. The present study investigated which subpopulations most benefit from oxygen intake therapy and determined the optimal regimen, including time and frequency of oxygen intake.

METHODS

Study population

This study was performed from January to June 2014. The general health status of 296 local residents was first investigated. To evaluate the effect of oxygen intake on

populations living at an altitude of 3658 m above sea level, 271 participants were enrolled (25 participants were excluded after being diagnosed with CMS). A total of 263 permanent residents were included to further investigate the effects of oxygen intake in subpopulations at this altitude (8 subjects discontinued during the study). All participants were selected randomly from local residents living 3658 m above sea level, and their ages ranged between 18 and 65 years. Exclusion criteria included cardiovascular or pulmonary disease, psychological disorders, anemia, tumors, and surgical history in the last 3 months. Diagnostic criteria for CMS were hemoglobin (Hb) concentrations ≥ 210 g/L and symptom scores ≥ 6 . Populations at high risk of CMS were defined as those with Hb between 180 and 210 g/L. Subjects with Hb <180 g/L were considered to be at low risk of CMS.^[8]

The study was undertaken with prior approval by the Ethical Committee of the Third Military Medical University. Written informed consents were obtained from all participants, peripheral venous blood and urine samples were collected, and related medical records were obtained.

Definition of chronic mountain sickness symptom score

This study used CMS symptom scores defined as follows. CMS symptom scores were graded according to the presence of dyspnea or palpitation, cyanosis, headache, tinnitus, vasodilation, insomnia, paresthesia, and Hb concentration. Each symptom had four score levels such as no, mild, moderate, and severe symptoms corresponding to 0, 1, 2, and 3 points, respectively. According to symptom scores, CMS symptoms were divided into two categories: mild (scores 0–5) and severe (scores ≥ 6).

Study grouping and oxygen intake procedures

The grouping strategy of this study is shown in Figure 1, the random number table was provided by a blind third party. A total of 263 subjects were divided into high- ($n = 161$) and low-risk ($n = 102$) groups and the cases in each group were divided into severe symptom and mild symptom subgroups. Of the 263 people participating in the subpopulation study at 3658 m above sea level, the severe symptomatic population at high risk of CMS (Hb between 180 and 210 g/L, CMS symptom scores ≥ 6 ; $n = 57$) was randomly administered 30-min daily oxygen intake via nasal catheter during lunch breaks at a flow rate of 2 L/min 7 times a week for 30 days (D group, $n = 28$) or received no oxygen intake (A group, $n = 29$). The population with mild symptoms and at high risk of CMS (Hb between 180 and 210 g/L, CMS

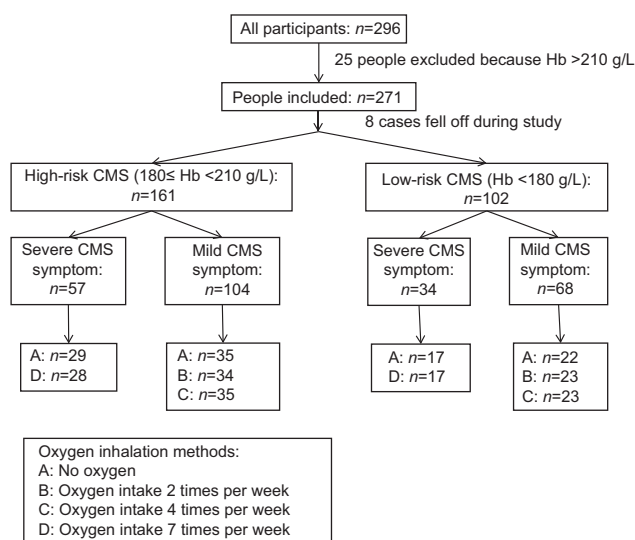


Figure 1: The grouping strategy of this study. CMS: Chronic mountain sickness; Hb: Hemoglobin.

symptom scores 0–5, $n = 104$) was randomly assigned to three groups: B ($n = 34$) and C ($n = 35$), who received 30-min daily oxygen intake via nasal tube 2 and 4 times a week for 30 days, respectively; and A ($n = 35$) who received no oxygen intake. Low-risk CMS controls ($n = 102$) were divided into two groups based on if they complained of any symptoms: severe symptoms (Hb < 180 g/L, CMS symptom scores ≥ 6 ; $n = 34$) and mild symptoms (Hb < 180 g/L, CMS symptom scores 0–5; $n = 68$). The group with severe symptoms was randomly assigned to two subgroups: D group ($n = 17$) was administered 30-min daily oxygen intake 7 times a week for 30 days, and A ($n = 17$) who did not receive any oxygen intake. The group with mild symptoms was randomly assigned to three subgroups: B ($n = 23$), who received 30-min daily oxygen intake twice weekly for 30 days; C ($n = 23$), who received 30-min daily oxygen intake 4 times weekly for 30 days; and A ($n = 22$), who received no oxygen intake.

Evaluation of oxygen intake efficacy

The alleviations of symptoms (e.g., headache, dyspnea, tinnitus, and cyanosis) and changes in their quantitative scores were recorded. Data on physiological biomarkers including heart rate, arterial oxygen saturation, as well as blood pressure, and results of routine blood and urine and biochemical marker testing, such as levels of alanine aminotransferase, creatinine, were also collected. Screening was conducted before, 15 and 30 days after inhalation therapy, and 15 days after therapy termination.^[10,11] In population at low risk of CMS, only blood cell count data were collected from each group during the outpatients' examination.

Statistical analysis

All the statistical analyses were performed using SPSS statistics for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous data are shown as median (Q1, Q3) if not normal distribution, or mean \pm standard deviation

(SD), and categorical data as percentages. Differences in continuous variables were tested by Wilcoxon rank sum test, independent t -tests between two groups, and analysis of variance (ANOVA) among three groups, respectively, whenever applicable. Two-tailed $P < 0.05$ was considered statistically significant, and P values were adjusted for multiple comparisons.

RESULTS

General health status of the population at high altitude

Of 296 residents who had lived long-term at 3658 m altitude, 25 (8.5%) were diagnosed with CMS. Among the remaining 271 residents enrolled in this study, 161 (54.4%) were at high risk of CMS, 102 (34.5%) were low-risk controls, and eight discontinued participation during the study.

Effects of different oxygen intake methods on a plateau 3658 m above sea level

CMS symptom scores decreased for oxygen inhalation methods B, C, and D at 15 and 30 days after oxygen intake, including dyspnea and palpitation and headache index, compared to before oxygen intake treatment [Table 1]. However, dyspnea/palpitation and headache index also decreased significantly for oxygen inhalation method A at all time points. Cyanosis index decreased significantly 30 days after oxygen intake only in group D [$Z = 2.701$, $P = 0.007$, Table 1]. Tinnitus index decreased significantly 15 and 30 days after oxygen intake and 15 days after termination in groups A and D, and decreased significantly 15 days after termination in the groups B and C [Table 1].

These results indicate that administration of oxygen 7 times/week could be a useful therapeutic regimen in a cohort of high-altitude residents at an altitude of 3658 m. In addition, oxygen inhalation twice weekly was also effective. Thus, oxygen inhalation therapy is beneficial for the general health of populations residing at high altitudes by attenuating hypoxia.

Effects of oxygen intake in subgroup populations at 3658 m altitude

Of 263 participants, 57 (21.7%) were categorized as having severe symptoms and at high risk of CMS, 104 (39.5%) as having mild symptoms and at high risk of CMS, and 102 (38.9%) as at low risk of CMS. Subgroup analysis was conducted to evaluate the efficacy of oxygen intake on various levels of dispositions to CMS.

Population at high risk of chronic mountain sickness with severe symptoms

The group of patients with severe symptoms and at high risk of CMS, who underwent group D's treatment method (7 times/week oxygen intake) had significantly improved total symptoms scores at 15 days (4 [2, 5] vs. 5.5 [4, 7], $Z = 2.890$, $P = 0.005$) and 30 days (3 [1, 5] vs. 5.5 [2, 7], $Z = 3.270$, $P = 0.001$) after oxygen intake compared to no oxygen intake, with blood oxygen saturation stably maintained at the same level as that at the time of

Table 1: Effect of different oxygen inhalation methods on the specific symptom score among the four oxygen inhalation methods

Items	Before intake	15 days after intake			30 days after intake			15 days after termination		
		Symptom score	Z	P	Symptom score	Z	P	Symptom score	Z	P
Dyspnea/palpitation										
Group A	1 (1, 1)	1 (0, 1)	5.003	<0.0001*	1 (0, 1)	5.428	<0.0001*	1 (0, 1)	5.493	<0.0001*
Group B	1 (1, 1)	0 (0, 1)	5.604	<0.0001*	0 (0, 1)	5.092	<0.0001*	0 (0, 1)	5.741	<0.0001*
Group C	1 (1, 1)	0 (0, 1)	4.155	<0.0001*	0 (0, 1)	4.068	<0.0001*	0 (0, 1)	4.809	<0.0001*
Group D	1 (1, 2)	0.5 (0, 1)	6.021	<0.0001*	0 (0, 1)	6.196	<0.0001*	1 (0, 1)	5.331	<0.0001*
Cyanosis										
Group A	0 (0, 1)	0 (0, 1)	0.743	0.458	0 (0, 1)	1.397	0.162	0 (0, 1)	0.921	0.357
Group B	0 (0, 0)	0 (0, 0)	-0.470	0.639	0 (0, 0)	-0.372	0.710	0 (0, 1)	-0.935	0.350
Group C	0 (0, 1)	0 (0, 1)	-0.976	0.329	0 (0, 1)	-0.655	0.512	0 (0, 1)	-0.787	0.431
Group D	1 (0, 1)	1 (0, 1)	1.203	0.229	0 (0, 1)	2.701	0.007*	0 (0, 1)	2.188	0.029
Headache										
Group A	1 (1, 1)	1 (0, 1)	4.263	<0.0001*	1 (0, 1)	3.890	0.0001*	1 (0, 1)	4.040	0.0001*
Group B	1 (0, 1)	0 (0, 1)	2.938	0.003*	0 (0, 1)	3.294	0.001*	0 (0, 1)	3.497	0.0005*
Group C	1 (0, 1)	0 (0, 1)	3.560	0.0004*	0 (0, 1)	3.112	0.002*	0 (0, 1)	4.115	<0.0001*
Group D	1 (1, 2)	0 (0, 1)	6.134	<0.0001*	0 (0, 1)	5.612	<0.0001*	0 (0, 1)	5.232	<0.0001*
Tinnitus										
Group A	1 (0, 1)	0 (0, 1)	3.377	0.001*	0.5 (0, 1)	2.836	0.005*	1 (0, 1)	2.734	0.006*
Group B	1 (0, 1)	0 (0, 1)	1.711	0.087	0 (0, 1)	1.573	0.116	0 (0, 1)	2.611	0.009*
Group C	1 (0, 1)	0 (0, 1)	2.319	0.020	0 (0, 1)	0.920	0.358	0 (0, 1)	3.302	0.001*
Group D	1 (1, 1)	0.5 (0, 1)	3.150	0.002*	0 (0, 0.5)	5.963	<0.0001*	0 (0, 1)	4.049	0.0001*

Data were showed as median (Q1, Q3). Oxygen inhalation methods: Group A: No oxygen intake, $n = 103$; Group B: Oxygen intake 2 times/week, $n = 57$; Group C: Oxygen intake 4 times/week, $n = 58$; Group D: Oxygen intake 7 times/week, $n = 45$. * $P < 0.05/3$ compared with before intake.

cessation, until 15 days after oxygen termination [Table 2]. Patients with CMS who were administered oxygen had significantly reduced Hb levels compared to those without oxygen intake, with the lowest levels occurring at 30 days (186.50 ± 8.71 vs. 190.45 ± 7.66 g/L, $P < 0.05$). However, no significant changes in nervous system function, such as cognitive ability (color average response time), sound recognition (sound average response time), sleep quality, systolic and diastolic blood pressure, blood oxygen saturation, and heart rate, were observed. Taken together, these observations in the group of participants at high risk for CMS with severe symptoms suggests that oxygen inhalation therapy may significantly alleviate clinical symptoms, including tinnitus and vasodilation. In addition, there were no rebound effects after ceasing oxygen intake treatment.

Population at high risk of chronic mountain sickness with mild symptoms

Among participants at high risk of CMS with mild symptoms, there were no significant differences in baseline demographic data, including age, height, body weight, and time residing at high altitude (data not shown). Compared to no oxygen intake, oxygen intake 2 or 4 times/week did not improved the total symptoms scores at 15 days (2 [1, 3], 3 [1, 4] vs. 3 [1.5, 5]; $\chi^2 = 2.490$, $P = 0.288$), and at 30 days (2 [0, 4], 2 [1, 4.5] vs. 3 [2, 5]; $\chi^2 = 3.730$, $P = 0.155$) after oxygen intake. The Hb levels in B and C groups remained stable during this observation period, and an obvious decrease was detected in C group 15 days after termination compared to levels in the A group (185.27 ± 9.30 vs. 196.52 ± 8.64 g/L,

$P < 0.05/2$). Sleep quality was significantly reduced in the B and C groups 15 days after stopping therapy. Oxygen treatment did not affect cognitive ability, sound recognition, and other indexes in this group. Physiological indexes such as blood oxygen saturation, heart rate, and blood pressure at rest showed no significant changes [Table 3].

Population at low risk of chronic mountain sickness

In blood cell count results, oxygen intake did not significantly change the white cell count and red cell count of the low-risk CMS population compared to no oxygen intake, neither in the severe symptomatic population [Table 4] nor in the mild symptomatic population [Table 5].

DISCUSSION

Although some people with long-term residence in high altitude areas are not diagnosed with CMS, they might still show typical symptoms and require medical assistance. Oxygen inhalation therapy might be the most effective and safest method to relieve symptoms such as dyspnea, headache, and tinnitus. However, different people respond differently to oxygen supplement, making individualized optimization necessary for better outcomes. This study evaluated the effects of oxygenation and might provide new insights into identifying new oxygen inhalation treatment strategies that could benefit the affected patient population.

The results of our study indicate that oxygen intake every day could significantly reduce symptoms among those who have lived for a long time at 3000–4000 m altitude and exhibit serious symptoms; among those with mild symptoms,

Table 2: Effects of oxygen intake in population at high risk of CMS with severe symptoms

Items	Before intake	15 days after intake	30 days after intake	15 days after termination
Total symptom score				
D	8 (7, 9)	4 (2, 5)*	3 (1, 5)*	3 (1, 5)
A	8 (7, 8)	5.5 (4, 7)	5.5 (2, 7)	5 (1, 6.5)
Hb (g/L)				
D	191.08 ± 7.09	189.57 ± 12.00	186.50 ± 8.71*	187.74 ± 10.85
A	190.98 ± 7.58	192.39 ± 8.04	190.45 ± 7.66	189.18 ± 11.24
Creatinine (μmol/L)				
D	77.44 ± 8.35	84.52 ± 12.78*	85.37 ± 13.68	78.93 ± 8.97
A	79.39 ± 10.09	79.44 ± 11.13	87.39 ± 14.80	79.40 ± 10.73
ALT (U/L)				
D	25.13 ± 9.81	21.84 ± 9.72	20.82 ± 9.24	22.88 ± 10.73
A	24.96 ± 9.00	22.26 ± 5.69	19.05 ± 11.17	20.79 ± 6.17
Cognitive ability (color average response time) (s)				
D	0.64 ± 0.08	0.63 ± 0.07	0.59 ± 0.12	0.61 ± 0.07
A	0.64 ± 0.13	0.64 ± 0.10	0.56 ± 0.15	0.63 ± 0.10
Sound recognition (sound average response time) (s)				
D	0.19 ± 0.05	0.18 ± 0.05	0.21 ± 0.10	0.18 ± 0.05
A	0.19 ± 0.05	0.17 ± 0.04	0.19 ± 0.09	0.17 ± 0.03
Sleep quality				
D	16 (12, 20)	10 (5, 13)	8.5 (3.5, 13)	9 (4, 12)
A	18 (16, 21)	13 (8.5, 17)	12 (6, 15)	12.5 (5, 15)
Systolic blood pressure (mmHg)				
D	113.11 ± 9.82	111.51 ± 10.61	114.61 ± 14.33	115.43 ± 10.02
A	111.26 ± 8.25	113.55 ± 9.19	115.29 ± 11.35	108.80 ± 9.36
Diastolic blood pressure (mmHg)				
D	67.84 ± 8.07	68.51 ± 12.33	73.43 ± 16.02	69.52 ± 9.34
A	66.87 ± 9.78	69.18 ± 9.08	69.26 ± 14.04	66.77 ± 8.42
Blood oxygen saturation (%)				
D	93.22 ± 1.98	91.91 ± 2.03	93.20 ± 2.38	92.91 ± 2.18
A	93.02 ± 1.96	92.36 ± 2.05	92.33 ± 2.71	92.55 ± 2.05
Heart rate (times/min)				
D	71.44 ± 10.58	73.98 ± 10.71	76.07 ± 13.43	74.57 ± 15.67
A	72.72 ± 11.00	76.34 ± 14.19	77.55 ± 10.84	78.16 ± 10.53

Data were showed as median (Q1, Q3) or mean ± SD. * $P < 0.05$ compared with no oxygen group. A: No oxygen intake; D: Oxygen intake 7 times/week; CMS: Chronic mountain sickness; SD: Standard deviation; Hb: hemoglobin; ALT: glutamic-pyruvic transaminase.

oxygen inhalation every other day positively influenced sleep quality without other significant adverse effects. Therefore, 30-min oxygen therapy at least twice weekly may be beneficial for maintenance of good health among people living in high altitude areas above 3000 m.

In these high-altitude areas, the effect of oxygenation largely depends on the duration and frequency of oxygen intake.^[12] The current study used nasal catheters and assigned different inhalation modes based on subgroup characteristics. Considering the advantageous effects of oxygen on symptom remission, sleep quality, oxygen saturation, and pulmonary artery pressure, overnight oxygenation could be more effective in improving sleep quality, thus enhancing treatment efficiency compared with daytime oxygenation.^[13]

The current study also observed significant improvement of symptoms in the population at high risk of CMS, lasting for at least 15 days after stopping treatment. Oxygen therapy was also associated with reduced Hb levels and maintenance of normal

blood pressure. Among healthy people at high altitude, oxygen inhalation showed no obvious effects on physical activity with no oxygen-induced side effects. These results suggest that oxygen inhalation at least twice weekly for 30 days could be effective with no relapse reported after termination.

Adverse events should also be taken into consideration. First, cessation of oxygen therapy might lead to withdrawal effects or addiction phenomena.^[13-17] During oxygenation, people may feel better, but once oxygen stops, especially after long-term daily oxygenation, people may feel tired or develop other adverse events, a theory that has not yet been thoroughly investigated.^[7,18-20] Previous studies have reported that subjects had no adverse reactions after stopping oxygen therapy. No adverse events were reported even several months later, and a similar trend has also been reported at extreme altitude where oxygen supplies are often turned off, without serious consequences.^[21] Although the subjects did not develop adverse reactions after daily oxygenation, oxygenation should be stopped. Termination

Table 3: Effects of oxygen intake in population at high risk of CMS with mild symptoms

Items	Before intake	15 days after intake	30 days after intake	15 days after termination
Total symptom score				
B	4 (3, 5)	2 (1, 3)	2 (0, 4)	2 (0, 4)
C	4 (3, 6)	3 (1, 4)	2 (1, 4.5)	2 (0, 5)
A	5 (3.5, 6)	3 (1.5, 5)	3 (2, 5)	3.5 (1.5, 5.5)
Hb (g/L)				
B	189.94 ± 6.88	192.60 ± 10.99	184.28 ± 11.42	188.32 ± 11.41
C	189.21 ± 6.84	189.28 ± 10.14	184.50 ± 7.80	185.27 ± 9.30*
A	190.51 ± 7.64	188.81 ± 9.42	186.69 ± 9.26	196.52 ± 8.64
Creatinine (μmol/L)				
B	78.88 ± 9.23	85.57 ± 12.01*	86.84 ± 12.46	78.74 ± 8.27
C	80.74 ± 9.02	87.61 ± 12.73*	89.51 ± 12.69	80.38 ± 19.29
A	78.94 ± 8.98	78.26 ± 10.28	85.90 ± 11.10	80.21 ± 8.38
ALT (U/L)				
B	30.94 ± 18.64	22.81 ± 8.77	19.38 ± 8.50*	22.62 ± 9.94
C	24.71 ± 8.31	22.30 ± 12.86	20.26 ± 13.94	22.84 ± 10.38
A	25.20 ± 12.33	20.34 ± 5.67	20.82 ± 19.35	21.36 ± 12.87
Cognitive ability (color average response time) (s)				
B	0.65 ± 0.08	0.64 ± 0.08	0.57 ± 0.15	0.61 ± 0.07
C	0.67 ± 0.10	0.64 ± 0.07	0.59 ± 0.11	0.62 ± 0.08
A	0.65 ± 0.08	0.64 ± 0.09	0.58 ± 0.12	0.61 ± 0.09
Sound recognition (sound average response time) (s)				
B	0.19 ± 0.06	0.17 ± 0.04	0.21 ± 0.14	0.17 ± 0.05
C	0.18 ± 0.04	0.19 ± 0.07	0.20 ± 0.12	0.17 ± 0.03
A	0.18 ± 0.03	0.18 ± 0.03	0.19 ± 0.06	0.17 ± 0.04
Sleep quality				
B	12 (7, 16)	7 (3, 10.5)	5 (2, 9)	4 (2, 7)*
C	10 (7, 14)	8 (4, 12)	6 (3, 9)	5 (0, 9)*
A	12 (8.5, 16)	8 (6, 14)	7 (4, 14)	7 (3, 12)
Systolic blood pressure (mmHg)				
B	111.79 ± 8.93	113.81 ± 8.20	116.59 ± 12.57	113.37 ± 11.65
C	113.14 ± 10.64	113.67 ± 9.10	112.87 ± 11.27	113.33 ± 10.23
A	112.12 ± 10.55	113.20 ± 9.19	116.26 ± 10.54	114.02 ± 11.01
Diastolic blood pressure (mmHg)				
B	65.84 ± 7.86	67.47 ± 7.83	70.62 ± 9.21	67.47 ± 10.35
C	67.03 ± 9.42	68.48 ± 11.29	72.72 ± 12.58	69.73 ± 8.48
A	65.51 ± 9.56	66.91 ± 9.88	70.78 ± 11.16	68.07 ± 7.63
Blood oxygen saturation (%)				
B	91.96 ± 5.80	91.93 ± 2.16	92.69 ± 2.60	92.09 ± 2.17
C	92.79 ± 1.93	92.09 ± 1.98	92.91 ± 2.04	93.00 ± 2.03
A	92.91 ± 2.29	91.95 ± 2.05	92.39 ± 1.82	92.61 ± 2.06
Heart rate (times/min)				
B	71.18 ± 10.19	75.62 ± 10.78	76.57 ± 10.59	75.54 ± 10.27
C	69.98 ± 10.44	72.33 ± 11.03	75.75 ± 11.70	75.42 ± 10.64
A	71.28 ± 11.41	73.63 ± 11.77	78.00 ± 10.92	76.18 ± 11.70

Data were showed as median (Q1, Q3) or mean ± SD. * $P < 0.05/2$ compared with no oxygen group. A: No oxygen intake; B: Oxygen intake 2 times/week; C: Oxygen intake 4 times/week; CMS: Chronic mountain sickness; SD: Standard deviation; Hb: hemoglobin; ALT: glutamic-pyruvic transaminase.

of oxygen for 2 weeks not only resulted in no adverse reactions but also the beneficial effects of oxygenation remained.^[22-24] At altitudes of 3000–4000 m above sea level, administration of inhaled oxygen several times a week after continuous administration might help prevent withdrawal effects, the signs of which might vary in different people. Second, oxygen therapy could reduce the intrinsic ability of habituation. Acclimatization to the plateau might be a natural process at 4000 m altitude above sea level,

and acclimatization quality depends on self-regulating mechanisms, which could be artificially interrupted by oxygenation daily or several times weekly, thus reducing adaptability to life on plateaus. In this context, the results of our study suggest that oxygenation even several times a week did not seem to impair acclimatization. Individual ability to acclimate to altitude is based on a complex of factors including self-feeling and labor efficiency. In addition, a number of studies have shown that repeated hypoxia may

Table 4: Effects of oxygen intake on blood cell count in population at low risk of CMS with severe symptoms

Blood cell counts	Before intake	15 days after intake	30 days after intake	15 days after termination
White blood cell count ($\times 10^9/L$)				
D	6.15 \pm 1.38	6.34 \pm 1.42	6.67 \pm 1.53	5.88 \pm 1.12
A	6.50 \pm 1.31	6.06 \pm 1.08	6.33 \pm 1.28	5.87 \pm 1.23
Red blood cell count ($\times 10^{12}/L$)				
D	5.63 \pm 0.46	5.72 \pm 0.39	5.72 \pm 0.41	5.68 \pm 0.43
A	5.89 \pm 0.68	5.74 \pm 0.51	5.79 \pm 0.43	5.69 \pm 0.43

Data were showed as mean \pm SD. A: No oxygen intake; D: Oxygen intake 7 times/week; CMS: Chronic mountain sickness; SD: Standard deviation.

Table 5: Effects of oxygen intake on blood cell count in population at low risk of CMS with mild symptoms

Blood cell counts	Before intake	15 days after intake	30 days after intake	15 days after termination
White blood cell count ($\times 10^9/L$)				
B	6.19 \pm 0.91	6.60 \pm 1.28	6.61 \pm 1.31	6.21 \pm 1.25
C	6.09 \pm 1.52	6.43 \pm 1.58	6.42 \pm 1.45	5.81 \pm 1.24
A	6.01 \pm 1.39	6.08 \pm 1.16	6.24 \pm 1.35	5.78 \pm 1.12
Red blood cell count ($\times 10^{12}/L$)				
B	5.74 \pm 0.43	5.75 \pm 0.44	5.77 \pm 0.42	5.70 \pm 0.43
C	5.70 \pm 0.45	5.71 \pm 0.47	5.71 \pm 0.49	5.64 \pm 0.45
A	5.74 \pm 0.45	5.69 \pm 0.38	5.81 \pm 0.40	5.75 \pm 0.33

Data were showed as mean \pm SD. A: No oxygen intake; B: Oxygen intake 2 times/week; C: Oxygen intake 4 times/week; CMS: Chronic mountain sickness; SD: Standard deviation.

result in oxygen-rich, high blood pressure.^[25-27] Repeated hypoxia might also alter the body's oxygen-rich redox status, which causes dysfunctions of vascular endothelial cells; however, hypoxia had been present for extended length of time in these previous studies.^[28,29] Both normal oxygen and hypoxia may also be experienced at high altitudes. Subjects with hypoxia for 30 min every day (typically at 4500 m above sea level) in 2 consecutive weeks could experience vascular response and central nervous system damage due to hypoxia. A 60-min simulation in low-pressure tanks at 4500 m 4 times daily for 4 consecutive weeks was shown to harm the normal function of blood vessels, which manifested as elevated blood pressure, reduced blood antioxidant capacity, increased lipid peroxides, suppressed endothelial function, etc.^[30-33] However, controversy remains and long-term follow-up studies are necessary to obtain a solid conclusion.

Oxygen therapy in high-altitude areas can relieve symptoms, improve sleep quality, and reduce pulmonary artery pressure in patients with CMS, those at high risk for CMS, and healthy individuals living on the plateau; however, these benefits might not last after stopping inhalation. However, a small percentage of the study population maintained the beneficial effects of oxygen therapy in an oxygen-independent manner

for 15 days after cessation of oxygen therapy, without any rebound events. Our results suggest that oxygenation does not reduce personal acclimatization to life at high altitudes, as evidenced by the lack of adverse effects such as poor sleep quality, various CMS symptoms, and brain inefficiency, which is the most important indicator to determine effects of oxygenation in long-term residents of high-altitude area. In addition, certain objective physiological indices such as blood oxygen saturation, heart rate, and vascular ultrasonography, which are the common evaluation methods to detect vessel oxygenation, also supported the beneficial effect of oxygenation for residents of high-altitude areas.

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Conflicts of interest

There are no conflicts of interest.

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