Performance of runners and swimmers after four weeks of intermittent hypobaric hypoxic exposure plus sea level training

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1Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas and University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; 2Institut Nacional d’Educació Física de Catalunya, Universitat de Barcelona, Barcelona, Spain; 3New South Wales Institute of Sport, Sydney, Australia; 4Australian Institute of Sport, Canberra, Australia; 5Faculty of Human Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; and 6Exercise Physiology Laboratory, School of Education, Flinders University, Adelaide, Australia

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Rodríguez FA, Truijens MJ, Townsend NE, Stray-Gundersen J, Gore CJ, Levine BD. Performance of runners and swimmers after four weeks of intermittent hypobaric hypoxic exposure plus sea level training. J Appl Physiol 103: 1523–1535, 2007. First published August 9, 2007; doi:10.1152/japplphysiol.01320.2006.—This double-blind, randomized, placebo-controlled trial examined the effects of 4 wk of resting exposure to intermittent hypobaric hypoxia (IHE, 3 h/day, 5 days/wk at 4,000–5,500 m) or normoxia combined with training at sea level on performance and maximal oxygen transport in athletes. Twenty-three trained swimmers and runners completed duplicate baseline time trials (100/400-m swims, or 3-km run) and measures for maximal oxygen uptake (Vo2max), ventilation (Ve,max), and heart rate (HR,max) and the oxygen uptake at the ventilatory threshold (Vo2 at VT) during incremental treadmill or swimming flume tests. Subjects were matched for sex, sport, performance, and training status and divided randomly between hypobaric hypoxia (Hypo, n = 11) and normobaric normoxia (Norm, n = 12) groups. All tests were repeated within the first (Post1) and third weeks (Post2) after the intervention. Time-trial performance did not improve in either group. We could not detect a significant difference between groups for a change in Vo2max, Ve,max, HR,max, or Vo2 at VT after the intervention (group × test interaction P = 0.31, 0.24, 0.26, and 0.12, respectively). When runners and swimmers were considered separately, Hypo swimmers appeared to increase Vo2max (+6.2%, interaction P = 0.07) at Post2 following a precompetition taper and increased Vo2 at VT (+8.9 and +121%, interaction P = 0.007 and 0.006, at Post1 and Post2). We conclude that this “dose” of IHE was not sufficient to improve performance or oxygen transport in this heterogeneous group of athletes. Whether there are potential benefits of this regimen for specific sports or training/tapering strategies may require further study.

altitude; hypobaria; running; swimming

ALTITUDE TRAINING has been widely incorporated in the training regimens of elite athletes. However, the benefits for sea level performance of athletes after living and training at moderate altitude (~2,200–2,500 m) for 2–4 wk are controversial. Despite growing scientific evidence to the contrary (20, 35, 42), living and training at moderate altitude (~1,800–3,000 m) remains popular among athletes and coaches (15, 61, 62), in part because of persistent anecdotal reports of success, as well as limited resolution of scientific studies (28).

An increasingly popular approach to altitude training is the “live high-train low” (LH-TL) strategy, where athletes live and sleep in a hypoxic environment (~2,500 m) but train near sea level to ensure high-quality training (34, 35). In the last 7 years, suitably controlled studies using different LH-TL protocols have consistently found small but significant increases in performance (~1.5%) in events lasting ~50 s to 17 min (35, 38, 54). There is strong evidence that the performance benefit of LH-TL is causally related to increased red cell volume (RCV) and maximal oxygen uptake (Vo2max) when the magnitude and duration of altitude exposure are sufficient to allow the erythropoietic process to take place (11, 34, 35, 54, 60). With shorter-duration altitude exposures, other mechanisms, including changes in muscle buffering capacity and efficiency, have been proposed (21, 30).

Because there are relatively few places in the world where LH-TL can be readily achieved by terrestrial variations in altitude, the use of so-called “altitude houses” (normobaric hypoxia induced by nitrogen dilution) was introduced by Rusko and colleagues (47). Based on the data from numerous laboratories, including field and simulated-altitude house conditions, it appears that a minimum of 12–16 h/day of continuous hypoxia exposure for at least 3 wk, at altitudes of 2,100–2,500 m, is necessary to induce a statistically and physiologically significant increase in RCV, hemoglobin mass, and Vo2max in trained athletes (8, 37, 48). However, this requirement for prolonged periods of exposure has limited the broad-based application of this technology. Devices designed to deliver severe hypoxia for very short periods of time (repetitive exposures of 5 min at a time lasting 1 h or more) have been disappointing in their failure to stimulate erythropoiesis or improve performance in controlled trials (29). Recently, another promising technique for administering short-term hypoxia combined with sea level training has been proposed as a method to stimulate red blood cell production and aerobic performance (39). This method, termed “intermittent hypoxia exposure” (IHE), applies severe hypobaric hypoxia (~4,500–5,500 m) at rest for 1.5–5 h/day for 2–3 wk. The rationale of IHE was partly based on the observation that brief exposures to relatively high levels of hypoxia stimulate the release of erythropoietin (EPO) in animals and humans (16, 32, 42). Previous results in mountaineers and active nonathletic
subjects (10, 39, 42), as well as trained swimmers (40), have shown significant improvements of \( V_{\text{O}_2\text{max}} \) and oxygen kinetics, as well as some red blood cell parameters. However, all of these IHE studies have assumed an erythropoietic effect from indirect markers such as increased hematocrit and reticulocytes, red blood cell count, and hemoglobin concentration (9, 10, 42), which may be altered by hydration or hypoxia-induced release of premature red cell forms from the bone marrow (24). Moreover, the results of most IHE studies (indeed almost all altitude studies) suffer from a lack of randomization, double-blinding, or placebo control, which may have potent effects on performance by itself (13).

Therefore the purpose of this study was to perform a randomized, double-blind, placebo-controlled trial to investigate the effects of IHE (3 h/day, 5 days/wk, for 4 wk) combined with sea level training on performance and maximal oxygen transport parameters in trained competitive athletes. We hypothesized that, in contrast to placebo conditions, IHE would have a synergistic effect on training at sea level, thus inducing a significant increase in \( V_{\text{O}_2\text{max}} \) and other indexes of oxygen transport capacity and improving performance in sport-specific time trials.

Because of the comprehensive nature of the measurements and the multiple mechanisms examined through the same basic experiment by a team of international collaborators, the results of the present investigation are presented in five separate but closely related publications and abstract presentations. This article reports the effects on performance and maximal oxygen transport parameters; a second article focuses on the hematological adaptations to IHE (22); a third article examines the effect of the intervention on autonomic function (19); and, finally, a fourth and fifth article (published in abstract form) examine the effects on submaximal economy and related variables such as velocity at \( V_{\text{O}_2\text{max}} \) [Truijens et al. (57)] and ventilatory acclimatization to IHE such as hypoxic and hypercapnic ventilatory responses (56).

The results of this study have been presented as preliminary reports in a series of companion communications presented at the 2004 Annual Meeting of the American College of Sports Medicine (23, 41, 53, 55–57).

METHODS

Subjects

Twenty-eight athletes (13 runners and 15 swimmers) of both sexes (17 men and 11 women) were recruited from mostly local and regional high school, collegiate, and masters swimming and running teams. The selection criterion for runners was to have recent (last 12 mo) 3,000-m run performance times under 9:00 min:s (males) and 10:05 min:s (females). Selection criteria for swimmers were to have recent 200-m best times under 2:00 min:s (males) and 2:18 min:s (females). Exclusion criteria included residence at altitude greater than 1,000 m in the previous 6 mo or recent illness or injuries preventing normal training and racing. All subjects gave their informed written consent to the study that had received approval from the Institutional Review Boards of the University of Texas Southwestern Medical Center, Presbyterian Hospital of Dallas, and the Australian Institute of Sport. Three male subjects were excluded from the study before the intervention period due to incompatibility with their training and working schedules; two other male subjects dropped out within the first 2 wk of the intervention. Thus 23 subjects, 12 men and 11 women, successfully completed the intervention protocol and testing and were used for data analysis. Descriptive characteristics of these subjects are provided in Table 1. Two subjects were unable to complete the second set of posttesting for logistical reasons.

Study Design

The study was designed as a randomized, balanced, double-blind, placebo-controlled trial, in which the experimental intervention consisted of exposure to intermittent hypobaric hypoxia (IHH) or placebo in a hypobaric chamber (3 h/day, 5 days/wk) for 4 wk. An outline of the study design and testing schedule is shown in Fig. 1.

Before the experimental intervention (Pre1, Pre2), all subjects performed duplicate baseline measurements to minimize learning effects, to obtain familiarization with all testing procedures and equipment, and to determine test-retest reliability by determining the typical error of each measurement (TEM) (27). After the baseline testing period, the subjects were matched according to sport, sex, time-trial performance, and training history and randomly allocated to either the treatment group [hypobaric hypoxia (Hypo)] or the placebo group [normoxia (Norm)]. By this technique, within each matched pair, there was a 50% chance of being assigned to the control or experimental group.

All measurements were repeated during the 1st (Post1) and 3rd wk (Post2) after the intervention period. This way both the immediate effects of IHE, as well as the off response of these effects, could be evaluated.

Hypobaric Chamber Exposure

A hypobaric chamber (Perry Baromedical, West Palm Beach, FL), located at the Institute for Exercise and Environmental Medicine, Dallas, was utilized for the experiment. This chamber has three separate locks that can be operated independently and controlled for simulated altitude and rate of ascent/descent. The air refresh rate was calculated to keep the fraction of inspired \( \text{CO}_2 \) (FICO\(_2\)) < 0.2%. Four chamber runs per day were scheduled to accommodate the living and training schedules of all subjects, divided into two treatment and placebo interventions each day in separate locks.

All subjects entered the chamber 3 h/day, 5 days/wk (from Monday to Friday) for four consecutive weeks (20 days in total). Three-hour exposures were chosen because that duration initiates robust and reproducible increases in EPO (16, 32, 42); 5 days/wk was chosen to allow the athletes to participate in longer-duration, sport-specific

| Table 1. Subjects characteristics and performance level (n = 23) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Hypoxia         | 11 [5 M, 6 F]   | 22.2 (7.0)      | 171.6 (8.2)     | 66.6 (12.2)     | 57.2 (3.35)     | 589.5 (75.7)    |
| Normoxia        | 12 [6 M, 6 F]   | 22.8 (9.3)      | 174.9 (9.9)     | 67.3 (12.1)     | 57.1 (5.5)      | 578.8 (63.9)    |
| Swimmers (S)    | 13 [7 M, 6 F]   | 20.2 (8.8)      | 178.0 (8.4)     | 73.0 (11.7)     | 57.15 (4.4)     | -               |
| Runners (R)     | 10 [5 M, 5 F]   | 25.6 (6.2)      | 167.2 (5.9)     | 59.1 (6.2)      | 584.1 (66.3)    | -               |
| Males (M)       | 12 [7 S, 5 R]   | 22.2 (9.0)      | 178.1 (9.1)     | 70.3 (12.0)     | 54.2 (2.8)      | 533.6 (23.4)    |
| Females (F)     | 11 [6 S, 5 R]   | 22.9 (7.5)      | 168.1 (5.6)     | 63.2 (11.0)     | 60.6 (3.4)      | 634.7 (54.2)    |

Values are mean (SD); n = 23 subjects, PR100m, personal record in 100-m freestyle (swimmers); PR3km, personal record in 3,000 m (runners).
training sessions and competitions, to allow brief recovery periods from the severe hypobaric hypoxia, and for logistical reasons regarding staffing of the hypobaric chamber and athlete acceptance of the intervention; 4 wk of exposure were considered necessary to produce an augmentation of the red cell mass (37). No exercise was undertaken while in the chamber, and all subjects were encouraged to remain awake during the exposure. Each chamber exposure, regardless of altitude, included a 10-min ascent and 10-min descent within the 3-h period. The Hypo group was exposed to a barometric pressure corresponding to a simulated altitude from 4,000 up to 5,500 m according to the following schedule (see Fig. 1): 4,000 m (days 1–2), 4,500 m (days 3–4), 5,000 m (days 5–6), and 5,500 m (days 7–20). For the Norm group, the first 10 min of exposure involved multiple pressure changes as follows: minute 1.5 = 1,800 m; minute 2.5 = 900 m; minute 5 = 3,700 m; minute 6 = 2,500 m; minute 7 = 3,000 m; minute 10 = 500 m, where it remained for the duration of the exposure. This approach was designed to provide sufficient pressure changes in the sinuses and tympanic membranes so that the placebo subjects would be unsure of the final resting pressure. Only the chamber technicians were aware of the treatment for each group, and all subjects and investigators were blinded until the end of the experiment when the data were examined and finalized. Blood O2 saturation (SpO2, %) was measured within the final 30 min of chamber exposure using a fingertip pulse-oximetry clip (model 505-US, Criticare Systems, Waukesha, WI), and all subjects were monitored every week (5th day of exposure) by research assistants who were not involved in the data collection or analysis. At the end of the study, each subject was asked to guess which intervention they received and to indicate the certainty of that guess (certain; not sure; no idea) to determine the effectiveness of the double-blind design.

To avoid iron depletion during the experiment, all subjects received oral liquid iron supplement (Feo-Sol, 9 mg elemental iron/ml) with dose (ranging from 5–15 ml, 1–3 times/day) adjusted based on plasma ferritin concentration.

**Training**

Individualized training plans were developed by the athletes and their coaches. They typically included two daily training sessions for both runners and swimmers. No special training goals or schedule changes were established during the experimental period according to the intervention, and all athletes continued training throughout the entire period of the study, which corresponded to the competitive season for the swimmers and the postcompetitive season for the runners. Careful matching of subjects resulted in matched pairs that were mostly members of the same team. This way, substantial differences in training programs between groups could be minimized. Additionally, each athlete kept a detailed training log of his or her daily routines, including training mode, volume, duration, and intensity (estimated using a 20-point Borg scale) of each workout so that any differences in training programs could be identified.

**Evaluation of Performance**

The primary outcome measure of this study was running and swimming performance at sea level, as measured both on the field (track or swimming pool) and in the laboratory (treadmill or swimming flume). An outline of the testing schedule is included in Fig. 1.

**Running time trial (3,000 m).** Time trials were conducted on a 400-m synthetic track (Southern Methodist University, Dallas, TX) twice before and after the intervention. The runs were in men’s and women’s heats in the morning (7:00–8:00 AM). Athletes were instructed to achieve the best time possible on each time trial. Experienced pace setters (athletes not otherwise involved in the project) were utilized to set a fast, competitive pace for the first 1,600 m of the 3,000-m race to ensure physiological rather than tactical performance. The pace-setter athlete ran the same preselected race pace in both the prealtitude and postaltitude time trials. Time was recorded for each subject to the nearest 0.1 s.

**Swimming time trial (100 and 400 m).** Time trials were conducted in a 50-m outdoor pool (Southern Methodist University, Dallas, TX)
twice before and after the intervention. The swims were in men’s and women’s heated baths in the afternoon (4:00-5:00 PM). A recovery period of 45 min was allowed between the 100-m and the 400-m trial. Swimmers were asked to achieve the best time possible on each trial time. Time was recorded for each subject to the nearest 0.1 s.

**Treadmill evaluation.** After a 15-min warm-up, each runner performed two tests. The first consisted of 5-min runs on a calibrated research treadmill (model 48, Trackmaster, Pensacola, FL) at three submaximal speeds (8, 10, and 12 mph for men; and 8, 9, and 10 mph for women, respectively). This protocol served to evaluate submaximal treadmill running economy from the VO2 attained during the final 5 min at each speed. These results, as well as those referring to submaximal economy in swimming, are reported elsewhere in abstract form [Truijens et al. (57)]. After a recovery period (ca. 10 min), they performed an incremental, maximal test to volitional exhaustion, using a protocol with constant velocity (10 mph for men and 9 mph for women) and an increase in grade of 2% every 2 min.

**Swimming flume evaluation.** All swim testing was conducted in a motorized swimming flume (Unidyne, Minneapolis, MN) housed within the performance laboratory at the Institute for Exercise and Environmental Medicine in Dallas, TX. A full calibration procedure was undertaken to establish the linearity and the relationship between engine power and water speed using a water flowmeter. After a 15-min warm-up, all swimmers performed two tests. The first consisted of 3-min swims in the swimming flume at three submaximal water speeds (1.1, 1.2, 1.3 m/s for men and 1.0, 1.1, 1.2 m/s for women) separated by a 2-min rest period to determine swimming economy (Truijens et al.; 57).

After 10 min of rest they performed a maximal test to volitional exhaustion, using an incremental protocol with an increase of 0.2 m/s in flume speed every 1 min, with the initial speed being 0.9 and 1.0 m/s for women and men, respectively.

**Oxygen uptake measurement.** Oxygen uptake (VO2) was measured simultaneously with the Douglas-bag technique and an online system for breath-by-breath measurements. Hand-timed Douglas bag collections (30–60 s) were considered standard for all oxygen uptake measurements. Breath-by-breath data served as backup and was used for identification of oxygen kinetics analysis (steady states and plateaus) and determination of the ventilatory threshold.

Gas fractions were analyzed using a mass spectrometer (Marquette MGA 1100, Milwaukie, WI) that was calibrated twice a day and confirmed before each test and used for both Douglas bags and the breath-by-breath system. Separate systems were dedicated to treadmill and flume testing throughout the study. Ventilatory volume was measured with a 120-liter Tissot spirometer. In addition, heart rate (HR) was monitored continuously (Polar CIC, Port Washington, NY). The online system for breath-by-breath measurements consisted of two one-way valves to direct flow, two sample lines for measuring gas fractions, and a turbine flowmeter (VMM, Interface Associates) for measuring ventilation. Breath-by-breath data were collected, displayed, and stored on a computer and analyzed using customized software. Maximal oxygen uptake (VO2max) was considered the highest value measured in any bag collected for at least 30 s during the maximal test. The VO2 at the ventilatory threshold (VT) (l/min) was determined from the breath-by-breath data by a single, blinded, experienced observer during simultaneous examination of multiple plots of VO2 vs. VE, VO2 vs. VE/VO2, VO2 vs. CO2 production (VCO2), and VO2 vs. VE/VCO2 using commercial software (First Breath, Marquette, Milwaukie, WI) according to standard criteria (1).

**Statistics**

The reliability of measurements was quantified using the typical error of measurement expressed as percentage of the mean [TEM% = [(SD of difference scores/√2)/mean] × 100], calculated from the duplicate baseline measurements (Pre1, Pre2).

To evaluate the effects of the intervention, a statistical comparison was conducted between the Pre-Best score (highest or lowest score from Pre1 and Pre2) and the two scores obtained after the intervention period (Post1 and Post2) in both experimental groups. This conservative approach was based on the assumption that for tests requiring a maximal effort on the part of the subject (such as VO2max and field performance), the highest value observed is most likely to represent a true maximal effort and therefore most representative of the true “maximal” value for that measurement. This reasoning, similar to that employed in the interpretation of pulmonary function testing, reduces the impact of a possible submaximal effort before the intervention on the results of the experiment. VT being a submaximal, more subjective parameter, the Pre-Mean score (mean value from Pre1 and Pre2) was used for comparisons after the intervention period to minimize the bias in breakpoint determination. Data analysis was complicated by the fact that two subjects assigned to the placebo group were unable to complete the Post2 tests for logistical reasons. Therefore the change from preintervention to the first week after the intervention (Pre-Best to Post1) was taken as the primary statistical comparison with the most statistical power (i.e., complete data on all subjects) to determine the effectiveness of the intermittent hypoxia exposure. Because of the small subject numbers, the investigators elected not to use a general linear model or impute data for these missing values at the Post2 time point in the primary comparison. To assess the effect of persistence of the primary effect over time, a comparison among all time points (Pre-Best, Post1, and Post2) was performed with the two placebo subjects having missing data removed from the statistical comparisons to avoid the effect of missing values.

Therefore, a two-way repeated-measures ANOVA with main effects and interaction of group (Hypo vs. Norm) and test (Pre-Best vs. Post1, including all subjects, followed by Pre-Best vs. Post1 and Post2 with casewise deletion) was used for analysis. As part of our prespecified, secondary exploratory analysis, runners and swimmers were examined separately using a two-way ANOVA for repeated measures (RM-ANOVA) involving group (Hypo vs. Norm) and test (Pre-Best vs. Post1 and Post2). Finally, a three-way ANOVA with test, group, and sport type (swimmers vs. runners) was conducted to evaluate directly the differences between swimming and running athletes. Where a significant effect was obtained, a post hoc pairwise multiple comparison analysis was performed with the Tukey test to identify differences. Precise \( P \) values are reported and interpreted according to APS guidelines (14). All tests were performed using SigmaStat 3.0 (SPSS). Unless otherwise specified, data are presented as means (SD), and 95% confidence intervals (95% CI) of the mean values are presented when appropriate.

**RESULTS**

**Subjects and Chamber Exposure**

Twenty-three subjects, 12 men and 11 women (Table 1), successfully completed the intervention protocol of the original total of 28 subjects. Five male subjects did not complete the chamber exposure due to incompatibility with their training and working schedule and were excluded from the study, although they performed some of the tests, which are eventually included in some analyses not related to the main hypotheses (i.e., method reliability measures).

Subjects completed 94% of the chamber exposures with an average number of missing sessions of 1.1 (SD 1.5) out of 20, with no difference between groups \( (P = 0.46) \). Clinical symptoms noted during the 108 chamber exposures included seven isolated episodes of ear pain and one case of left maxillary sinus pain during changes in chamber pressure, three episodes of dull frontal headache, and one case during the first week of exposure of nausea and more severe headache requiring treat-
ment with Tylenol. These symptoms were reported by both experimental and control groups. No subject had to abandon the experiment because of health conditions related to the exposure in the hypobaric chamber. At the end of the study, 91% of all subjects were able to correctly guess in which group they were included; however, only 50% in each group were certain about their guess, with no difference between hypoxia or control groups (Chi square $P = 0.84$).

Average $\text{SpO}_2$ levels for the 4 wk of exposure were 68% (SD 9), 70% (SD 9), 68% (SD 5), and 68% (SD 7) for weeks 1, 2, 3, and 4, respectively for the Hypo group, and 98% (SD 1) (weeks 1–4) for the Norm group.

No change in body mass was observed within ($P = 0.91$) or between groups (group by test interaction, $P = 0.88$).

**Training**

All athletes were able to combine their training with the experimental procedures and chamber exposures throughout the period of the study. During the 4 wk of chamber exposure, their average training volume was 10.2 h/wk (SD 2.0), including an average of 4 (SD 3) intense workouts per week. Training was closely matched among the groups as determined from the training log information regarding weekly training load (Fig. 2). There was no statistically significant difference in total training volume ($P = 0.15$), or intensity (number of intense weekly workouts, $P = 0.11$) between both experimental groups throughout the intervention period.

The training logs also made it clear that the swimmers started a progressive taper period toward the end of intervention phase that continued in the period between the first and second posttest. This training period aimed at performance improvement in preparation for a major competition and was characterized by a marked decrease in training distance (Hypo, $-23.6$%; Norm, $-21.8$%) from the average training distance during the intervention period to the second posttest with no marked changes in intensity.

Table 2 shows mean and SD values for main maximal performance measures along the whole intervention period in both the Hypo and Norm groups along with the typical error of measurement calculated from the repeat baseline measurements (TEM%).

**Primary Analysis**

**Time-trial performance.** When expressed as relative percent change from the preintervention best value to the first postmeasurement, there was no significant change in performance in the Hypo group [$+2.6$% (95% CI = 0.9–4.3%)] compared with the Norm group [$+1.3$% (95% CI = 0.3–2.2%)]; this result was not influenced by considering either the 100-m or the 400-m time trial as the criterion measurement for the swimmers (Table 2, Fig. 3). There was no additional change in performance from Post1 to Post2 [Hypo group: $+1.2$% (95% CI = $-0.4$ to 2.8%); Norm group: $+2.3$% (95% CI = 0.3–4.2%)]. Overall, no significant time-trial performance changes were observed which could be attributed to the intervention (group by test interaction $F_{1,19} = 1.66$, $P = 0.20$).

Maximal oxygen uptake. There also was no change in absolute $\text{VO}_2\text{max}$ as a direct result of the intervention from the preintervention best value to the first postmeasurement (Hypo: $+0.01$ l/min (95% CI = $-0.10$ to $-0.12$ l/min); Norm: $-0.07$ l/min (95% CI = $-0.15$ to $0.00$ l/min)]. Thus there was no specific effect of IHE compared with placebo immediately after the intervention period or later (group by test interaction $F_{1,19} = 1.19$, $P = 0.31$). Figure 4 shows the absolute $\text{VO}_2\text{max}$ measured during the experiment, including Post1 and Post2 measurements.

Maximal HR, $\dot{V}E$, and VT. There were no significant changes in maximal HR ($\text{HR}_{\text{max}}$) between ($P = 0.09$) or within ($P = 0.06$) experimental groups (group by test interaction $F_{1,18} = 1.41$, $P = 0.26$), consistent with an equivalent, maximal effort during all treadmill and flume tests (Table 2). Similarly, maximal respiratory exchange ratio was $1.2 \pm 0.1$ for all groups at all time points. Maximal $\dot{V}E$ ($\dot{V}E_{\text{max}}$) did not change between before and immediately after the intervention ($P = 0.81$) or within groups ($P = 0.83$ and 0.35, respectively).
Table 2. Maximal performance measures with TEM before and after intermittent exposure to hypoxia (Hypo group) or placebo (Norm) (N = 12; 7 Swimmers and 5 Runners)

<table>
<thead>
<tr>
<th>Time-trial performance, s</th>
<th>Hypo (n = 11; 6 Swimmers and 5 Runners)</th>
<th>Norm (n = 12; 7 Swimmers and 5 Runners)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre1</td>
<td>Pre2</td>
</tr>
<tr>
<td>100-m swim</td>
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<tr>
<td>All</td>
<td>59.5 (3.5)</td>
<td>60.7 (2.3)</td>
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<tr>
<td>Swimmers</td>
<td>54.5 (7.3)</td>
<td>51.6 (7.0)</td>
</tr>
<tr>
<td>Runners</td>
<td>58.5 (10.4)</td>
<td>58.0 (10.7)</td>
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<tr>
<td>400-m swim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>192.6 (10.3)</td>
<td>191.6 (10.8)</td>
</tr>
<tr>
<td>Swimmers</td>
<td>188.7 (6.7)</td>
<td>189.5 (8.8)</td>
</tr>
<tr>
<td>Runners</td>
<td>195.0 (12.1)</td>
<td>193.2 (12.9)</td>
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<td>3,000-m run</td>
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<tr>
<td>All</td>
<td>119.7 (16.8)</td>
<td>116.2 (17.2)</td>
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<tr>
<td>Swimmers</td>
<td>110.3 (16.4)</td>
<td>107.6 (18.4)</td>
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<tr>
<td>Runners</td>
<td>127.3 (14.4)</td>
<td>126.5 (8.6)</td>
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<td>VO2max, ml·kg⁻¹·min⁻¹</td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>2.86 (0.54)</td>
<td>2.82 (0.56)</td>
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<tr>
<td>Swimmers</td>
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<td>2.83 (0.60)</td>
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<tr>
<td>Runners</td>
<td>2.82 (0.55)</td>
<td>2.82 (0.58)</td>
</tr>
</tbody>
</table>

Values are means (SD). TEM%, typical error of measurement, expressed as coefficient of variation with [95% confidence interval]. Pre1 and Pre2 are duplicate baseline measurements before the experimental intervention. Post1 and Post2 refer to 1st and 3rd wk after the intervention, respectively. VO2max, maximal oxygen uptake; HRmax, maximal heart rate; V˙O2max, maximal ventilation; VO2 at VT, oxygen uptake at ventilatory threshold. *Group by test interaction (P < 0.05) compared with highest/lowest value (Pre-Best) of 2 preexposure tests (Pre-Mean for VO2 at VT). †Significant differences (2-way repeated-measures ANOVA, Tukey. P < 0.05) compared with highest/lowest value (Pre-Best) of 2 preexposure tests (Pre-MEAN for VO2 at VT). §Two subjects (1 runner, 1 swimmer) did not complete the Post2 tests; their full set of data was not included in the statistical comparisons.

Although the mean V˙O2 at VT obtained before the intervention (Pre-Mean) increased immediately after the intervention (test effect F1,19 = 5.12, P = 0.01), the change being significant in the Hypo group only [Hypo: +5.0% (95% CI = 0.7–9.4%), P = 0.046; Norm: −0.7% (95% CI = −4.3 to 2.8%), P = 0.998], this change could not be attributed directly to the hypoxic treatment (group by test interaction F1,19 = 2.25, P = 0.12).

Secondary Analysis

The secondary analysis was a subgroup analysis between runners and swimmers, and changes between first and second postintervention tests.

Time-trial performance. There were no significant changes in swimming performance in the 100-m time trials [Hypo swimmers: 1.0% (95% CI = 0.4–1.6%); Norm swimmers: 1.5% (95% CI = 0.1–2.8%)] or 400-m time trials [Hypo swimmers: 1.0% (95% CI = −0.4 to 2.5%); Norm swimmers: 1.5% (95% CI = 0.4–2.6%) immediately after the intervention or 2 wk later [Hypo swimmers: 0.5% (95% CI = −0.4 to 1.4%); Norm swimmers: 1.1% (95% CI = −1.4 to 3.6%); and Hypo swimmers: −0.5% (95% CI = −1.8 to 0.8%); Norm swimmers: 2.7% (95% CI = 0.3–5.2%), respectively, between (P = 0.82 and 0.92, respectively) or within (P = 0.42 and 0.41, respectively) experimental groups (group by test interactions, F1,10 = 0.05 and 1.41, P = 0.95 and 0.27, respectively) (Fig. 3)].

Running performance in the 3-km time-trial deteriorated after the intervention period within both groups (P = 0.002). Post hoc comparisons showed that the impairment was significant in the Hypo runners [slower by 4.6% (95% CI = 3.3–5.8%) and 3.2% (95% CI = 2.2–4.3%) at Post1 and Post2, respectively, P < 0.01] but not in the Norm runners [slower by 0.3% (95% CI = −0.7 to 1.3%) and 1.6% (95% CI = 0.4–2.9%), respectively, P = 0.31; group by test interaction F1,7 = 4.25, P = 0.04].

Maximal oxygen uptake and ventilation. Separate two-way RM ANOVA with sport type raised the possibility that there may have been a different response between the runners and swimmers for VO2max. While no significant changes were noted in the VO2max of runners of either experimental group in absolute or relative values (Table 2), the swimmers exposed to hypoxia appeared to have increased their VO2max more than the Norm swimmers during the taper between Post1 and Post2 tests [Hypo swimmers: +6.2% (95% CI = 4.5–7.8%), P = 0.006; Norm swimmers: +1.7% (95% CI = −0.7 to 4.2%), P = 0.06; group by test interaction F1,19 = 3.05, P = 0.07]. When expressed in values relative to body mass, this change was more pronounced and reached conventional statistical significance [Hypo swimmers: +7.5% (95% CI = 6.2–8.8%), P = 0.003; Norm swimmers: −2.1% (95% CI = −0.8 to −3.4%), P = 0.07; group by test interaction F1,19 = 3.61, P = 0.046]. Although the numbers of subjects when broken down by sport were small, increasing the chance of type II error,
when a three-way ANOVA was performed examining the effect of test, group, and sport, the interaction was $P = 0.06$.

Maximal ventilation significantly increased within both experimental groups in the second test after the intervention period (test effect $F_{1,19} = 4.00, P = 0.03$), the increase being significant for the Hypo group only [Hypo: $+7.9\%$ (95% CI = 3.4–12.5%), $P = 0.009$; Norm: $+2.3\%$ (95% CI = −3.0 to 7.7%), $P = 0.49$], although the increase could not be attributed

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Fig. 3. Individual (small symbols; thin lines) and mean changes (%; large symbols, dark lines) in 100-m (A) and 400-m (B) swimming performance, as well as 3-km running performance (C), before and after chamber exposure to intermittent hypoxia (Hypo) or placebo (Norm). Values are means with 95% confidence intervals in brackets ([95% CI]). $P$ values are for post hoc analyses.
The primary goal of conventional or simulated altitude training for competitive athletes is to enhance performance. Since the demonstration that “intermittent” exposure to altitude could lead to improved performance in competitive athletes (11, 35, 54), numerous other strategies have been described in

**IHE as a Stimulus for Improved Performance**

The primary goal of conventional or simulated altitude training for competitive athletes is to enhance performance. Since the demonstration that “intermittent” exposure to altitude could lead to improved performance in competitive athletes (11, 35, 54), numerous other strategies have been described in

![Comparison of VO2max changes between normoxia and hypoxia](http://jap.physiology.org/)
an attempt to broaden the access to this type of training (34, 42). The key features of the “living high-training low” model have been identified as living high enough, long enough to stimulate the process of altitude acclimatization (predominantly increased RCV and aerobic power), while maintaining normoxic, high-quality training (11, 34). In the studies by Levine and Stray-Gundersen (35), this goal was achieved by living at an altitude of 2,500 m (20–22 h/day), and training once or twice daily at 1,200 m for 1 mo. Similar results have been achieved with even less frequent exposure to normoxic training, of 2–3 times/wk (34), and have been confirmed by numerous other investigative groups (7, 26, 59).

Rusko and colleagues (33, 46, 47) demonstrated very similar outcomes (accelerated erythropoiesis, increased aerobic power, and improved performance) by spending 12–16 h/day in a simulated, normobaric hypoxic environment. However, other investigators, using shorter-duration exposures to these moderate hypoxic stimuli (equivalent to 2,500–3,000 m) of 8–10 h/day for 1–3 wk have not observed increases in hemoglobin mass or aerobic power (2, 3), although they have observed a performance enhancement associated with variable improvements in exercise economy and buffer capacity of skeletal muscle (12, 21, 50). Together these studies have suggested that there may be a threshold “dose” of altitude/hypoxia exposure.
that is necessary to mediate different aspects of the acclimatization response and that may ultimately lead to improvements in performance for competitive athletes (34, 36, 37, 42, 44, 49).

Recently, it has been hypothesized that more severe hypoxia, delivered for shorter periods of time, could be used to achieve the same outcome, with less burden on the athlete. For example, an old Russian concept of alternating 5 min of severe hypoxia equivalent to an altitude of ~5,000 m followed by 5 min of normoxia and repeated for 1 h or more has been proposed for this purpose (52). However, a carefully controlled study of this technique has failed to find any evidence of a physiological effect of this approach or any impact on aerobic power or running performance in highly competitive athletes (29).

On the basis of a robust foundation of research demonstrating that more sustained periods of severe hypoxia could lead predictably to an increase in EPO concentration in animals and humans (16), Rodriguez and colleagues proposed that 3 h/day of hypobaric hypoxia could be the optimal compromise between intensity and duration of exposure and have presented provocative preliminary results. For example, initial proof-of-concept studies in mountaineers and moderately trained subjects suggested that short durations of such exposure could provide a “preacclimatization” that improved performance at altitude (9, 10, 39, 43). Subsequently preliminary reports involving world-class endurance track cyclists (45) and national-level swimmers (40) used a similar protocol to the present experiment exposing athletes to simulated altitudes of 4,000–5,500 m for 3 h/day, 5 days/wk for 11–14 days and were similarly encouraging for improving performance at sea level from 0.9 to 2.9%. Other investigators have delivered similar degrees of hypoxia but at normal atmospheric pressure to endurance athletes in an attempt to avoid the physical aspects and technical requirements of administering hypobaric hypoxia of this severity. For example, Katayama et al. (30) have used a “nitrogen tent” to deliver shorter periods (90 min) of normobaric hypoxia equivalent to a simulated altitude of 4,500 m for 90 min, 3 days/wk, for 3 wk to six male endurance runners and six matched but unblinded controls. The hypoxia group showed a significant improvement in 3-km running time (~1.3%), running time to exhaustion during maximal exercise, and submaximal efficiency (economy), but not VO2max; these changes were transient and returned to baseline 3 wk after cessation of the hypoxic stimulus. Similar results were observed in a subsequent study when the hypoxic stimulus was delivered daily, but over a shorter total period of time (14 consecutive days) (31).

The major problem with virtually all previous studies examining IHE, and indeed all altitude training studies except for that of Julian et al. (29), has been the failure to include a true placebo altitude control group. To our knowledge, the present study is the first randomized, double-blind placebo-controlled investigation to have administered prolonged IHE to athletes, and the results were clear and compelling: no improvement in performance, and no demonstrable evidence of a robust altitude acclimatization effect by any of the many measures examined in this project, including erythropoiesis (22), ventilatory acclimatization (56), or autonomic function (19, 53). Several explanations for the discrepancy between this study and the preliminary results cited above may exist.

The most straightforward explanation is that this approach to simulated altitude training simply does not elicit true physiological adaptations. If so, then the small improvements in performance noted in previous studies were more likely the result of a placebo (13), or training camp effect (35), than a specific physiological outcome of altitude acclimatization. It has been proposed that when the duration of normoxia exceeds the duration of hypoxia exposure, then the “off response” or deacclimatization process overwhelms whatever “on response” or acclimatization process may be stimulated by the hypoxia exposure (34, 37). This problem of limited duration of hypoxia may have been compounded by the 2 days off each week in the present experimental design. Such a hypothesis has a strong basis in the cellular and molecular biology of the hypoxia response program, including rapid ubiquitination of the hypoxia-inducible factor 1-α when it is hydroxylated in response to the presence of oxygen (51, 58).

A number of alternative explanations also deserve to be considered. First of all, performance changes after altitude exposure may be affected by numerous factors in addition to the specific effects of altitude, including genetic endowment, health status, psychological factors, fatigue, and of course training. Even in the most carefully controlled study, it may be difficult to determine with certainty whether reported performance changes are caused by hypoxia/altitude exposure, by altered training, or simply from placebo effects (25, 34, 40, 44). It is possible that the measurements of performance (100- and 400-m swim, and 3-km run time trials) used in this study were not sensitive enough to measure a significant change in performance capacity, a problem that is exacerbated by the relatively small sample size and sport stratification used in the study. In fact, the TEM (95% CI) for the swimming and running tests ranged from 1.0 to 2.6%, and 1.1 to 3.9%, respectively (see Table 2). According to Hopkins et al. (28), simulations show that the smallest worthwhile enhancement of performance for an athlete in an international event is 0.7–0.4% of the typical within-athlete random variation in performance between events. Our study was underpowered to detect such a small difference, if the real effect of the IHE was smaller than our TEM.

Second, this experiment was the longest study to date delivering such severe, sustained hypobaric hypoxia for a full 4 wk. Previous preliminary reports ranged from 11 days for hypobaric hypoxia to 3 wk for normobaric hypoxia. We cannot exclude the possibility that this intensity of altitude simulation may have also had negative side effects, such as impaired recovery, poor sleep and appetite, and added stress of trying to fit 3 h of chamber exposure (true for the placebo group as well) into an already tight schedule for these athletes. Indeed, such an effect may have been observed in our subgroup analysis of runners who had a deterioration in their performance after the intervention. However, even in studies where EPO is injected directly, it appears to take at least 2–3 wk to document a clear erythropoietic effect (4–6, 17). Moreover, there appears to be a direct relationship between the duration of IHE exposure in numbers of days, and the magnitude of the response, with a minimal response requiring at least 3–4 wk (37, 49). Therefore although a shorter duration would likely have had less undesirable effects, it also would likely have limited the overall acclimatization response.
Third, even if the inclusion of a placebo control group strongly supports the lack of response seen in the experimental group, the inability to obtain complete blinding of the subjects (91% of them correctly guessed in which group they were included, even if only 50% declared themselves to be certain about their guess) may have limited the effectiveness of the design and played a role in reducing the motivation of the control subjects. This may have particularly affected those who did not have the extra motivation of an immediate competition (e.g., the runners). If anything, though, such an effect should have magnified any group differences in performance outcomes and underscores the absence of a difference in response between groups.

IHE, Sport, and Late Changes in the Oxygen Transport System

Although it was very clear that there was no difference in response between hypoxia and placebo groups soon after completion of the intervention, there were some intriguing trends toward improvements in VO\textsubscript{2max} (and associated VE\textsubscript{max}) and VO\textsubscript{2} at the VT, which became manifest in the 2 wk following completion of the intervention. When analyzed by sport group, these changes mostly appeared related to changes in the group of hypoxia-exposed swimmers.

There are a number of possible hypotheses that can be generated from these results and deserve discussion. First, the improvements in the swimmers were observed during a taper before a major competition. Moreover, the improvements in VO\textsubscript{2max} were present in both groups of swimmers, although they appeared more robust in the hypoxia-exposed athletes. Therefore, the simplest explanation is that both swimming groups improved VO\textsubscript{2max}, with no statistical difference between them ($P = 0.07$), because of the taper. Conversely, it could be hypothesized that the withdrawal of the negative aspects of the severe hypoxia exposure, when combined with the recovery during the taper, allowed the expression of a true altitude effect, although the mechanism of such an effect that would become manifest after prolonged removal of the hypobaric hypoxia is unclear, and certainly not related to changes in red cell mass (22) or hypoxic and hypercapnic ventilatory control (56), neither of which changed in this experimental model. It should be emphasized that unlike traditional altitude training camps where it has been hypothesized that a period of reacclimatization to sea level might be necessary to see the full effect of altitude training, athletes engaged in IHE spent most of their time in a normoxic environment and performed all their training under normoxic conditions. Furthermore, there was no improvement in the postaltitude period in the runners, making it unlikely that the postexposure improvement in the swimmers represents a generic “delayed” response to altitude.

Second, there were other distinguishing characteristics between the groups that may have contributed to the observed differences. These included the fact that the swimmers were Dallas residents and continued to live at home and train with their local teams; in contrast, many of the runners were from out of town and trained more independently in what for them was the “off season.” Global training plans were also different between the two sports; thus based on the training logs, the swimmers trained almost twice the total volume as the runners over the course of the study. The swimmers had the specific motivation of a major competition and thus trained harder and more consistently, while the runners may have been less motivated. Altogether, the hypotheses that swimming and/or tapering interacts with IHE will have to be tested in future studies with a more specific design.

Conclusions

Using a carefully controlled double-blind balanced design, this dose of hypobaric hypoxia (3 h/day, 5 days/wk for 4 wk) was not sufficient to have a synergistic effect on performance over sea level training in this heterogeneous group of competitive endurance athletes. Considering both runners and swimmers as a group, we also could not detect a difference between groups in the change of VO\textsubscript{2max}, VE\textsubscript{max}, or VT during maximal exercise soon after the intervention. The potential use of IHE in the context of a precompetition taper in swimmers or other athletes who taper prominently before competition could be considered as a topic for future research.

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1534 INTERMITTENT HYPOXIA AND SEA LEVEL PERFORMANCE

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