Intermittent Hypobaric Hypoxia Induces Altitude Acclimation and Improves the Lactate Threshold

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CASAS M, CASAS H, PAGES T, RAMA R, RICART A, VENTURA JL, IBANEZ J, RODRÍGUEZ FA, VISCOR G. *Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold.* **Aviat Space Environ Med 2000; 71:125–30.**

The physiological responses to short-term intermittent exposure to hypoxia in a hypobaric chamber were evaluated. The exposure to hypoxia was compatible with normal daily activity. The ability of the hypoxia program to induce hematological and ventilatory adaptations leading to altitude acclimation and to improve physical performance capacity was tested. Six members of a high-altitude expedition were exposed to intermittent hypoxia and low-intensity exercise (in cycle-ergometer) in the INEFC-UB hypobaric chamber over 17 d, 3–5 $h \cdot d^{-1}$, at simulated altitude of 4,000 m to 5,500 m. Following this hypoxia exposure program, significant increases were found in packed cell volume (41 to 44.6%; $p < 0.05$), red blood cells count (4.607 to 4.968 10^6 cells $\cdot \mu L^{-1}$; $p < 0.05$), and hemoglobin concentration (14.8 to 16.4 g $\cdot dL^{-1}$; $p < 0.05$), thus implying an increase in the blood oxygen transport capacity. Significant differences in exercise blood lactate kinetics and heart rate were also observed. The lactate vs. exercise load curve shifted to the right and heart rate decreased, thus indicating an improvement of aerobic endurance. These results were associated with a significant increase in the ventilatory anaerobic threshold ($p < 0.05$). Significant increases ($p < 0.05$) in pulmonary ventilation, tidal volume, respiratory frequency, O_2 uptake, CO_2 output and ventilatory equivalents to oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$) were observed at the ventilatory threshold and within the transitional zone of the curves. We conclude that short-term intermittent exposure to moderate hypoxia, in combination with low-intensity exercise in a hypobaric chamber, is sufficient to improve aerobic capacity and to induce altitude acclimation.

Keywords: hypoxia, metabolic and ventilatory adaptations, hypobaric chamber, erythropoiesis, aerobic capacity.

CLIMBERS ADAPT to high altitude by spending several days or weeks at progressively higher altitudes, a process known as acclimatization, which delays high mountain expeditions. Some adaptative responses to altitude, such as an increase in hemoglobin and erythrocytic mass or some ventilatory changes are among the physiological key factors emulated when training at altitude to improve performance (28). On the other hand, the prolonged exposure to hypoxia causes a certain degree of physical impairment, weight loss due to a considerable decrease of the muscular mass (13,14), as well as psychological deterioration (19) and neurological impairment (7,28).

The term acclimation refers to the adaptative changes produced under a controlled laboratory setting. Training in hypobaric chambers has been used as an alternative procedure to induce acclimation to altitude (19,27), and also to improve performance at sea level by training at moderate simulated altitude equivalent to 2,300 m (25,26). Unfortunately, permanent exposure for the time necessary to induce significant adaptative responses according to this procedure, even if effective, is not compatible with normal daily activity during the acclimation period. In addition, it may induce the altitude deterioration phenomenon and, thus, a paradoxical impairment of physical performance capacity of subjects. Pre-acclimation to hypoxia, through intermittent exposure in a hypobaric chamber has been studied by Nagasaka et al. (17) using a protocol based on 5 $h \cdot d^{-1}$ of exposure to 6,000 m, on 3 consecutive days, followed by 1 h for 1 d at 8,000 m. This procedure induced a considerable increase in ventilation and arterial P_{O_2} and a decrease in arterial P_{CO_2}, without significant changes in RBC count.

In a recent study in our laboratory, intermittent short-term hypobaric hypoxia (1.5 $h \cdot d^{-1}$ at 4,000–5,500 m for 3 wk) elicited an increase in erythrocyte mass based on the activation of endogenous EPO secretion (submitted). Similar results were obtained with an even shorter intermittent exposure (3 to 5 $h \cdot d^{-1}$ at 4,000–5,500 m for 9 d) (21).

The aim of the present study was to confirm whether the physiological responses to short-term intermittent exposure to hypoxia in a hypobaric chamber induce hematological and ventilatory adaptations, which could

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This manuscript was received for review in November 1998. It was revised in June 1999. It was accepted for publication in August 1999.

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lead to acclimation to altitude and to the improvement of aerobic capacity.

METHODS

A group of six elite climbers, members of a high-altitude expedition, five men (mean age 28 yr, range 23–33, mean weight 76.9 ± 5.9 kg, and height 183.8 ± 6.6 cm) and one woman (age 25 yr, weight 54.6 kg, and height 163.4 cm), were exposed to intermittent hypoxia and low-intensity exercise over 17 d in the INEFC-UB hypobaric chamber located at sea-level (Barcelona, Spain). All subjects were informed about the objective of the study and the experimental protocol. The study was performed with their written consent, and in accordance with the recommendations of the Declaration of Helsinki.

Simulated altitude was 4,000 m at the first session (614 hPa; Po_2=129 hPa) and was progressively increased to 5,500 m (504 hPa; Po_2=105 hPa). Exposure sessions lasted 3 h at the beginning of the program and were increased to a maximum of 5 h · d^{-1}. All subjects combined passive exposure to hypoxia with low-intensity exercise on a cycle ergometer (Monark AB model, Varberg, Sweden) in order to compensate the training reduction caused by the duration of the exposure sessions. Exercise lasted 15 min per each hour of exposure, and was performed at an individually pre-determined heart rate (ranging from 120 to 130 bpm, corresponding to their individual 100 W workload at sea level). All hypobaric exposure sessions were performed in the evening, at the end of the daily working schedule.

Before and after exposure to the hypobaric hypoxia program, medical status, performance capacity, hematological profile and some biochemical parameters were evaluated. Full medical examination included medical history, physical characteristics, rest electrocardiogram, and ergospirometric measurements: forced vital capacity (FVC), forced expiratory volume at first second (FEV1) and Tiffenneau index (FEV1/FVC). Respiratory parameters were measured at BTPS conditions and recalculated at STPD. Individual physical performance capacity was established by means of a maximal incremental treadmill test at sea level with continuous "breath by breath" gas analysis (CPX-II, Medical Graphics, St. Paul, MN) and capillary blood lactate determination every 3 min. A modified Bruce exercise protocol was used including seven steps of increasing treadmill speed (from 1.7 to 6.0 mi · h^{-1}) and slope (from 10 to 22%) and adding to the classical incremental procedure intervals of 30 s between loads to allow for blood sampling. Blood lactate concentration was determined in arterialized blood samples (collected by earlobe puncture with 20 μl capillary tubes) by an enzymatic method based on lactate dehydrogenase (LDH) activity (Lactate-test, Boehringer-Mannheim, Mannheim, Germany) and quantified by spectrophotometry. Blood lactate kinetics was modeled using a log-log transformation procedure, in order to determine the two breaking points of each lactate curve (12). Using this method, three segments can be detected corresponding to initial baseline, transition and accumulation of blood lactate during the exercise test.

A complete hematological profile was also obtained from venous blood samples (10 ml collected from the antecubital vein), before and after the maximal incremental treadmill test. All venous blood samples were taken without stasis using plastic syringes. Samples were immediately placed on ice in EDTA di-K and heparin-lithium tubes, where they were kept until assayed.

Packed cell volume (PCV) measurements were made by centrifugation of capillary samples (Hemofuge, Heraeus, Hanau, Germany) for 5 min at 11,500 × g and were expressed as percentages. Red blood cells counts (RBC count) were determined using an automated cell counter (Coulter Counter Model ZF, Dunstable, UK). Total hemoglobin concentration ([Hb]) was assayed by Drabkin's method. The absorbance at 540 nm was determined with a Spectronic 2000 spectrophotometer (Baush & Lomb, Rochester, NY).

Venous blood was centrifuged at 3,000 × g for 10 min (URA 2640, Hamburg, Germany) and the separated plasma was kept in Eppendorf tubs. Plasma osmolality was measured with a micro-osmometer (3MO Advanced Instruments, Needham Heights, MA). Total plasma proteins were measured by spectrophotometric technique (Lowry's method).

Plasma iron was determined by electrothermal atomic absorption spectrometry using a Zeeman Varian Spectra A30. Serum ferritin was determined by ELISAT (Enzymun-test ferritin kit, Boehringer-Manheim, Mannheim, Germany). For accuracy of ferritin determinations the National Biological Standards Board (NBSB) 80/602 standard ferritin was used.

The rheological behavior of blood was studied by measuring plasma and whole blood apparent viscosities at shear rates ranging from 2.25 to 450 s^{-1}, using a cone-plate (0.8°) microviscosimeter (LVT-IIc/p, Brookfield Engineering Laboratories, Inc., Middleboro, MA). Because of the well-established Newtonian behavior of the plasma, and due to its low viscosity value, plasma viscosity was measured only at 450 s^{-1} in order to obtain the highest accuracy. Relative viscosity of blood was calculated for each shear rate as the quotient between the apparent viscosities of whole blood and plasma.

The hematological and hemorheological data were also determined 1 wk after the end of the expedition when the subjects had returned from the Himalayas, 1 mo after achieving their maximal altitude (about 8,500 m). The climbers stay in high altitude conditions for a total of 3 mo.

Statistical analysis included paired t-test and one-way ANOVA for the treatment of hematological and hemorheological data, and for the cardiorespiratory variables. Wilcoxon matched-pairs signed ranks test was used for the statistical analysis of the maximal cardiorespiratory values. All statistical tests were considered statistically significant at the level $p < 0.05$. All statistics were performed by the SPSS/PC (SPSS, Chicago, IL) and SigmaStat (Jandel, Eckrath, Germany)

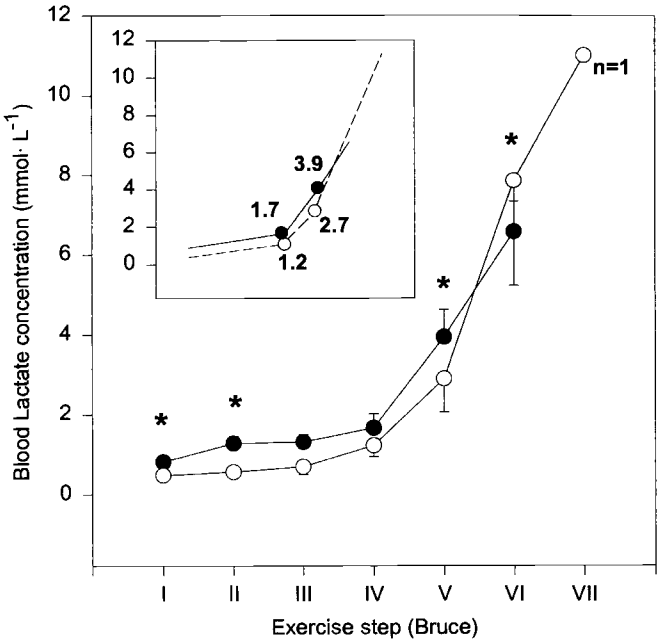

Fig. 1. Blood lactate concentration during the maximal incremental test at sea level, before (filled circles) and after (hollow circles) the acclimation period in the hypobaric chamber. Inset panel shows a double logarithmic linear fitting of blood lactate curves. The three segments separated by two breaking points correspond to the steady, transition and accumulation phases during exercise test. Mean values and standard errors are depicted. *Significant pre- vs. post-acclimation differences ($p < 0.05$).

software. Unless otherwise indicated, values are expressed as mean ± standard deviation.

RESULTS

Maximal Exercise Test

Following the acclimation program in the hypobaric chamber, all individual lactate-velocity curves showed differences in the lactate threshold, as indicated by a reduction in the lactate values for the same work-load (**Fig. 1**). In a similar fashion, the evolution of heart rate during the exercise test, showed significant differences at submaximal loads, but did not vary at maximal conditions (**Fig. 2**).

No significant differences ($p < 0.05$) were found in individual body mass (mean difference = −0.8%) nor any other anthropometric parameter after acclimation program.

Significant increases ($p < 0.05$) were observed in maximal pulmonary ventilation (mean difference = +8.3%) and in maximal pulmonary ventilation relative to body mass (+8.3%) in the maximal incremental test, when comparing these parameters before and after acclimation program.

Changes in maximal oxygen uptake relative to body mass (+6.2%; $p = 0.07$), in maximal oxygen pulse (+7%; $p = 0.0505$) and exercise time (+6.4%; $p = 0.07$) failed to prove statistically significant although a clear trend was observed in most subjects after the exposure to hypobaric hypoxia. Also, a non-significant decrease was observed in the heart rate for maximum loads (−1.5%). In addition to the interindividual variability in physical capacity, the Bruce protocol does not allow us to know with accuracy the work developed in each step by each subject. Consequently, we present cardiorespiratory variables vs. blood lactate concentration instead of workload. For more clarity in the representation, data were grouped according to the three segments of the lactate curve, corresponding to steady, transition and accumulation phases. After the acclimation program, significant differences ($p < 0.05$) were observed in O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$) and for CO_2 ($\dot{V}E/\dot{V}CO_2$), tidal volume ($\dot{V}T$), pulmonary ventilation ($\dot{V}E$), and respiratory frequency (fR). All these parameters were measured in relation to the lactate concentration during the maximal incremental test at sea level (**Fig. 3**). All these differences were also observed individually.

Hematological Profile

The results obtained from the venous blood samples are given in **Fig. 4**. Hematological changes were characterized by a significant increase ($p < 0.05$) in PCV (mean difference = +8.7%), RBC count (+7.8%) and hemoglobin concentration (+10.8%) after the acclimation period. As compared with initial levels, increased differences were observed in PCV (+23%, $p < 0.05$), RBC count (+12.6%, $p < 0.05$), and hemoglobin concentration (+24.3%, $p < 0.05$) after the return from the expedition. No significant differences were found in the hematimetric parameters (MCV, MCHC and MCH) either after the acclimation program or after returning from the expedition.

No significant differences were found in plasma proteins (+5,9%), plasma osmolality (+1.4%), serum iron (+2.3%) and ferritin (+3.8%) before and after the acclimation program.

Hemorheological Profile

No significant differences were found in the hemorheological profile at shear rates between 2.25 and 450 s^{-1}, although a slight increment in relative and appar-

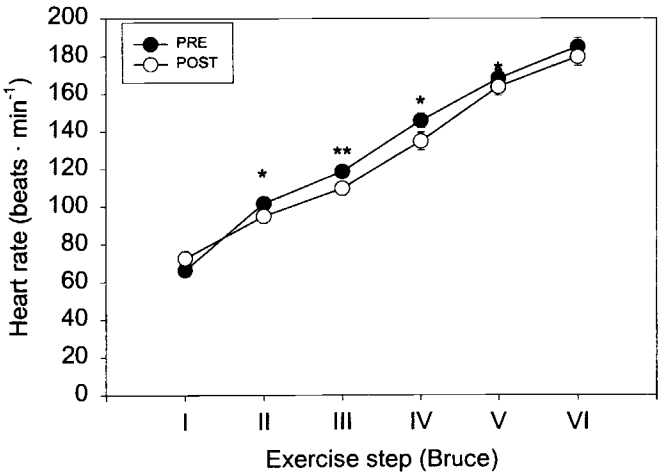

Fig. 2. Heart rate in relation to the exercise steps during the maximal incremental test at sea level, before (filled circles) and after (hollow circles) the acclimation period in the hypobaric chamber. Mean values and standard error bars are depicted. *Significant differences ($p < 0.05$).

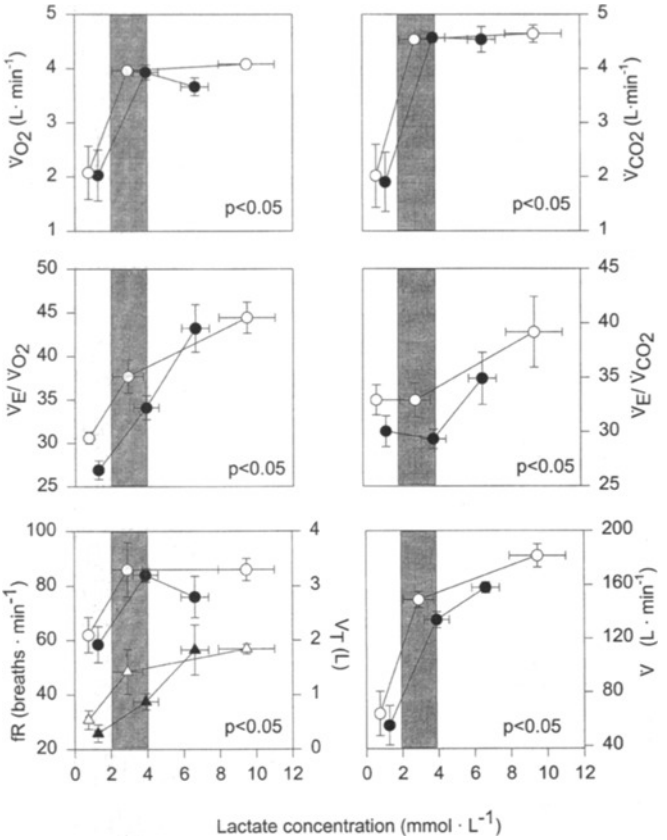

Fig. 3. Ventilatory changes in relation to the lactate concentration during the maximal incremental test at sea level, before (filled circles) and after (hollow circles) the acclimation period in the hypobaric chamber. The respiratory frequency was showed by means of triangles. The gray bar represents the transition zone of blood lactate concentration. The abbreviations are: O_2 uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$), ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$), pulmonary ventilation ($\dot{V}E$), respiratory frequency (fR), and tidal volume (VT). Mean values and standard error bars are depicted. In all points of each curve, significant differences ($p < 0.05$) were found between pre- vs. post-acclimation differences in relation to blood lactate concentration.

ent blood viscosity were observed after the acclimation period, reflecting the increased PCV. This rising trend vanished after the expedition.

DISCUSSION

Short-term intermittent exposure to hypoxia in a hypobaric chamber at a simulated altitude of 4,000 to 5,500 m induced acclimation to altitude and improved aerobic endurance in healthy subjects.

The oxygen requirements of the muscle increase during exercise but, in hypoxic conditions, the oxygen availability decreases, which reduces physical performance capacity (4,24,29). The most important adaptations to altitude (acclimation) are those concerning the oxygen transport system (i.e., the respiratory and circulatory systems, as well as the hematopoietic tissues). Neither the oxygen diffusion rate through the alveoli nor the mass circulatory transport to the tissues is hindered by altitude (24).

The acclimation program applied led to a significant rise of the erythrocytic mass, shown by a significant rise in PCV, RBC count, and hemoglobin concentration. These responses clearly indicate enhancement of the oxygen transport capacity of the blood. Changes in the blood oxygen transport capacity, as well as the erythropoietic response and the increase in the hemoglobin affinity for oxygen after hypoxia exposure, have also been reported (5,15,20,23). These adaptations continued during the expedition to high altitude, since the PCV, RBC count and hemoglobin concentration were higher after returning from the expedition than after the acclimation program. The further increments in the hematological parameters after returning from the expedition reflected the adaptative responses elicited after prolonged continuous stage at high altitude. On the other hand, a possible hemoconcentration or any other plasma volume change could be considered as negligible, as deduced from unchanged total plasma protein concentration and plasma osmolality.

As a consequence of the rise in the erythrocytic mass, an increase in blood viscosity could be expected. However, the hemorheological profile did not significantly change after the acclimation period, although a slight increasing trend was observed. In addition, the hemorheological profile observed after the expedition was almost identical to that observed before the acclimation period. Compensatory mechanisms that could eventually prevent the negative effects evoked by an increase in blood viscosity can be hypothesized. Assuming that plasma volume was unchanged, these mechanisms may be related with erythrocyte microrheological properties, such as erythrocyte deformability or RBC membrane fluidity. This phenomenon takes particular relevance when hemoglobin concentration exceeds 18 $g \cdot dL^{-1}$, since it has been described that blood viscosity increases markedly above these values (28).

In addition to hematological changes, the acclimation program in the hypobaric chamber also led to a significant increase in maximal pulmonary ventilation, similar to that found after acclimation to simulated and actual high altitude (21,22). Maximal pulmonary ventilation increased without a concomitant increase of the $\dot{V}O_{2max}$ and with a decrease of HR_{max}. A lower HR_{max} contribute to reduce maximal cardiac output and may limit maximal $\dot{V}O_{2max}$ (10). Although not statistically significant, a clear increase in maximal oxygen pulse was observed. This could be attributed mostly to the significant rise in hemoglobin concentration, but it can also be explained by the variation in stroke volume induced by the slightly enhanced contractility during exercise after altitude acclimation (1).

Although the increase in maximal exercise time also failed to prove statistically significant, a clear trend was again observed in three subjects. This increase can be explained by the improvement of the lactate threshold, which has been consistently related to the aerobic endurance capacity (16). Moreover, the reduction in the submaximal heart rate after the acclimation program, also can be interpreted as an indication of aerobic capacity improvement. Arterial blood lactate concentration during exercise increases in lowlanders when exposed to moderate altitude, while short-term adaptation includes a progressive decrease in the following days (3). The lower lactate accumulation during the

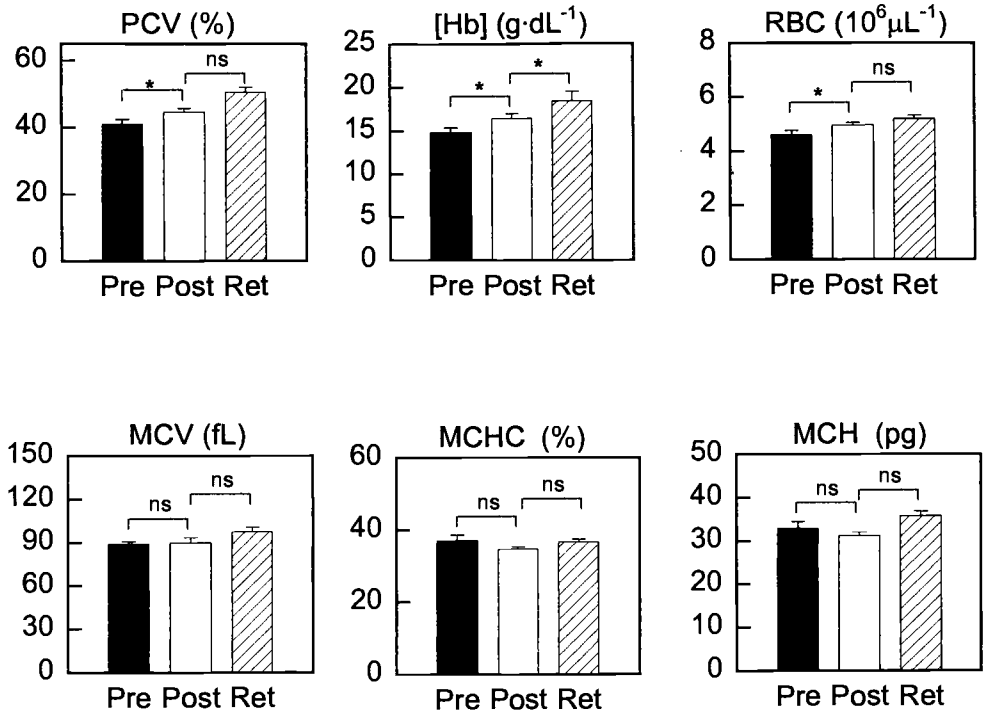

Fig. 4. Hematological changes before (filled bars) and after (hollow bars) the acclimation period in the hypobaric chamber, as well as after returning (striped bars) from the expedition to high altitude. Mean values and standard error bars are depicted. *Significant pre- vs. post-acclimation differences ($p < 0.05$) as well as post-acclimation vs. return from the expedition to high altitude.

incremental exercise test performed after acclimation program clearly reflects an enhancement of aerobic endurance capacity. In accordance with this hypothesis, we observed an increase in oxygen uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$), and for CO_2 ($\dot{V}E/\dot{V}CO_2$), tidal volume ($\dot{V}T$), pulmonary ventilation ($\dot{V}E$), and respiratory frequency (fR), in relation to the blood lactate concentration during the maximal incremental test when comparing the data before and after the acclimation program. These differences were significant in the transition zone of the blood lactate curve, thus, indicating an improvement of aerobic capacity. These findings together with unchanged $\dot{V}O_{2max}$ were coincident with results of Oelz et al. (18) and Ferretti et al. (6). These authors confirm that a higher $\dot{V}O_{2max}$ is not a critical physiological parameter for successful elite climbers. Indeed, the differences in $\dot{V}O_{2max}$ between elite climbers of varying success are not significant, although the elite sherpas have a higher aerobic-anaerobic threshold (8). In addition, Hochachka et al. (11) found a higher oxidative capacity due to the increase in the activities of oxidative enzymes after intermittent acclimation to hypoxia. These results are consistent with those of González et al. (9). A nonsignificant decrease was observed in the heart rate for maximum loads (−1.5%), which may be attributed to the improvement in oxygen transport capacity of the blood, as well as with other possible hemodynamic, hormonal and cellular adaptations (2).

None of the subjects presented symptoms of mountain sickness or physical deterioration during the exposure to simulated altitude. Thus, we consider that tolerance to intermittent hypobaric hypoxia exposure program was satisfactory.

We conclude that 17 d of intermittent exposure to moderate hypoxia in a hypobaric chamber, in combination with low intensity exercise, elicit the acclimation responses to high altitude. The exposure program also improves the aerobic capacity in healthy mountaineers, facilitating the adaptation to high altitude and becoming a suitable alternative to acclimatization "in situ". This kind of pre-acclimation program is of great interest for the preparation of high-altitude expeditions.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the collaboration of the UPC-Everest'95 climbers: Ernest Bladé, Néstor Bohigas, Albert Castellet, Manuel de la Matta, Xavier González, and Araceli Segarra. We also acknowledge J.M.Valentín for her valuable technical assistance as well as the Serveis Científico-Tècnics of University of Barcelona. We thank Mr. Robin Rycroft (Language Advice Service, Universitat de Barcelona) for his valuable help in the final correction of the manuscript. This study was partially supported by DGICYT grant PB96-0999.

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