

Individual variation in response to altitude training

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Chapman, Robert F., James Stray-Gundersen, and Benjamin D. Levine. Individual variation in response to altitude training. *J. Appl. Physiol.* 85(4): 1448–1456, 1998.—Moderate-altitude living (2,500 m), combined with low-altitude training (1,250 m) (i.e., live high-train low), results in a significantly greater improvement in maximal O₂ uptake ($\dot{V}O_{2\max}$) and performance over equivalent sea-level training. Although the mean improvement in group response with this “high-low” training model is clear, the individual response displays a wide variability. To determine the factors that contribute to this variability, 39 collegiate runners (27 men, 12 women) were retrospectively divided into responders ($n = 17$) and nonresponders ($n = 15$) to altitude training on the basis of the change in sea-level 5,000-m run time determined before and after 28 days of living at moderate altitude and training at either low or moderate altitude. In addition, 22 elite runners were examined prospectively to confirm the significance of these factors in a separate population. In the retrospective analysis, responders displayed a significantly larger increase in erythropoietin (Epo) concentration after 30 h at altitude compared with nonresponders. After 14 days at altitude, Epo was still elevated in responders but was not significantly different from sea-level values in nonresponders. The Epo response led to a significant increase in total red cell volume and $\dot{V}O_{2\max}$ in responders; in contrast, nonresponders did not show a difference in total red cell volume or $\dot{V}O_{2\max}$ after altitude training. Nonresponders demonstrated a significant slowing of interval-training velocity at altitude and thus achieved a smaller O₂ consumption during those intervals, compared with responders. The acute increases in Epo and $\dot{V}O_{2\max}$ were significantly higher in the prospective cohort of responders, compared with nonresponders, to altitude training. In conclusion, after a 28-day altitude training camp, a significant improvement in 5,000-m run performance is, in part, dependent on 1) living at a high enough altitude to achieve a large acute increase in Epo, sufficient to increase the total red cell volume and $\dot{V}O_{2\max}$, and 2) training at a low enough altitude to maintain interval training velocity and O₂ flux near sea-level values.

athletes; hypoxia; erythropoietin; exercise

ALTITUDE TRAINING is frequently used by competitive endurance athletes in an attempt to improve sea-level athletic performance (7). Despite several controlled studies demonstrating no group improvement in sea-level performance after living and training at altitude (2, 13), numerous anecdotal accounts exist describing a wide variance in performance after a traditional altitude training camp. Previously, we have demonstrated that a portion of the variability in sea-level performance after altitude training can be accounted for by a high prevalence of iron deficiency among trained athletes (22). However, subsequently, even when high-dose iron supplementation was initiated 6 wk before exposure to moderate-altitude living and low-altitude training (live high-train low), the individual variation in

improvements in 5,000-m run time remained substantial despite a mean improvement in group performance (14.1 ± 36.0 s, range 112 s slower to 55 s faster) (13, 23). Although a portion of this variability may be due to nonphysiological factors influencing exercise performance, maximal O₂ uptake ($\dot{V}O_{2\max}$), a physiological marker that is a strong correlate of endurance exercise performance, also showed an overall mean improvement ($2.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) with a similarly wide variability after altitude exposure (range -3.2 to $+8.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$).

In an effort to explain the substantial interindividual variability in the adaptive response to an altitude training camp, we retrospectively examined data from 39 athletes who lived at an altitude of 2,500 m and trained between altitudes of 1,200 and 3,000 m for 4 wk during the summers of 1994, 1995, and 1996. This examination attempted to determine which characteristics of acclimatization or training were different between athletes who responded to altitude training with a significant improvement in performance vs. athletes who were “nonresponders” to altitude training. Specifically, we hypothesized that the difference between responders and nonresponders to altitude training would be manifested through 1) an altitude-acclimatization pathway, dependent on the hematologic adaptation to altitude exposure, and 2) a training-response pathway, dependent on the maintenance of interval-training velocity and O₂ flux at altitude comparable to sea-level training values. A portion of these factors were then examined in a separate cohort of 22 elite athletes in a prospective fashion to confirm the relationships established in the retrospective analysis.

METHODS

Retrospective Analysis

Subjects. Thirty-nine distance runners (27 men, 12 women, age 21.6 ± 2.9 yr) were recruited from collegiate track and cross-country teams, local running clubs, and USA Track and Field development teams. All athletes were required to be competitive at a distance between 1,500 m and the marathon and to have a recent personal best 5,000-m time (or equivalent) of $<16 \text{ min } 30 \text{ s}$ for men and $<18 \text{ min } 30 \text{ s}$ for women. All were sea-level residents and could not have been to an altitude above 1,500 m for a period exceeding 1 wk in the previous 10 mo. All subjects gave their written informed consent to a protocol approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

Study design. An outline of the study design, including a detailed description of the project phases, methods used, and measurements completed, has been published elsewhere (13). A graphic depiction of the basic study time line is shown in Fig. 1. Briefly, all athletes completed 6 wk of supervised sea-level training, during which time familiarization with laboratory testing procedures and iron maintenance or re-

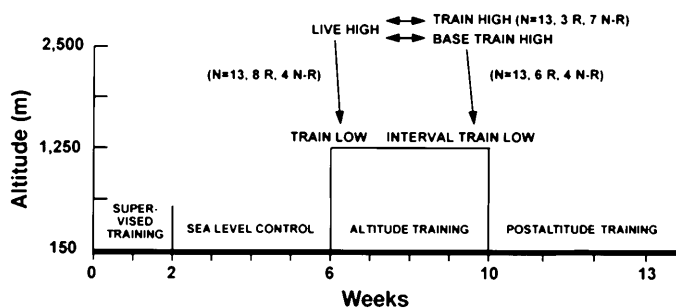


Fig. 1. Retrospective study consisted of 1) 2-wk sea-level "lead-in" phase designed to overcome effect of supervised training and initiate iron supplementation; 2) 4-wk sea-level control training camp to serve as a longitudinal control; 3) 4-wk altitude training camp with all groups living high (2,500 m; Live High) and performing either all training high (2,500–3,000 m; Train High), all training low (1,200–1,400 m; Train Low), or low-intensity "base" training high (2,500–3,000 m; Base Train High) and high-intensity "interval" training low (1,200–1,400 m; Interval Train Low); and 4) postaltitude training phase. Laboratory testing was completed at sea-level pre- and postaltitude, with field measures collected at altitude at 30-h and 14-day time points. *n*, No. of subjects; R, responders; N-R, non-responders. [Adapted from Levine and Stray-Gundersen (13).]

placement therapy were initiated for all subjects (22). At the conclusion of the 6-wk sea-level control period, laboratory and performance testing were completed, and all athletes were transported by van to Deer Valley, UT (2,500 m). All athletes lived at this altitude for a period of 28 days. Training followed three separate paradigms: 1) all training at a moderate altitude (2,500–3,000 m), designated "high-high" ($n = 13$; 9 men, 4 women); 2) all training at a low altitude (1,200–1,400 m), designated "high-low" ($n = 13$; 9 men, 4 women); or 3) low-intensity "base" training at moderate altitude, with high-intensity "interval" training at low altitude, designated "high-high-low" ($n = 13$; 9 men, 4 women). Moderate-altitude training took place on trails and roads in the Wasatch and Uinta mountain ranges. Low-altitude training occurred nearby (~30-min drive) in Salt Lake City, UT. The training program during the altitude training camp was designed to match the training program completed at sea level. Training was conducted according to an individualized template based on a 4-wk mesocycle, intended to provide increasing volume and intensity during the first 3 wk, with a slight taper in week 4 before laboratory and performance testing. When the subjects returned to sea level after the altitude training camp, plasma and blood volume were measured on the second day, a 5,000-m time trial was completed on the third day, and an incremental test of $\dot{V}O_{2\max}$ was measured on the fourth day after return from altitude.

Evaluation of performance. The primary outcome measure of this study was running performance, measured both on a track and in the laboratory on a treadmill.

TRACK EVALUATION. 5,000-m Time trial. Multiple 5,000-m time trials at select time points were conducted on a 400-m track. All time trials were performed at sea level in Dallas, TX, between 0700 and 0800, with temperature 22–26°C, humidity 80–100%, and wind velocity 0–10 km/h. To avoid the influence of racing strategies, all starts were staggered by at least 2 min.

TREADMILL EVALUATION. $\dot{V}O_{2\max}$. The primary treadmill evaluation measure was an incremental exercise test that used a modified Astrand-Saltin protocol (20). After a brief warm-up, subjects ran at 9.0 miles/h (mph) for men and 8.0 mph for women at 0% grade for 2 min. The grade was then increased 2% every 2 min until exhaustion, which usually occurred after 6–8 min. O_2 uptake ($\dot{V}O_2$) was measured by

using the Douglas bag method; gas fractions were analyzed by mass spectrometer (Marquette MGA 1100), and ventilatory volume was measured with either a Tissot spirometer or dry-gas meter (Collins). $\dot{V}O_{2\max}$ was defined as the highest $\dot{V}O_2$ measured from at least a 40-s Douglas bag. In nearly all cases, a plateau in $\dot{V}O_2$ was observed with increasing work rate, confirming the identification of $\dot{V}O_{2\max}$. Additionally, to verify that $\dot{V}O_{2\max}$ was achieved, on a separate day a supra-maximal treadmill run was performed with the measurement of $\dot{V}O_2$. The highest value obtained on either test was considered to be $\dot{V}O_{2\max}$.

Maximal steady state (MSS). MSS was estimated from the ventilatory threshold according to standard criteria and methods (3) as follows. By using breath-by-breath data from the incremental test of $\dot{V}O_{2\max}$, the $\dot{V}O_2$ at ventilatory threshold for all tests was determined by a single, blinded, experienced observer during simultaneous examination of multiple plots of $\dot{V}O_2$ vs. ventilation (\dot{V}_E), $\dot{V}O_2$ vs. $\dot{V}_E/\dot{V}O_2$, $\dot{V}O_2$ vs. $\dot{V}CO_2$ production ($\dot{V}CO_2$), and $\dot{V}O_2$ vs. $\dot{V}_E/\dot{V}CO_2$ by using either commercial (First Breath, Marquette) or proprietary software.

OTHER LABORATORY MEASURES. Blood compartments. Plasma volume, blood volume, and volume of red cell mass, or the total red cell volume, were measured at each testing time point at sea level. Plasma volume was measured by using the Evans blue dye indicator-dilution technique (17). Briefly, after the subjects rested quietly for least 30 min in the supine position, a known quantity of Evans blue dye was injected through a catheter placed in a peripheral vein, and venous blood was drawn at 10, 20, and 30 min after injection for the measurement of absorbance at 620 and 740 nm via spectrophotometry (model DU 600, Beckman). Hematocrit was measured by microcapillary centrifugation, and blood volume was estimated by dividing plasma volume by 1 minus hematocrit, by using appropriate corrections for trapped plasma and peripheral sampling (17). Total red cell volume was defined as blood volume minus plasma volume.

Erythropoietin (Epo) and hemoglobin concentration. Plasma Epo concentration and hemoglobin concentration were measured at sea level, before the altitude training camp, after 30 h and 14 days of exposure to 2,500 m, and on return to sea level. All blood samples were obtained between 0600 and 0700 while the subjects were in a fasted, resting state. Epo concentration was determined by an ^{125}I radioimmunoassay, by using a commercially available kit (model DSL-1100, Diagnostic Systems Laboratories) and a Cobra auto-gamma counter. Hemoglobin concentration was determined by using an Instrumentation Laboratories CO-oximeter.

Pulmonary diffusing capacity for CO (DL_{CO}). A CO-rebreathing method (19) was used to measure DL_{CO} during rest and steady-state exercise (16.1 km/h, 0% grade). Measures completed during exercise were calculated in absolute terms as well as normalized to $\dot{V}O_{2\max}$.

Arterial oxygen saturation (Sa_{O_2}) during exercise at simulated altitude. A submaximal, steady-state treadmill exercise bout was performed pre- and postaltitude in a hypobaric chamber, at a simulated altitude of 2,700 m. Sa_{O_2} was estimated by using pulse oximetry (Ohmeda 3700), with values accepted only when the pulse was within 2 beats/min of electrocardiogram recordings of heart rate.

Sa_{O_2} during sleep at sea level and altitude. Pulse oximetry was used to determine Sa_{O_2} during sleep (measured between 0200 and 0300), both prealtitude and after 30 h at altitude.

Evaluation of Training.

TRAINING LOGS. Each runner kept a detailed training log book that included duration and intensity of each workout, along with resting and training heart rate (Polar). Logs also

included description of well-being, fluid intake, body weight, and quantity and quality of sleep, and the logs were reviewed weekly by investigators and staff. Diet was also monitored to ensure adequate nutrition.

TRAINING STIMULUS. To derive an index that would allow us to quantify the training stimulus and compare training among the groups, we used the method of Banister and Wenger (4) for the calculation of training impulse (TRIMPS). This method multiplies the duration of a training session by the average heart rate achieved during that session, weighted for exercise intensity. Total training time and an estimate of training distance were calculated from the information in the training logs.

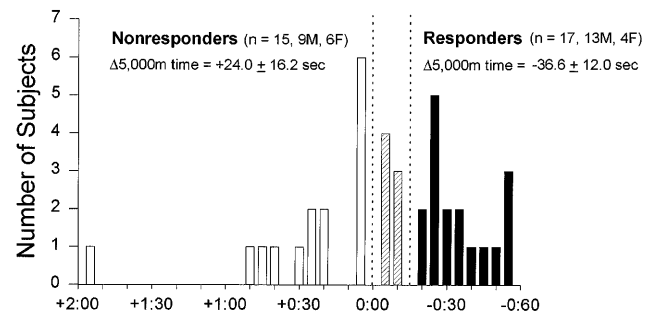
TRAINING CHARACTERIZATION. To precisely quantify the metabolic requirements of a typical training session, running velocity and $\dot{V}O_2$ were measured during typical base and interval training under all training conditions: sea level (Dallas, TX; 150 m) and low (Salt Lake City, UT; 1,250 m) or moderate altitude (Deer Valley and/or Bonanza Flats, UT; 2,700 m). After 2 wk of acclimatization, $\dot{V}O_2$ in the field was measured with a small telemetry device (K2, Cosmed) that combines a turbine flowmeter built into a face mask to measure ventilation with a polarographic electrode to measure expired oxygen fraction. This device assumes a respiratory exchange ratio of 1.0, which may underestimate $\dot{V}O_2$ at very high work rates (14). Testing sessions were conducted on measured trails, allowing the calculation of mean running velocity. The standard interval training session was composed of four to six repetitions of 1,000-m runs.

Prospective Analysis

A prospective analysis of data collected in the summer of 1997 was completed to confirm our stated hypotheses and any relationships established through the retrospective analysis. The prospective analysis examined responses of 22 elite distance runners (14 men, 8 women, age 24.8 ± 2.5 yr) who completed 4 wk of altitude training after the high-high-low model, in the same Deer Valley and Salt Lake City, UT, setting. In this prospective group, the measures completed were 1) Epo and hemoglobin concentrations at four time points (2 days prealtitude, 18 h at altitude, 20 days at altitude, and 18 h after return to sea level), 2) $\dot{V}O_{2\max}$ (2–4 days prealtitude and 4–48 h postaltitude), and 3) 3,000-m time trial performance (1 day prealtitude and 3 days postaltitude).

Statistics

To examine the individual variability in response to 4 wk of altitude exposure and training, athletes were divided into groups classified as responders and nonresponders to altitude training. For the retrospective analysis, this grouping (Fig. 2) was based on the change in sea level 5,000-m time before and after the altitude training camp as follows: nonresponders, ≤ 0 -s improvement in 5,000-m time ($n = 15$, 9 men, 6 women; 7 high-high, 4 high-high-low, 4 high-low), responders, ≥ 14.1 -s improvement in 5,000-m time ($n = 17$, 13 men, 4 women; 3 high-high, 6 high-high-low, 8 high-low). An improvement of >14.1 s for the responder classification was chosen on the basis of the mean improvement in the high-low group and high-high-low group athletes (14.1 ± 36.0 s). Because these two altitude training strategies (high-low and high-high-low) have been clearly demonstrated to produce significant performance improvements (13, 23), it was rationalized that an improvement greater than the mean observed in those two groups would be indicative of a strong responder to altitude training. The seven subjects (3 high-high, 3 high-high-low, 1 high-low) with a 5,000-m time improvement between 0 and



Change in Sea-Level 5,000m Time After Altitude Training (min:sec)

Fig. 2. Histogram displaying variation in change (Δ) in 5,000-m run time after 4 wk of altitude training in 39 athletes. Athletes were retrospectively divided into groups of responders (filled bars), nonresponders (open bars), and indeterminate (hatched bars) on basis of change in 5,000-m performance (see METHODS). *n*, No. of subjects; M, men; F, women; +, increase in time; -, decrease in time; dotted lines, cutoff for group definitions.

14.1 s were excluded from the analysis, to establish distinct group differences. For the prospective analysis, responders and nonresponders were classified in a similar fashion to the retrospective analysis, on the basis of individual improvement in 3,000-m time trial performance after altitude training [i.e., ≤ 0 -s improvement = nonresponder; \geq the mean improvement (5.8 s) = responder].

Because it not known whether certain physiological variables, such as Epo concentration, blood volume, and total red cell volume, have a Gaussian distribution, these variables were first analyzed by using the D'Agostino *D* statistic for normality testing. No significant departures from normality were found. However, to be statistically conservative, we tested the above dependent variables by using both nonparametric (Wilcoxon matched pairs and Kruskal-Wallis) and parametric (Student's *t*) tests. Data for the above variables are presented in Table 2 both nonparametrically as medians with the full range of observed values and parametrically as means \pm SD. All other dependent measures were analyzed by using Student's *t*-tests. For all comparisons, the α for statistical significance was set at $P \leq 0.05$.

RESULTS

Retrospective Analysis

Subject characteristics for the group of responders and nonresponders examined in the retrospective analysis are shown in Table 1. Despite the post hoc group classifications, no prealtitude differences were observed in anthropometric, hematologic, treadmill, or running performance measures between groups.

Measures of Acclimatization

Epo concentration, blood volume, and total red cell volume are presented in Table 2. There were no divergent statistical results on the basis of whether parametric or nonparametric tests were used. Epo concentration increased significantly in both groups after 30 h at 2,500 m. However, the responders had a significantly larger increase in mean Epo concentration compared with the nonresponders, both in absolute terms (6.5 ± 3.3 vs. 4.7 ± 3.0 mU/ml; $P \leq 0.05$) and when expressed as a percentage of sea-level baseline (152.0 ± 5.7 vs. $134.3 \pm 10.3\%$; $P \leq 0.05$; Fig. 3). After 14 days at

Table 1. Subject characteristics: retrospective cohort

	Nonresponders (n=15)	Responders (n=17)
Gender	9 M, 6 F	13 M, 4 F
Age, yr	21.7 ± 3.0	21.4 ± 3.0
Weight, kg	61.7 ± 6.2	63.3 ± 6.2
Height, cm	171.3 ± 7.0	174.8 ± 8.1
VO _{2max} , ml·min ⁻¹ ·kg ⁻¹	64.1 ± 4.7	65.0 ± 5.8
Hb, g/dl	13.7 ± 0.8	13.7 ± 0.8
Training classification	4 High-low 4 High-high-low 7 High-high	8 High-low 6 High-high-low 3 High-high

Values are means ± SD; n, no. of subjects. M, men; F, women; VO_{2max}, maximal O₂ uptake; Hb, hemoglobin concentration; high-low, living at high altitude (2,500m) and all training at low altitude (1,200–1,400 m); high-high-low, living at high altitude (2,500 m) and low-intensity “base” training at high altitude (2,500–3,000 m) and high-intensity “interval” training at low altitude (1,200–1,400 m); high-high, living (2,500 m) and all training at high altitude (2,500–3,000 m).

altitude, responders still had a significantly higher mean Epo concentration than at prealtitude; however, there was no significant difference between the mean Epo concentration prealtitude and after 14 days in the nonresponders. Both groups demonstrated a significant increase in hemoglobin concentration and hematocrit from before to after the altitude training camp. A significant 8% increase in the total red cell volume was observed in the responders, with no change in the nonresponders after 4 wk at altitude (Fig. 4A). Mean blood volume was significantly lower in the nonresponders after 4 wk at altitude, but it was not different in the responders. VO_{2max} was significantly increased by 7% in the responders postaltitude, with no change in

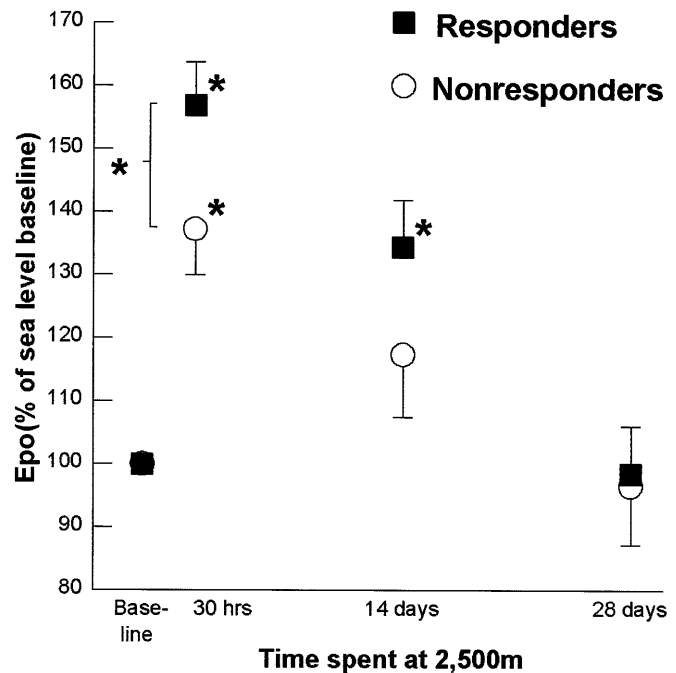


Fig. 3. Erythropoietin (Epo) concentration measures at 4 time points in retrospective group of responders and nonresponders to altitude training. Baseline and 28-day blood samples were drawn at sea level; 30-h and 14-day blood samples were drawn at 2,500 m. Values are means ± SE. Statistical comparisons are within groups vs. baseline time point, unless indicated by open bracket. * P ≤ 0.05.

the nonresponders (Table 3). Between groups, VO_{2max} was also significantly higher postaltitude in the responders vs. the nonresponders (69.2 ± 6.8 vs. 64.4 ± 4.7 ml·min⁻¹·kg⁻¹; P ≤ 0.05) despite no prealtitude difference. The postaltitude measure of MSS VO₂ was also

Table 2. Hematologic responses to altitude: retrospective cohort

	Pre-Alt	Alt-30 h	Alt-14 days	Post-Alt
<i>Nonresponders</i>				
Epo, mU/ml	13.7 ± 5.9 (13.1, 6.3–20.9)	18.4 ± 7.3* (17.7, 8.0–37.5*)	15.4 ± 6.6 (13.1, 8.3–33.3)	13.3 ± 5.0 (12.5, 6.3–26.3)
Epo, % of SL baseline		137.2 ± 29.3* (129.8, 91.4–208.2*)	117.3 ± 27.2 (111.7, 73.1–175.4)	102.4 ± 32.7 (96.5, 54.3–183.8)
Total red cell volume, ml/kg	28.9 ± 4.8 (26.4, 22.3–35.8)			29.1 ± 5.0 (28.7, 20.9–36.4)
Blood volume, ml/kg	83.9 ± 12.9 (83.6, 59.4–100.5)			77.2 ± 10.6* (76.5, 58.9–95.6*)
Hemoglobin, g/dl	13.7 ± 0.8			15.0 ± 0.9*
Hematocrit, %	39.4 ± 2.7			42.5 ± 3.2*
<i>Responders</i>				
Epo, mU/ml	12.5 ± 4.0 (12.1, 7.6–23.7)	19.0 ± 4.6* (17.7, 12.7–28.6*)	16.2 ± 4.2* (14.9, 11.5–28.6*)	12.3 ± 5.8 (12.1, 5.5–20.3)
Epo, % of SL baseline		156.9 ± 28.7*† (158.7, 102.3–210.2*†)	134.3 ± 30.9* (134.1, 88.0–206.2*)	100.6 ± 15.5 (99.4, 64.0–122.2)
Total red cell volume, ml/kg	29.2 ± 4.0 (29.2, 22.3–38.7)			31.5 ± 4.1* (30.7, 25.1–40.5*)
Blood volume, ml/kg	83.5 ± 12.2 (84.0, 53.5–99.8)			83.7 ± 8.5 (82.6, 68.3–99.1)
Hemoglobin, g/dl	13.7 ± 0.8			14.8 ± 0.8*
Hematocrit, %	39.1 ± 2.7			41.4 ± 2.0*

Values are means ± SD with median response with the range of observed values in parentheses. SL, sea level; Alt, altitude; Pre-Alt, prealtitude; Post-Alt, postaltitude; Epo, plasma erythropoietin concentration. *Significant difference from Pre-Alt, P ≤ 0.05. †Significant difference from nonresponders, P ≤ 0.05.

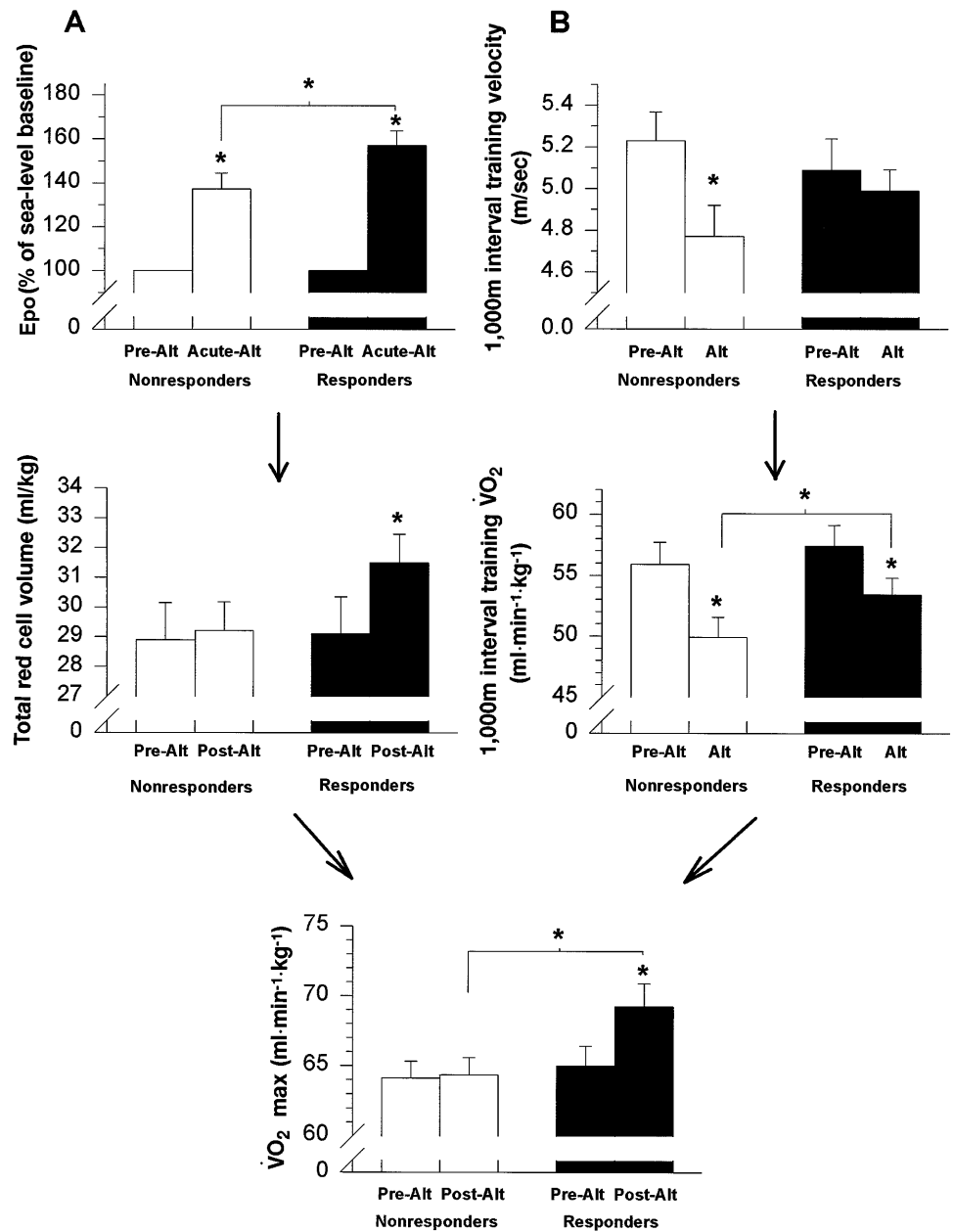


Fig. 4. A: acclimatization responses of responders and nonresponders to altitude (Alt), depicting change in Epo concentration from sea level to 30 h at 2,500 m (Acute-Alt; expressed as percentage of sea-level baseline), change in total red cell volume from pre- (Pre-Alt) to postaltitude (Post-Alt), and change in maximal O₂ uptake (V̇O_{2max}) from pre- to postaltitude. B: training responses of responders and nonresponders to altitude, depicting 1,000-m interval training velocity and O₂ uptake (V̇O₂) measures at sea level and after 14 days at altitude. Statistical comparisons are within groups vs. pre-altitude time point, unless indicated by open brackets. Values are means ± SE. *P ≤ 0.05.

significantly higher in the responders vs. the nonresponders (59.0 ± 9.1 vs. 52.4 ± 4.9 ml·min⁻¹·kg⁻¹; P ≤ 0.05), despite no prealtitude difference. However, the MSS occurred at the same percentage of V̇O_{2max} be-

tween groups both pre- and postaltitude, suggesting that this difference was primarily due to an increase in V̇O_{2max} and was not due to a fundamental shift in the factors that regulate the ventilatory threshold. Gender

Table 3. Performance, treadmill, and training responses to altitude: retrospective cohort

	Nonresponders			Responders		
	Pre-Alt	Alt-14 days	Post-Alt	Pre-Alt	Alt-14 days	Post-Alt
5,000-m time, min:s	17:24 ± :91		17:38 ± :98*	17:11 ± :76		16:34 ± :75*†
V̇O _{2max} , ml·min ⁻¹ ·kg ⁻¹	64.1 ± 4.4		64.4 ± 4.7	65.0 ± 5.8		69.2 ± 6.8*†
MSS V̇O ₂ , ml·min ⁻¹ ·kg ⁻¹	50.2 ± 8.5		52.4 ± 4.9	54.2 ± 5.3		59.0 ± 9.1*†
MSS V̇O ₂ , %V̇O _{2max}	81.8 ± 3.1		81.9 ± 2.5	84.1 ± 3.6		82.4 ± 6.9
Interval-training velocity, m/s	5.2 ± 0.5	4.8 ± 0.6*		5.1 ± 0.6	5.0 ± 0.4	
Interval V̇O ₂ , ml·min ⁻¹ ·kg ⁻¹	55.9 ± 7.0	44.9 ± 6.1*		57.4 ± 6.7	54.0 ± 5.8*†	

Values are means ± SD. V̇O₂, O₂ consumption; MSS, maximal steady state. *Significant difference from Pre-Alt, P ≤ 0.05; †Significant difference from nonresponders, P ≤ 0.05.

differences within groups were present in variables that classically differ between male and female athletes, such as $\dot{V}O_{2\max}$, hemoglobin, hematocrit, and total red cell volume. However, no difference between genders in the response of these variables to altitude or training was found in either the group of responders or nonresponders.

Training Response Measures

No significant difference was found between groups for either TRIMPS, training duration, or estimated total mileage, during the sea-level training phase or the altitude training camp (Fig. 5). Interval training velocity at altitude significantly declined by almost 9% within the group of nonresponders but was not significantly different within responders (Fig. 4B). At altitude, nonresponders ran their intervals at a significantly slower pace than did responders, despite maintaining similar training velocities between groups at sea level. Both groups demonstrated a significant reduction in interval $\dot{V}O_2$ at altitude, as measured by the K2 device. However, the responders were able to

maintain a significantly higher $\dot{V}O_2$ during altitude interval training compared with nonresponders, despite no difference between groups in sea-level interval $\dot{V}O_2$ measures. As with measures of acclimatization, no gender difference within groups of responders and nonresponders was found in any training response measure.

Additional Measures

Fourteen of the 17 responders and 11 of the 15 nonresponders completed a steady-state run at a simulated altitude of 2,700 m, both before and after the altitude training camp. No difference was found between groups in pulse oximetry measures of Sa_{O_2} , either before (responders $80.3 \pm 3.5\%$, nonresponders $80.4 \pm 3.8\%$) or after the altitude training camp (responders $84.7 \pm 4.7\%$, nonresponders $83.5 \pm 3.7\%$). The increase in Sa_{O_2} from before to after the altitude training camp was significant in both groups, demonstrating a similar degree of ventilatory acclimatization in both responders and nonresponders. Measures of sleeping Sa_{O_2} (both at sea level and altitude) and measures of DL_{CO} completed at rest and during exercise (expressed both in absolute terms and normalized to $\dot{V}O_{2\max}$) were not significantly different between responders and nonresponders.

Prospective Analysis

After 4 wk of high-high-low altitude training, 22 elite distance runners demonstrated a significant improvement in 3,000-m run time of 5.8 ± 9.2 s ($P \leq 0.05$). With use of the same criteria to assign responder and nonresponder classifications as done in the retrospective analysis [i.e., responders > the group mean improvement (5.8 s) in 3,000-m time; nonresponders ≤ 0 -s improvement in 3,000-m time], nine subjects (5 men, 4 women) were assigned to the responder group while five subjects (all men) were classified as nonresponders. In this prospective analysis, mean Epo concentration significantly increased in the responders from prealtitude to 18 h at 2,500 m (8.8 ± 2.6 vs. 18.3 ± 5.8 mU/ml; $P \leq 0.05$), whereas the nonresponders did not demonstrate a significant difference (10.1 ± 2.7 vs. 14.9 ± 3.9 mU/ml; $P = 0.11$). $\dot{V}O_{2\max}$ was significantly increased in the responders after altitude training [change in $\dot{V}O_{2\max}$ ($\Delta\dot{V}O_{2\max}$) 3.4 ± 2.1 ml \cdot min $^{-1}$ \cdot kg $^{-1}$; $P \leq 0.05$] but was not different in the nonresponder group ($\Delta\dot{V}O_{2\max}$ 0.1 ± 2.1 ml \cdot min $^{-1}$ \cdot kg $^{-1}$).

DISCUSSION

The principal new observations from the present study are that the individual variability in the response to altitude training may be accounted for by two mechanistic pathways: an altitude-acclimatization effect, i.e., an increase in O_2 -carrying capacity and $\dot{V}O_{2\max}$, and a training effect, i.e., maintenance of training velocity and O_2 flux near sea-level values, facilitating improvements in $\dot{V}O_{2\max}$ and race performance. These findings extend our previous observations in endurance

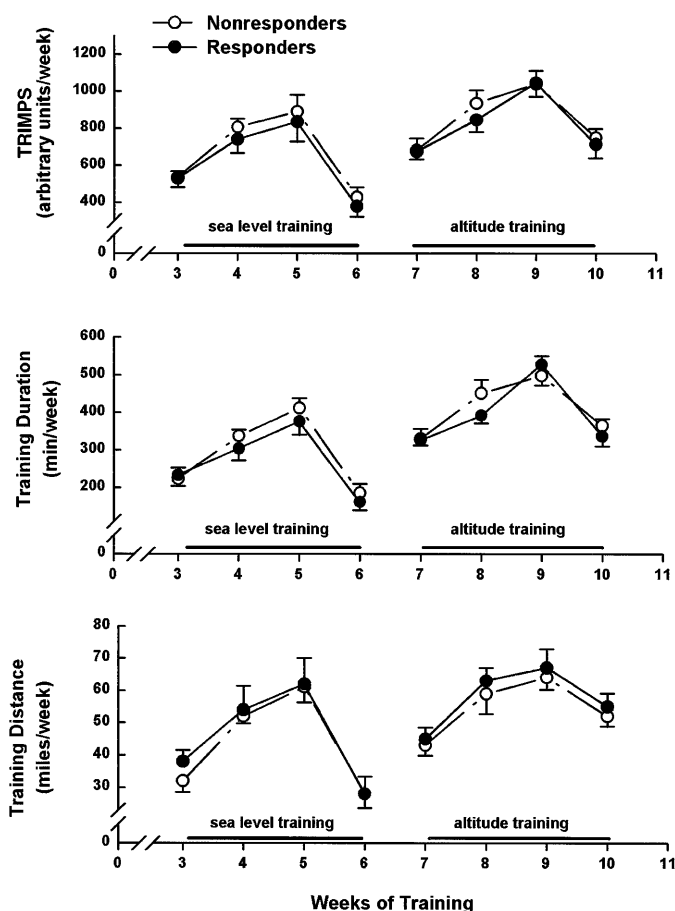


Fig. 5. Quantification of training during 4-wk mesocycles of sea-level and altitude training in responders and nonresponders. *Top*: training impulse (TRIMPS) per week, calculated as described in METHODS on basis of a weighted score incorporating training duration and training heart rate. *Middle*: training duration obtained from training logs. *Bottom*: estimated training distance per week, obtained by multiplying training duration by appropriate speed calculated for a given training session. Values are means \pm SE.

athletes, regarding appropriate altitude training strategies (13, 23).

High-Altitude Acclimatization Pathway

Acclimatization to high altitude includes a number of physiological and hematologic adaptations that theoretically should improve O₂ transport to skeletal muscle during exercise (12). Performance enhancement in the group of responders was, in part, due to a series of robust acclimatization responses to high altitude: a greater acute and sustained increase in Epo → increase in total red cell volume → increase in $\dot{V}O_{2\max}$ → significant improvement in 5,000-m run time (Fig. 4A). Why the responder group demonstrated a more augmented Epo response at 2,500 m is not readily clear and is likely dependent on several factors. At a moderate altitude (2,315 m) similar to the one used in this study, Gunga et al. (10) found a wide variation in Epo response after 48 h. In their study of 29 mountaineers, they reported median increase in Epo was 10.1 mU/ml, with increases at the 25th and 75th percentiles of 5.8 and 16.3 mU/ml, respectively. For comparison, after 30 h at 2,500 m, the 39 endurance athletes in the retrospective analysis had a median increase in Epo of 5.9 mU/ml, with increases at the 25th and 75th percentiles of 4.1 and 8.2 mU/ml. Although the Epo concentration after acute exposure to altitude within subjects is likely proportional to the severity of the hypoxic stress (8, 16), the present data also confirm a wide variability of Epo response to a fixed altitude among subjects. These individual differences in the magnitude of Epo response at a common altitude could be influenced by several factors such as individual differences in hypoxic ventilatory drive, O₂ half-saturation pressure of hemoglobin, or sensitivity to hypoxia at the point of Epo release, and many of these factors may be genetically inherited traits (21).

Several studies that have examined the time course of Epo response to moderate altitude note a maximal Epo increase at 2 days postascent (1, 16). It could be argued that our acute altitude measure of Epo concentration (30 h after arrival) occurred before this hormone reached a peak level in the blood. If, for example, the Epo concentration of nonresponders did not peak until a much later time than did that of the responders, the timing of this measure could possibly account for the significant difference between groups. We do not believe this is the case because after 14 days at 2,500 m, Epo concentrations were still significantly elevated over sea-level values in the responders but had returned to near sea-level values in the nonresponders (Fig. 3). Moreover, Epo was measured at the same time points in both groups. This observation, combined with the subsequent differences between responders and nonresponders in total red cell volume and $\dot{V}O_{2\max}$, leads us to believe that the differences in Epo concentration are true physiological differences and are not dependent on sampling time points or individual differences in the achievement of a peak Epo response.

A key observation emphasizing the importance not only of Epo production but also of erythropoiesis as the

primary mechanism for this altitude-related effect is the finding that nonresponders, despite a significant acute increase in Epo concentration after 30 h at 2,500 m, did not display an increase in the total red cell volume. Previously, we have demonstrated that athletes with low serum ferritin levels do not increase total red cell volume after 4 wk at altitude, despite an acute increase in Epo (22, 24). However, all athletes in this investigation received vigorous oral iron supplementation (as high as 400 mg of elemental iron/day in some athletes) during the 6 wk before altitude exposure, and there was no difference in prealtitude serum ferritin measures between groups (nonresponders 29.1 ± 15.5 mU/ml, responders 33.3 ± 18.6 mU/ml). Therefore, we conclude that the difference in total red cell volume in this study is not summarily explained by frank iron deficiency. Additionally, it is interesting to note that nonresponders had a classic normalization of Epo concentration back to sea-level values after 4 wk at 2,500 m, despite failing to augment O₂-carrying capacity through an increased total red cell volume. Ultimately, whether the difference in the increase in total red cell volume between groups is due to a contrasting individual amount of Epo release to a given hypoxic stimulus or due to the same proportional Epo release to different hypoxic stimuli is difficult to determine. Responders could have had greater diffusion limitations during rest, greater ventilation-perfusion mismatch, or a blunted hypoxic drive. However, we did not observe any group differences in the decrease in SaO₂ either during sleep or exercise at altitude nor differences in DL_{CO} or magnitude of ventilatory acclimatization between groups.

Another possible difference between responders and nonresponders is the sensitivity of the bone marrow stem cells to a given concentration of Epo, as well as individual differences in the rate of Epo catabolism. No data collected in this study allow comment on this point; however, there was a significant difference in the Epo concentration between groups of responders and nonresponders. Thus the simplest explanation of the present data is that the erythropoietic difference between groups is found in the kidney, where the magnitude of Epo release was different for similar levels of desaturation. Regardless of the specific mechanism, however, we propose that, for nonresponders, a greater hypoxic stimulus may be necessary to induce a sufficiently large release in Epo and augment red cell production.

Both nonresponders and responders demonstrated a significant and surprisingly similar increase in hemoglobin concentration after altitude exposure. However, in the nonresponders, the hemoglobin increase was due primarily to a significant decrease in plasma volume with no change in the total red cell volume. In contrast, the responders increased hemoglobin concentration via an increased total red cell volume and reduced plasma volume, thereby maintaining a constant blood volume. One published model relating the effect of the combination of changes in blood volume and hemoglobin concentration on $\dot{V}O_{2\max}$ (26) accurately predicts a 248 ml/min

change in $\dot{V}O_{2\max}$ in the responders (actual $\Delta\dot{V}O_{2\max} = 245$ ml/min) and only a 91 ml/min change in the nonresponder group (actual $\Delta\dot{V}O_{2\max} = 57$ ml/min). These hematologic acclimatization differences between responders and nonresponders reinforce the concept that changes in hemoglobin concentration alone are insufficient in predicting resultant changes in $\dot{V}O_{2\max}$ and physical performance after an altitude training camp.

An altitude-acclimatization pathway for predicting responders and nonresponders to altitude training was also confirmed in the prospective analysis. Although the data collection in the prospective analysis was not as extensive (total red cell volume, interval-training velocity, and interval-training $\dot{V}O_2$ were not measured), the differences in the change in acute Epo concentration and $\dot{V}O_{2\max}$ between responders and nonresponders are comparable to, and equally compelling as, the differences discovered in a retrospective manner. Unlike the retrospective analysis, the group of nonresponders did not demonstrate a significant increase in mean Epo concentration from prealtitude to acute altitude. Because of the limited number of subjects ($n = 5$) in the nonresponder group, we likely did not have enough statistical power to demonstrate a significant difference in mean Epo concentration from sea level to acute altitude with our observed treatment effect (P value of 0.11). However, a between-groups comparison of the change in Epo from prealtitude to acute altitude shows a similar trend (change in Epo: nonresponders 4.8 ± 5.1 mU/ml; responders 9.5 ± 6.2 mU/ml, $P = 0.12$), and a power analysis of the Epo data gives an estimate of three additional subjects necessary for this relationship to achieve statistical significance (with a power of 0.80 and an alpha of 0.05). Therefore, we believe that this prospectively derived data confirm the relationships established in our retrospective analysis.

Training-Response Pathway

A well-known consequence of acute exposure to altitude is a reduction in maximal aerobic power and exercise performance. Highly trained athletes appear to be even more susceptible to a reduction in $\dot{V}O_{2\max}$ at altitude, because of the large reduction in Sa_{O_2} (5) secondary to pulmonary gas-exchange limitations at high work rates (6, 11). The reduction in Sa_{O_2} is believed to cause a 1% reduction in $\dot{V}O_{2\max}$ for every 1% drop in Sa_{O_2} below 92% (18), a threshold that many highly trained athletes are below during maximal exercise, even at sea level (5, 6, 11, 18). Therefore, because of this reduction in O_2 transport, some elite athletes are not able to maintain the high work rates or training velocities at altitude necessary to maintain competitive fitness (20). This concept is reflected in the nonresponders, who demonstrated a 9% reduction in interval-training velocity and a significantly lower $\dot{V}O_2$ during interval training (Fig. 4B). We propose that the reduction in interval-training intensity contributed to the nonresponders' reductions in 5,000-m performance after altitude training, despite maintaining $\dot{V}O_{2\max}$ at precamp levels (15).

It is important to note that not all athletes trained at the same altitude, because more than two-thirds of all athletes performed interval-training sessions at a "low" altitude of 1,250 m (see Table 1). Certainly, training at a lower altitude allows for faster running speeds and higher $\dot{V}O_2$ values to be maintained, compared with training at moderate altitudes. Because it is known a priori that a high-low strategy results in a significant improvement in performance compared with traditional high-high-altitude training, the responder classification should be (and was) biased toward the athletes who performed their interval training at low altitude. However, over one-half of the nonresponders performed their interval training at a low altitude of 1,250 m, whereas three athletes who performed all of their training at moderate altitude demonstrated the necessary improvements in performance to be classified as responders. These examples demonstrate that, for some athletes, the low altitude of 1,250 m may still be "high" enough to impair training, and in fact $\dot{V}O_{2\max}$ has been shown to be significantly reduced in many endurance athletes at mild, simulated altitudes between 580 and 1,000 m (5, 9, 25). In contrast, some athletes with an excellent ability to tolerate hypoxic exercise were able to maintain running speed and O_2 flux even at a moderate altitude (2,700 m); these are examples that emphasize the varying degree of hypoxic exercise tolerance that exists among the athletic population, which has a direct effect on the training response at altitude.

Implications for Performance

We speculate that these findings could be applied in a manner that would serve to minimize the number of athletes who do not respond to an altitude training camp with an increase in performance. By screening the erythropoietic and training velocity response to acute altitude, either shortly after arrival at altitude or in a laboratory setting (e.g., a hypobaric chamber), adjustments could be made in the altitude(s) where living and interval training take place, or perhaps individual assignment of appropriate living and training altitudes could be made before an altitude training camp. A screening procedure of this type may also identify athletes who could use the classic form of altitude training (high-high) and still experience performance gains, thereby minimizing the inconvenience of traveling to a low-altitude site several days per week, while expanding the number of available altitude training sites. Similarly, athletes who apparently will not respond adequately to altitude, regardless of an individual prescription of living and training altitudes, might also be determined. This type of athlete would likely be better served by staying at an appropriate sea-level training site, sparing the expense and inconvenience of relocating to an altitude training camp for 3–4 wk. However, more research is needed in this area.

In conclusion, these data demonstrate that athletes who respond to altitude training with a significantly large improvement in performance 1) have a significantly larger acute increase in Epo concentration and total red cell volume compared with athletes who do not

improve and 2) are able to maintain interval-training velocity at low or moderate altitude near sea-level speeds while maintaining a significantly higher $\dot{V}O_2$ during interval training compared with athletes who are nonresponders to altitude training. We propose that the number of nonresponders to altitude training may be minimized by the individual assignment of living and training altitudes, on the basis of screening of the erythropoietic and training-velocity response to acute altitude exposure.

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