RESEARCH ARTICLE

Effect of extreme altitude mountaineering on iron status

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Introduction Hypoxia is a stress condition which causes an increased requirement for oxygen transport. In recent years, mountain exploration has gained popularity. The work of such investigators as West, Basnyat, Roach, Schoene, Bailey, Hackett, Bartsch, Milledge, or Imray, who have investigated the influence of hypoxia on the human body since the 20th century, has greatly contributed to the understanding of the physiological and pathophysiological processes that occur during stay at high altitude. People who climb the peaks above 8000 m are typically subjected to a prolonged stay at extreme height, defined as an elevation above the level of 5500 m.

It is known that hypoxia stimulates erythropoiesis and promotes hemoglobin synthesis.[1-3] The elevated serum levels of erythropoietin were observed in individuals exposed to the altitude of 4530 m. They also showed an increased iron uptake within 24 hours, suggesting a direct effect of erythropoietin on hemoglobin synthesis by the existing marrow population.[1] Moreover, an increase in the rates of red blood cell (RBC) formation and plasma iron turnover was observed already after 2 hours since arrival at an altitude of 4530 m, and was maintained throughout the subsequent days.[3]

We hypothesize that iron bioavailability may become impaired in a state of accelerated erythropoiesis at high altitude. Therefore, the main objective of this study was to determine the effect of exposure to extreme altitude on the RBC line and iron metabolism.

Methods We analyzed 11 Caucasian individuals (10 men, 1 woman) who participated in an expedition to climb the Himalayan summits: K2 (8611 m) or Broad Peak (8051 m). The mean (SD) age of the participants was 40 (8) years (range, 30–60 years). None of them had any severe cardiopulmonary disease. Patent foramen ovale (PFO) had been diagnosed in 1 person, and 1 individual had a 5-year history of well-controlled hypertension treated with amlodipine (2.5 mg/d). Another participant suffered from a reflex syncope. The female participant took oral contraception.

All participants were experienced climbers who had been at an altitude above 7000 m at least once and at an altitude above 4000 m on numerous occasions. A few months before the expedition, they had trained 3 to 4 times a week, for 1 to 2 hours per day on average (mostly running, cycling, and climbing). The endurance capacity of all participants was objectively evaluated by a cardiopulmonary exercise test. The maximal oxygen consumption (VO_{2max}) was measured during the maximal incremental exercise on a motorized treadmill T-2100 (GE Medical Systems Information Technologies, GE Healthcare, Milwaukee, Wisconsin, United States), using the Bruce protocol. Written informed consent to participate in the study was obtained from all subjects, and the protocol was approved by the Human Studies Committee of the Medical University of Silesia, Katowice, Poland.

Blood tests were performed 3 times: 2 to 3 weeks before departure for the expedition, after arrival from the expedition (a mean [SD] of 8 [3] days after leaving the altitude above 2300 m), and at least 6 months after the expedition. Blood samples were collected from fasting subjects in the morning, from the antecubital vein, and drawn into tubes for analysis (Monovette® Serum for biochemical analysis and Monovette® EDTA K for blood cell count analysis; Sarsted AG&Co, Nümbrecht, Germany). The analysis was done immediately after blood collection. The samples were centrifuged at 3500 rpm for 15 minutes for the separation of the serum. The tests were performed using a Cobas® c501 analyzer (biochemistry) (Roche Diagnostic, Indianapolis, Indiana,

United States) and Sysmex XE-2100™ analyzer (blood cell count) (Sysmex Corporation, Japan). All measurements were performed in the 3rd Department of Cardiology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Silesian Center for Heart Disease in Zabrze, Poland.

All results were expressed as mean and SD. The value of reticulocyte hemoglobin equivalent (Ret-Hb) obtained from the analyzer in fmol/l was recalculated to pg as fmol of hemoglobin equal to 16.1 pg.[4] The comparisons of the measurements taken before the expedition to those obtained after the expedition, and of those taken 6 months after the expedition to those obtained immediately after, were made by the Wilcoxon signed--rank test (Statistica 10, StatSoft, Inc., Dell Software, Tulsa, Oklahoma, United States). Statistical significance was determined at a *P* value of less than 0.05.

Results Participants spent from 47 to 56 days at an altitude above 2300 m and from 36 to 44 days at an altitude above 4900 m attempting to climb K2 or Broad Peak. None of the subjects suffered a severe episode of high altitude sickness during the expeditions. The individual with PFO experienced a self-limited transient ischemic attack during climbing.[5] In the period between the end of the expedition and 6 months after the expedition, one person was at the altitude for a few days (the highest point reached was 6200 m). This exposure was more than 3 months before the third measurement.

The mean (SD) body weight, body surface area, and body mass index of the study group before the expedition were 76.67 (9.36) kg, 1.93 (0.16) m^2, and 24.24 (1.30) kg/m^2, respectively. The mean (SD) VO_{2max} in the cardiopulmonary exercise test was 56.6 (8.2) ml/kg/min. The results of laboratory measurements obtained at the 3 timepoints are presented in TABLE 1.

Discussion The results of our study show that exposure to extreme altitude in experienced climbers increases the RBC count and iron and ferritin levels, while it decreases reticulocyte and Ret--Hb levels, which may indicate functional iron deficiency.

Ret-Hb is considered an indicator of the red cell quality and the current iron status.[6,7] Moreover, it reflects iron availability during RBC production, just like reticulocytes signal the marrow erythropoietic activity 3 to 4 days after iron has been actively incorporated into hemoglobin.[2] Hypoxia induces erythropoietin stimulation, which increases the requirement for iron. After the expedition, we observed an increase in the RBC count. However, as previously mentioned, the higher rate of erythropoiesis at altitude may impair adequate iron incorporation into RBCs. After a long-term stay at high altitude, the erythropoietin effect may be diminished due to inadequate iron availability for accelerated erythropoiesis. The iron mobilization is insufficient for the demand, whereas the iron reserve is normal or increased. Therefore, iron deficiency occurs as a result of its impaired mobilization during an increased rate of erythropoiesis, even though the iron storage is sufficient. This may impair iron bioavailability without its deficiency. In our study, this was evidenced by reduced Ret-Hb values and increased ferritin concentrations after the return from the expedition.

The functional iron deficiency and related parameters of iron metabolism were investigated in patients on hemodialysis.[7] Ret-Hb is a useful marker of iron deficiency and early predictor of response to intravenous iron supplementation in patients on regular hemodialysis.[7] Therefore, it may be considered as a marker of the iron status in people exposed to a long-term stay at extreme altitude. Interestingly, iron depletion may exacerbate hypoxic pulmonary hypertension,[8] which may contribute to the development of subclinical or clinical manifestations of high--altitude pulmonary edema even in healthy climbers.[9] The key source of dietary iron is heme in hemoglobin and myoglobin in red meat.[10] A diet rich in red meat may result in a higher iron status.[11] In a previous study, the iron status was reported to be more favorable in elite runners on a diet rich in meat.[12] In our study, the climbers were on a diet which included large amounts of red meat. We hypothesized that this might have affected iron and ferritin concentrations.

Study limitations Our study has several limitations including a relatively small sample size, the lack of measurements taken at high altitude, insufficient diet control during the expedition, and the lack of a control group. Moreover, every expedition aiming to climb a peak above 8000 m has an individual acclimatization pattern, including the time of exposure to extreme altitude. Therefore, our results may not be extrapolated to the general population of climbers who return from an expedition.

Despite the above limitations, we believe that our research provides additional insight into iron metabolism after a prolonged stay in the state of hypoxia. Therefore, our results may serve as the basis for a larger, well-controlled trial investigating iron supplementation and early detection of potential functional iron deficiency. Further studies are needed to evaluate this phenomenon and provide adequate recommendations.

Conclusions The results of our study may indicate functional iron deficiency among climbers participating in the expeditions to K2 and Broad Peak. The deficiency may result from a prolonged exposure to the hypoxic environment. We recommend that a standard blood test is performed and the iron status evaluated in every person planning high-altitude climbing. The estimation of Ret-Hb levels may support the diagnosis of impaired iron bioavailability related to high-altitude exposure.

TABLE 1 Laboratory measurements in climbers before the expedition, shortly after the expedition, and 6 months after the expedition

Parameter		Measurement 1[a]	Measurement 2[b]	Measurement 3[c]	*P* value[d]	*P* value[e]
RBC, $10^6/\mu l$		4.92 (0.34)	5.46 (0.42)	4.84 (0.32)	0.003	0.01
WBC, $10^3/\mu l$		5.37 (1.28)	6.13 (1.67)	5.88 (1.68)	0.05	0.26
Hb, mmol/l		9.2 (0.42)	10.48 (0.61)	9.2 (0.59)	0.003	0.01
Hematocrit		0.43 (0.02)	0.48 (0.03)	0.43 (0.03)	0.003	0.01
PLT, $10^3/\mu l$		221.27 (48.19)	189.64 (52.71)	244.38 (34.58)	0.01	0.01
Ret, ‰		11.13 (5.10)	5.14 (2.25)	13.62 (7.29)	0.003	0.01
Ret-Hb	fmol/l	2.18 (0.09)	2.10 (0.12);	2.2 (0.09);	0.01	0.03
	pg	ca. 35.1 (1.45)	ca. 33.81 (1.93)	ca. 35.42 (1.45)		
Iron, μmol/l		21.58 (6.97)	27.57 (6.8)	20.41 (10.59)	0.04	0.26
Ferritin, ng/ml		114.35 (58.87)	147.99 (55.82)	140. 57 (53.88)	0.01	0.24
Creatinine, μmol/l		84.91 (8.35)	87.73 (13.84)	97.25 (14.8)	0.65	0.40
ALT, U/l		20.53 (8.79)	55.2 (63.76)	23.25 (8.26)	0.01	0.02
ASP, U/l		27.32 (5.18)	35.96 (33.28)	24.5 (9.64)	0.11	0.40
Na, mmol/l		141.18 (1.47)	140.64 (2.29)	140.38 (0.92)	0.52	0.53
K, mmol/l		4.55 (0.42)	4.59 (0.40)	4.45 (0.39)	0.80	0.26
TP, g/l		67.78 (3.71)	71 (5.22)	71.67 (5.16)	0.04	0.03
Albumin, g/l		46.27 (1.97)	43.73 (2.57)	47.25 (2.25)	0.004	0.01
TC, mmol/l		5.15 (0.79)	4.92 (1.44)	5.53 (0.84)	0.93	0.75
LDL-C, mmol/l		2.93 (0.74)	3.02 (0.72)	3.32 (0.79)	0.48	0.35
HDL-C, mmol/l		1.78 (0.3)	1.67 (0.29)	1.8 (0.32)	0.13	0.60
TG, mmol/l		0.95 (0.44)	1.26 (0.36)	1.13 (0.59)	0.047	0.17

Data are expressed as mean (SD). A *P* value of less than 0.05 was considered significant.

a 2–3 weeks before departure for the Broad Peak/K2 expedition

b Mean (SD) 8 (3) days after leaving the altitude above 2300 m

c 6 months after the expedition

d Differences between measurements 2 and 1

e Differences between measurements 3 and 2

Abbreviations: ALT, alanine transaminase; ASP, aspartate transaminase; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low--density lipoprotein cholesterol; K, potassium; Na, sodium; PLT, platelet; RBC, red blood cell; Ret, reticulocytes; Ret-Hb, reticulocyte hemoglobin equivalent; TC, total cholesterol; TG, triglycerides; TP, total protein; WBC, white blood cell

The profile of biochemical parameters may differ depending on the type of the expedition and duration of stay at high altitude. The diet is particularly important, and nutrition consults are recommended for all climbers to ensure proper diet during the expedition. Although our results cannot be extrapolated to a general population of high-altitude climbers, they may serve as guidance as to what abnormalities can be expected in these individuals.

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