Exercise improvement in aerobic performance capacity

I. Improvement in aerobic performance capacity

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J Appl Physiol 100: 1238–1248, 2006; doi:10.1152/japplphysiol.00742.2005.—This study investigates whether a 6-wk intermittent hypoxia training (IHT), designed to avoid reductions in training loads and intensities, improves the endurance performance capacity of competitive distance runners. Eighteen athletes were randomly assigned to train in normoxia [normoxic and hypoxic incremental test to determine maximal oxygen uptake (VO2 max) improvement at sea level has been reported in trained cyclists (39)]. In addition, maximum oxygen uptake (VO2 max) improvement at sea level in professional cyclists (39). In addition, significant maximum oxygen uptake (VO2 max) improvement at sea level has been reported in trained subjects after hypoxic exercise bouts of 2- to 12-min duration (38). Recent evidence also demonstrated no beneficial effects of IHT programs, when the hypoxic exercise intensity is set below 80% of normoxic VO2 max (44, 46). Collectively, these findings point to a pivotal role for a minimal hypoxic exercise duration and intensity in IHT models, especially in trained athletes. Based on these observations, we assumed that two successive hypoxic training bouts, of 12–20 min, performed at the second ventilatory threshold (VT2) (~80% of normoxic VO2 max) are likely to comply with the above information. Moreover, integrated within the usual normoxic training of competitive runners, the intermittent nature of such specific hypoxic sessions would allow maintaining high levels of total training load and may elicit significant improvement of endurance performance capacity.

Characterization of the endurance performance capacity in athletes involves incremental exercise testing, allowing for the determination of the ventilatory fatigue thresholds [first ventilatory...
threshold (VT1) and VT2, VO2 max, as well as their associated minimal running velocities (vVT1, vVT2, and vVO2 max). Additionally, since vVO2 max falls among the significant predictors of endurance performance (4, 5), the time to exhaustion at vVO2 max (Tlim) is thought to constitute an important determinant of the endurance performance capacity. Despite its athletic relevance, the effect of IHT on Tlim in endurance athletes remains unknown. Since the maximal rate (i.e., VO2 max or vVO2 max) (6, 23) and/or kinetic changes in the O2 flux adjustment (13) are expected to contribute to Tlim performance, the possible influence of IHT on both of these respective properties of aerobic metabolism is also not elucidated.

Therefore, the purpose of this study was to test the hypotheses that an original IHT model, including two weekly moderate-duration (24–40 min) and high-intensity (VT2) hypoxic sessions within the usual normoxic training of already trained athletes, 1) improves running velocities at sea level due to amelioration of aerobic energy provision, including VO2 max; and 2) lengthens Tlim at sea level with concomitant adaptations of aerobic metabolism properties, mainly VO2 max and/or oxygen uptake (VO2) kinetics.

METHODS

Subjects

Eighteen highly trained male distance runners were recruited from local athletic teams and completed the study before the beginning of their competitive season. Their main physical and physiological characteristics are shown in Table 1. After all the potential risks were explained, the athletes gave a voluntary written consent to participate to the protocol, approved by our hospital and national review boards. In the weeks before and during the study, the subjects lived under the altitude of 300 m and were engaged in a regular training schedule comprising five training sessions per week, including two weekly training sessions performed specifically at VT2 (49). Their respective individual training schedule remained unaltered during the experimental period. All were highly motivated to participate in the study, familiar with treadmill running, and with current 10,000 m or equivalent personal-best times of <35:00 (min:s).

Table 1. Anthropometric data and performance capacity of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Hypoxic Group</th>
<th>Normoxic Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>9</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>70.6±2.2</td>
<td>71.3±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180±1</td>
<td>180±2</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>30.3±6.3</td>
<td>30.3±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>11.5±0.8</td>
<td>12.1±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>[Hb], g/dl</td>
<td>15.3±0.2</td>
<td>15.3±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Hct, %</td>
<td>45.1±0.8</td>
<td>46.0±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>VO2 max, ml/kg·min⁻¹</td>
<td>64.2±1.2</td>
<td>61.5±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>vVO2 max, km/h</td>
<td>19.6±0.6</td>
<td>19.0±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>VT2, % VO2 max</td>
<td>89.7±1.5</td>
<td>88.7±1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. Hypoxic and normoxic groups are groups that included only two training sessions at the velocity corresponding to the second ventilatory threshold (VT2) in their usual weekly training schedule and performed under hypoxic or normoxic condition, respectively. %Body fat is the percentage of body fat determined according to Durnin and Womersley (16). [Hb], hemoglobin concentration; Hct, hematocrit; VO2 max, maximal oxygen uptake determined in the normoxic incremental test; vVO2 max, the lowest running speed associated with VO2 max in the normoxic incremental exercise test. VT2 was determined during the normoxic incremental test. NS, no significant difference between hypoxic and normoxic groups.

Experimental Design

As shown in Fig. 1, the study was organized in four successive phases: a basal medical examination, the pretraining treadmill performance evaluation, the training process, and the posttraining treadmill performance evaluation.

Basal medical examination. Two weeks before the beginning of the training period, each subject came to the laboratory for anthropometric measurements, physical examination, resting electrocardiography, and echocardiography recordings. To verify their exercise and hypoxic tolerance under careful cardiac monitoring, all athletes also performed maximal graded cycle tests in normoxia and hypoxia. These tests did not reveal any abnormality that could prevent the subjects from being included in the experimental protocol.

Pre- and posttraining treadmill performance evaluation. In the week before and after the training intervention, all of the subjects performed three exercise tests on a motorized treadmill (Gymrol 2500 SP, Tecmachine), which were separated by at least 24 h of rest: 1) a treadmill incremental exercise test (IET) to exhaustion in Nor [IETN; inspired O2 fraction (FIO2) = 20.9%], 2) a treadmill IET to exhaustion in Hyp (IETH; FIO2 = 14.5%, equivalent to an altitude of 3,000 m); and 3) a normoxic all-out test at pretraining VO2 max. For a given subject, all tests were performed at the same time of day in a climate-controlled environment (21–23°C).

Training program. During the 6 wk of the study, both groups continued their usual training program (5 sessions/week), including their two weekly sessions at VT2 that were performed in the laboratory. All of the laboratory training sessions were performed under careful supervision of an experienced physician. For the group who trained in normoxia (Nor group), VT2 was determined during the IETN, and for the group who trained in hypoxia (Hyp group), VT2 was determined during the IETH. Each VT2 session began with a 10-min warm-up at 50% VO2 max (<VT1), followed by two periods at VT2 (time run at VT2 specified in Fig. 1), separated by 5-min recovery at 60% VO2 max. For the Hyp group, the subjects trained under hypoxic conditions only during the running periods at VT2 by breathing through face masks connected to a mixing chamber via appropriate tubing. Warm-up and recoveries were performed under normoxia. The training load during the laboratory sessions was organized into two 3-wk periods in which the exercise duration at VT2 increased progressively (Fig. 1). At the 4th wk, the training velocity was readjusted to maintain an exercise heart rate (HR) corresponding to the one achieved at the first training session. Throughout the study, each athlete underwent a total of 12 controlled laboratory training sessions. No athletes withdrew from the study before the achievement of the posttraining treadmill performance evaluation, and none complained of health complications throughout the study.

Procedures

Altitude simulation. Normobaric hypoxic conditions corresponding to an altitude of 3,000 m (FIO2 = 14.5%) were simulated by diluting ambient air with nitrogen via a mixing chamber, with the dilution being constantly controlled by a PO2 probe (Alti-Train2500, Sport and Medical Technology). This device allows the inspired PO2 to be set at a predetermined value to simulate altitude. The precision of the PO2 is of ±0.82 Torr. The respiratory effort induced by the device at 6 l/s was negligible (<0.01 W).

Treadmill tests. The IETh or the IETN were performed in random order on a motorized treadmill with 0% slope, to determine VT1, VT2, VO2 max, the associated velocities, and the running economy (RE) in both conditions of oxygen availability. During each IET, the initial running speed was set at 10 km/h and increased by 1 km/h every 2-min until volitional exhaustion. Each subject was encouraged to give a maximum effort. Arterialized blood samples were obtained from the earlobe at rest, at exhaustion, as well as at the first and third minute of recovery to determine total blood lactate concentration ([La]).

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The all-out running test was performed in normoxia at pretraining $V\dot{O}_2\text{max}$, i.e., the same absolute running speed before and after training. The test began by 10-min warm-up at 60% of the subject’s $V\dot{O}_2\text{max}$ (lower than $V\dot{T}_1$ in all subjects). The subjects were then connected to the test equipments during a 5-min period of rest and immediately asked to run at their individual $V\dot{O}_2\text{max}$ for as long as possible. The transition from rest to $V\dot{O}_2\text{max}$ occurs within a 20-s delay (range 17–23 s), necessary for the treadmill to reach the desired speed. No information about the time elapsed was provided to the athletes. During this test, arterialized blood samples were obtained from the earlobe at rest, at exhaustion, as well as at the 1st and 3rd min of recovery to determine total blood [La].

**HR monitoring.** During all of the running tests, as well as during the controlled training sessions, HR was continuously monitored by telemetry (Polar Vantage, Kempeley, Finland).

**Gas exchange measurements.** During all tests, inspiratory ($V_i$) and expiratory minute ventilation ($V_e$), $V\dot{O}_2$, and carbon dioxide output ($V\dot{CO}_2$) were measured breath by breath with an open-circuit metabolic cart with rapid O2 and CO2 analyzers (Sensor Medics MSE, Yorba Linda, CA). Before each individual exercise test, the pneumotachograph was calibrated with several strokes given by a 3-liter calibration syringe. The gas analyzers were calibrated by using reference gases with known O2 and CO2 concentrations (12% O2, 5% CO2, FIO2, and fraction of O2 in the expired air (FEO2) were analyzed continuously for each breath. Therefore, $V\dot{O}_2$ was calculated in normoxia and hypoxia by the following formula, where all parameters are expressed in STPD conditions: $V\dot{O}_2 = V_i \times FIO2 - V_e \times FEO2$.

During the IET, each athlete was encouraged to give a maximal effort. Peak treadmill velocity was defined as the last achieved running speed sustained for at least 30 s. $V\dot{O}_2\text{max}$ was always defined as the highest 30-s averaged $V\dot{O}_2$ value. As previously described by Billat and Koralztein (4), $V\dot{O}_2\text{max}$ was defined as the minimal velocity at which $V\dot{O}_2\text{max}$ occurred. In detail, if $V\dot{O}_2\text{max}$ was reached during the last stage, which was maintained >90 s, that particular velocity was taken as $V\dot{O}_2\text{max}$. If that velocity eliciting $V\dot{O}_2\text{max}$ was sustained <60 s, then $V\dot{O}_2\text{max}$ was taken as the velocity at the previous stage. If that velocity eliciting $V\dot{O}_2\text{max}$ was maintained between 60 and 90 s, then $V\dot{O}_2\text{max}$ was considered to be equal to the velocity during the previous stage plus the half velocity increase between the last two stages, i.e., (1 km/h)/2 = 0.5 km/h (29).

Ventilatory thresholds were assessed by using established criteria (3, 49). $V\dot{T}_1$ corresponds to the break point in the plot of $V\dot{CO}_2$ as a function of $V\dot{O}_2$. At that point, the ventilatory equivalent for O2 ($V\dot{E}/V\dot{O}_2$) increases without an increase in the ventilatory equivalent for CO2 ($V\dot{E}/V\dot{CO}_2$). $V\dot{T}_2$ was located between $V\dot{T}_1$ and $V\dot{O}_2\text{max}$, when $V\dot{E}/V\dot{CO}_2$ starts to increase while $V\dot{E}/V\dot{O}_2$ continues to increase.

The oxygen pulse ($O_2p$) was calculated as the ratio between $V\dot{O}_2$ and HR, also representing stroke volume times arteriovenous oxygen difference [$\Delta(a-v)O_2$] (30). RE was defined as the rate of $V\dot{O}_2$ for a given submaximal work rate (9). Therefore, RE corresponds to the 1-min average of the $V\dot{O}_2$ values recorded at the end of the 12 km/h stage during each IET. This speed was lower than $V\dot{T}_1$ for all of the subjects in both environmental conditions and allows an estimation of RE for an exercise intensity expected to be mainly aerobic. To provide additional insights in the effect of IHT on RE, we also determined RE at 18 km/h in IETN and at 15 km/h in IETH. These running speeds amounted to ~92 and 90% of the respective normoxic and hypoxic $V\dot{O}_2\text{max}$, corresponding to recommended speed for RE determination in athletes (10).

**Blood O2-carrying capacity and lactate.** On the first day of the treadmill performance evaluation before and after training, blood was drawn from an antecubital vein in each group to immediately measure
hematocrit (Hct) and hemoglobin concentration. Earlobe blood samples obtained during all running tests were also immediately analyzed for total blood [La] by an enzymatic method.

**Oxygen saturation.** During each exercise test, hemoglobin saturation was monitored continuously by earlobe pulse oximetry (Oxymetrix-Medical System).

### VO₂ Kinetics

**Data modeling.** To describe the VO₂ kinetics (\[VO₂(t)\]) during the all-out test, we used a mathematical model with two exponential functions (2):

\[
\dot{V}O_2(t) = \dot{V}O_2b + A_1[1 - e^{-(t-t_d1)/(\tau_1)}]U_1 + A_2[1 - e^{-(t-t_d2)/(\tau_2)}]U_2 \tag{I}
\]

where \(U_1 = 0 \) for \( t < t_d1 \) and \( U_1 = 1 \) for \( t \geq t_d1 \); \( U_2 = 0 \) for \( t < t_d2 \) and \( U_2 = 1 \) for \( t \geq t_d2 \); \( \dot{V}O_2b \) is the rate of \( \dot{V}O_2 \) at rest before the start of the all-out test; \( A_1 \) and \( A_2 \) are the asymptotic amplitudes for the first and second exponential terms, respectively; \( \tau_1 \) and \( \tau_2 \) are the time constants and represent the time to reach 63% of the total amplitude of the respective fast and slow \( \dot{V}O_2 \) components; \( t_d1 \) and \( t_d2 \) represent the time delays for the fast and the slow components, respectively. As the initial cardiodynamic phase of the \( \dot{V}O_2 \) adjustment to a rest-to-exercise transition does not influence the fast component of \( \dot{V}O_2 \) (36) and because we focused on the fast and slow components of the \( \dot{V}O_2 \) response, the cardiodynamic phase was excluded from analysis by removing the data from the first 20 s of the all-out test. The parameters of the model were determined with an iterative procedure that minimizes the sum of the mean squares of the differences between the model \( \dot{V}O_2 \) estimates and the corresponding \( V_{O2} \) measurements. To exclude aberrant breaths from analysis, breath-by-breath \( \dot{V}O_2 \) values that were greater than three standard deviations from the modeled \( \dot{V}O_2 \) were removed and assumed to represent events unrelated to the physiological response of interest (31, 39). These values represented <1% of the total data.

**Slow component of \( \dot{V}O_2 \) kinetics.** Because the asymptotic value of the second exponential term is not necessarily reached at the subject’s exhaustion, the amplitude of the slow component was computed as \( A_2^* \) (7):

\[
A_2^* = A_2[1 - e^{-(t_{lim} - t_d2)/(\tau_2)}] \tag{2}
\]

where \( t_{lim} \) is the time at the end of the all-out exercise test. Moreover, to compare the amplitude of the \( \dot{V}O_2 \) slow component at consistent time before and after training, we also calculated the amplitude of the \( \dot{V}O_2 \) slow component achieved posttraining when the subjects attained their pretraining \( t_{lim} \) value (\( A_{2old}^* \)).

**\( O_2 \) deficit calculation.** According to Whipp and Ozyener (51), the fast component of the \( \dot{V}O_2 \) kinetics represents an “expected \( \dot{V}O_2 \)” whereas the slow component is the manifestation of an “excess \( \dot{V}O_2 \)” occurring later during exercise (i.e., after \( t_d2 \)). Consequently, the oxygen deficit (\( O_2 \)def) is estimated from the area between the fast-component response curve and the fast-component asymptote (13):

\[
O_2\text{def} = (t_d1 \times A_1) + (\tau_1 \times A_1) \tag{3}
\]

where \( O_2\text{def} \) is in milliliters, \( t_d1 \) and \( \tau_1 \) are in seconds, and \( A_1 \) is in milliliters per second.

**Computation of the time sustained at pretraining \( \dot{V}O_2 \) max.** Besides \( t_{lim} \) which could be considered as a mechanical parameter of endurance performance (reflecting the total mechanical work performed at \( \dot{V}O2_{max} \)), we also calculated a metabolic correlate (Eq. 4), from the time sustained while the athlete ran at >95% of pretraining \( \dot{V}O_2 \) max \((\dot{V}O_2 @ \dot{V}O_2_{max})\). This percentage was chosen to account for a 5% random error in the determination of \( \dot{V}O_2 \) max (33) and also because all athletes did not necessarily reach 100% \( \dot{V}O_2 \) max in \( t_{lim} \) testing (13).

\[
t_{lim}@\dot{V}O_2_{max}(s) = t_{lim} - TA_{\dot{V}O_2_{max}} \tag{4}
\]

where \( t_{lim} \) is the time to exhaustion while the athletes ran at the pretraining minimal velocity associated with \( \dot{V}O_2 \) max \((s) \), and the time to attain \( \dot{V}O_2 \) max \((TA_{\dot{V}O_2_{max}}) \) corresponds to the time necessary to reach 95% of pretraining \( \dot{V}O_2 \) max \((s) \). Depending on whether the \( \dot{V}O_2 \) kinetics were better described by a mono- or a double-exponential model, \( TA_{\dot{V}O_2_{max}} \) was computed from the equations below.

1) For the monoeponential model (fast component in Eq. 1)

\[
TA_{\dot{V}O_2_{max}} = t_d1 - \tau_1 \times \ln[1 - (0.95 \times \dot{V}O_2_{max} - \dot{V}O_2b)/A_1] \tag{1}
\]

2) For the double-exponential model (fast + slow component in Eq. 1)

\[
TA_{\dot{V}O_2_{max}} = t_d2 - \tau_1 \times \ln[1 - (0.95 \times \dot{V}O_2_{max} - \dot{V}O_2b - A_1/A_2)] \tag{1}
\]

### Evaluation of Training

All athletes were asked to report their individual training schedule into detailed training logs, including duration, distance, and intensity of each training sessions. Laboratory as well as field work bouts were taken into account to provide both quantitative and qualitative characterization of the overall training load. Duration and intensity of the training sessions performed out of the laboratory were assessed based on the running velocity spread out in four intensity zones: low (<\(v\)VT1), moderate (\(v\)VT1 - \(v\)VT2), heavy (\(v\)VT2 - \(v\)VO2 max), and severe intensity (\(>v\)VO2 max).

### Statistics

Whether a mono- or biexponential model better described the \( \dot{V}O_2 \) kinetics during the all-out tests was determined using a Fisher test. We used the bootstrap method to obtain an estimation of the accuracy of the parameters describing the \( \dot{V}O_2 \) kinetics (7, 8, 17). This method, creating 1,000 different samples of the same size than the original data set, allows the determination of a coefficient of variation for each mathematical parameter on an individual basis.

Data were first tested for distribution normality and variance homogeneity. Subsequently, the differences between groups before the training period were analyzed with the Mann-Whitney procedure. To test for both treatment (Hyp vs. Nor) and time (before vs. after) effects on each of the measurements during the training period, we used a two-way ANOVA for repeated measures. When significant modifications were found, the Student-Newman-Keuls post hoc procedure was performed to localize the difference. Pearson linear regression analysis was used to determine any potential linear relationship between variables. All statistical analyses were performed with the SigmaStat 3.0 software (SPSS, Chicago, IL), and the level of significance was chosen for \( P < 0.05 \). Values are means ± SE.

### RESULTS

The anthropometric and treadmill performance characteristics of the athletes are shown in Table 1. No significant differences were reported between the two experimental groups before the training period. Moreover, in both groups, the training period did not modify anthropometric and blood parameters, including body mass (Hyp after: 70.5 ± 2.2 kg, nonsignificant (NS); Nor after: 71.3 ± 2.2 kg, NS), hemoglobin (Hyp after: 15.8 ± 0.5 g/dL, NS; Nor after: 15.7 ± 0.5 g/dL, NS), and Hct (Hyp after: 46.4 ± 1.5%, NS; Nor after: 46.9 ± 1.2%, NS).

### Training Load

**Laboratory training sessions.** At the beginning of the study according to the training environment, the Hyp group trained at a significantly lower running speed (Table 2). These different running speeds corresponded to the same exercise HR, whether expressed in absolute (Hyp: 166 ± 3 vs. Nor: 172 ± 3 beats/min; NS) or in relative value (Hyp: 96 ± 1 vs.
training on results of the IETH. Only the Hyp group significantly improved submaximal and maximal running velocities (Table 3) under hypoxia. Indeed, \( v_{\text{VT1}} \), \( v_{\text{VT2}} \), and \( v_{\text{VO2 max}} \) increased, respectively, by +7%, +8%, and +5% after IHT. \( v_{\text{VO2 max}} \) associated with these velocities improved in the same proportions by +7, +7, and +5%, respectively (Fig. 2A), but RE did not change. The maximum \( O_2 p \) \( (O_2_{\text{pmax}}) \) improved (+5%) only in the Hyp group after IHT (Table 3). Conversely, the Nor group demonstrated no improvement of all of these parameters under hypoxic conditions.

Exercise Capacity in Normoxia

IET. \( v_{\text{VO2 max}} \) improved significantly by +4% and +3% and \( v_{\text{VT2}} \) increased significantly by +5% and +3% in the Hyp and Nor groups, respectively \((P < 0.05)\), under normoxic conditions (Table 3). However, only the Hyp group significantly enhanced \( O_{\text{pmax}} \) as well as \( O_{2} \) at \( v_{\text{VT2}} \) by +5 and +7%, respectively \((P < 0.05)\), with no modification of the RE (Fig. 3).

Table 3. Running velocities, running economy, and selected maximal physiological parameters measured in normoxic and hypoxic incremental tests before and after the 6-wk training period

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypoxic Group</th>
<th>Normoxic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>( v_{\text{peak}} ), km/h</td>
<td>( 20.5 \pm 0.2 )</td>
<td>( 17.7 \pm 0.3 )</td>
</tr>
<tr>
<td>Normoxia</td>
<td>( 20.9 \pm 0.2 )*</td>
<td>( 18.4 \pm 0.2 )†</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>( 19.8 \pm 0.4 )</td>
<td>( 17.2 \pm 0.4 )</td>
</tr>
<tr>
<td>( v_{\text{VT2}} ), km/h</td>
<td>( 15.4 \pm 0.2 )</td>
<td>( 16.6 \pm 0.2 )‡</td>
</tr>
<tr>
<td>Normoxia</td>
<td>( 18.0 \pm 0.2 )</td>
<td>( 18.9 \pm 0.1 )†</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>( 15.4 \pm 0.2 )</td>
<td>( 15.1 \pm 0.3 )</td>
</tr>
<tr>
<td>( O_2_{\text{pmax}}, \text{ml terminal beats}^{-1} \text{kg}^{-1} )</td>
<td>( 2.1 )</td>
<td>( 1.8 )</td>
</tr>
<tr>
<td>Normoxia</td>
<td>( 2.8 )</td>
<td>( 1.9 ) NS</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>( 3.0 )</td>
<td>( 2.4 )</td>
</tr>
<tr>
<td>( O_{2} ) leveling off (yes/no), no.</td>
<td>( 1.05 \pm 0.02 )</td>
<td>( 1.04 \pm 0.03 )</td>
</tr>
<tr>
<td>Normoxia</td>
<td>( 1.05 \pm 0.02 )</td>
<td>( 1.04 \pm 0.03 )</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>( 1.04 \pm 0.02 )</td>
<td>( 1.06 \pm 0.01 )</td>
</tr>
</tbody>
</table>

Values are means ± SE. Pre and Post, before and after the 6-wk training period; \( v_{\text{peak}} \), \( v_{\text{VO2 max}} \), \( v_{\text{VT1}} \), \( v_{\text{VT2}} \); running velocities achieved during the incremental exercise test at exhaustion, at \( O_{2_{\text{pmax}}} \) and at the second and first ventilatory threshold, respectively; \( O_{2_{\text{pmax}}} \), HR\(_{\text{max}}\), \( V_{\text{E}}_{\text{max}} \), \( [L_a]_{\text{max}} \), and \( \text{RE}_{\text{max}} \); maximal values for oxygen pulse, heart rate, ventilation, blood lactate, and respiratory exchange ratio, respectively; \( O_{2} \) leveling off, number of subjects who have/have not reached a \( O_{2} \) plateaus at the end of the incremental test. Significant differences between Pre and Post values: *\( P < 0.05 \), †\( P < 0.05 \), ‡\( P < 0.03 \).
O₂pmax increased (+6%) only in the Hyp group after IHT (Table 3). The Nor group disclosed no significant changes, neither for exercise V˙O₂ nor for RE.

All-out exercise test. The all-out exercise tests were performed in normoxia at the same absolute running velocity before and after training, i.e., pretraining vV˙O₂ max. After training, this speed amounted to 96 and 97% of the posttraining vV˙O₂ max for the Hyp and Nor group, respectively, therefore corresponding to the same relative running speed in both groups. As shown in Fig. 3, training significantly enhanced Tlim in the Hyp but not in the Nor group (+35 vs. +10%, P < 0.05). Similar changes in the time sustained at pretraining vV˙O₂ max were obtained when the transition period required for treadmill speed stabilization was subtracted from Tlim (+35 vs. +10%, P < 0.05). Concomitantly, the end-exercise V˙O₂ achieved during the all-out test increased in the Hyp group only (+6%, P < 0.05), whereas the maximal [La] values remained unchanged after training (Table 4).

The kinetics of V˙O₂ response of a typical subject from the Hyp and Nor group are shown in Fig. 4. Training did not modify parameters of the fast component of V˙O₂ kinetics (Table 4) and O₂def remained unchanged (Hyp group: before 3,319 ± 266 vs. after 3,372 ± 469 ml O₂, NS; Nor group: before 2,793 ± 239 vs. after 2,563 ± 169 ml O₂, NS). A slow
Table 4. Training effects on the time until exhaustion and the parameters of the V\textsubscript{O\textsubscript{2}} kinetics

<table>
<thead>
<tr>
<th></th>
<th>Hypoxic Group</th>
<th></th>
<th>Normoxic Group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>Values</td>
<td>CV mean (%)</td>
<td>Values</td>
<td>CV mean (%)</td>
</tr>
<tr>
<td>t\textsubscript{d1}, s</td>
<td>18.0 ± 1.7</td>
<td>13.9</td>
<td>20.5</td>
<td>19.3 ± 2.2</td>
</tr>
<tr>
<td>t\textsubscript{r1}, s</td>
<td>31.0 ± 4.4</td>
<td>19.8</td>
<td>22.4</td>
<td>29.7 ± 2.1</td>
</tr>
<tr>
<td>A\textsubscript{1}, ml/min</td>
<td>3,605 ± 159</td>
<td>3.825 ± 202</td>
<td>3.3</td>
<td>3.680 ± 138</td>
</tr>
<tr>
<td>t\textsubscript{d2}, s</td>
<td>136.1 ± 15.3</td>
<td>16.0</td>
<td>28.7</td>
<td>179.1 ± 13.7</td>
</tr>
<tr>
<td>t\textsubscript{r2}, s</td>
<td>157.3 ± 38.1</td>
<td>25.4</td>
<td>44.5</td>
<td>163.4 ± 39.7</td>
</tr>
<tr>
<td>A\textsubscript{2}, ml/min</td>
<td>475 ± 101</td>
<td>352 ± 92</td>
<td>30.2</td>
<td>269 ± 65</td>
</tr>
<tr>
<td>A\textsubscript{3} old, ml/min</td>
<td>475 ± 92</td>
<td>(n = 5)</td>
<td>(n = 5)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>TA V\textsubscript{O\textsubscript{2} max}, s</td>
<td>344 ± 66</td>
<td>207 ± 34</td>
<td>187 ± 32</td>
<td>264 ± 61</td>
</tr>
<tr>
<td>T\textsubscript{lim} @ V\textsubscript{O\textsubscript{2} max}, s</td>
<td>228 ± 47</td>
<td>577 ± 75*</td>
<td>319 ± 46</td>
<td>281 ± 73</td>
</tr>
<tr>
<td>EE V\textsubscript{O\textsubscript{2}}</td>
<td>62.7 ± 1.3</td>
<td>66.8 ± 1.5*</td>
<td>62.0 ± 0.4</td>
<td>61.6 ± 1.1</td>
</tr>
<tr>
<td>EE HR, beats/min</td>
<td>176 ± 3</td>
<td>179 ± 3</td>
<td>177 ± 3</td>
<td>178 ± 4</td>
</tr>
<tr>
<td>EE [La], mmol/l</td>
<td>7.7 ± 0.6</td>
<td>7.2 ± 0.7</td>
<td>9.5 ± 0.8</td>
<td>9 ± 1.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. CV mean coefficient of variation estimated by the bootstrap method; A\textsubscript{1} and A\textsubscript{2}, amplitude terms for V\textsubscript{O\textsubscript{2}}; t\textsubscript{d1} and t\textsubscript{d2}, time delays to onset of each component; t\textsubscript{r1} and t\textsubscript{r2}, time constants of each component; A\textsubscript{3 old}, amplitude of the postraining slow component obtained when the subject reached his pretraining T\textsubscript{lim} (only 5 and 6 subjects demonstrated a slow component of the V\textsubscript{O\textsubscript{2}} kinetics in the hypoxia and normoxia groups, respectively); EE V\textsubscript{O\textsubscript{2}}, end-exercise oxygen uptake; TA V\textsubscript{O\textsubscript{2} max}, time to reach pretraining V\textsubscript{O\textsubscript{2} max}, T\textsubscript{lim} at V\textsubscript{O\textsubscript{2} max}, time sustained at pretraining V\textsubscript{O\textsubscript{2} max}; EE HR and EE [La], end-exercise values for heart rate and blood lactate, respectively. Significant differences between Pre vs. Post values, *P < 0.05.

**DISCUSSION**

**Major Findings**

This study demonstrates that, when the hypoxic sessions of an IHT program features moderate duration (24–40 min) and high intensity (VT\textsubscript{2}), significant improvements of V\textsubscript{O\textsubscript{2} max} are obtained in already trained athletes, not only at altitude but also at sea level. Despite similar total training load (i.e., absolute and relative values), no such amelioration in the maximal rate of O\textsubscript{2} fluxes was observed in a control group exercising under permanent normoxia. The second finding of this work is that the present IHT program significantly lengthened T\textsubscript{lim}, specifically in the Hyp group, without significant changes in V\textsubscript{O\textsubscript{2}} kinetics. These results suggest that IHT did not change the control of O\textsubscript{2} flux adjustment to high-intensity exercise in competitive runners. Moreover, T\textsubscript{lim} improvement in the Hyp group was correlated neither with V\textsubscript{O\textsubscript{2} max} nor with ventilatory thresholds changes.

Maximal Aerobic Capacity and Ventilatory Thresholds

In hypoxia. This study demonstrates that the present IHT program elicits significant improvements of maximal and submaximal running velocities under hypoxia (vV\textsubscript{O\textsubscript{2} max}, vVT\textsubscript{2},...
and \( v_{VT1} \). Accordingly, all of the athletes of the Hyp group required an increase of the training velocity under hypoxia (+0.4 km/h) to maintain the initial HR values throughout the 6-wk IHT program. Since no RE changes resulted from the training period, the improvements observed in running speeds are mainly due to significant increases in the associated \( O_2 \) flux rates in the Hyp group only (\( \dot{V}O_2_{max} \) and \( \dot{V}O_2 \) at the ventilatory thresholds). These findings expand the observations reported by Terrados et al. (43) in professional cyclists, demonstrating a specific increase of exercise capacity under hypoxia after altitude training only. Moreover, the present data also extend to already trained athletes the results obtained in untrained subjects, in which some consensus has been reach about the beneficial effect of hypoxic training on \( \dot{V}O_2_{max} \) at altitude (21, 47).

At sea level, the effects of IHT on the aerobic performance capacity at sea level remains highly debated, especially in trained subjects (32). Despite both groups improving their running velocities at sea level (\( \dot{V}O_2_{max} \) and \( \dot{V}O_2 \) at \( VT_2 \)) in quite near proportions, the underlying physiological adaptations may well have been different. \( \dot{V}O_2_{max} \) and \( \dot{V}O_2 \) increased in the Nor group, through concomitant changes of \( \dot{V}O_2 \) and RE values (although not statistically significant). Conversely, one important result of this study is that the running speed improvements of the Hyp group were associated with increases in \( \dot{V}O_2_{max} \) and \( \dot{V}O_2 \) at \( VT_2 \), with no RE alterations. These findings suggest that a normoxic training effect was present in the Nor group over the 6-wk period and that this effect was further potenalized by IHT in the Hyp group, through an additional effect of IHT vs. normoxic training on aerobic power. This amelioration of aerobic power in the Hyp group is further exemplified by the increased \( \dot{V}O_2 \) at exhaustion during the all-out test. According to the specific intensity and duration of the present hypoxic training sessions, our results are in agreement with previous observations (38, 44, 46). Studies reporting no improvement in \( \dot{V}O_2_{max} \) after IHT either used lower hypoxic exercise intensity (at \( VT_1 \)) (46) or shorter hypoxic exercise bouts (0.5–1 min) (44). On the other hand, similar increase in \( \dot{V}O_2_{max} \) has been recently reported with an IHT model, including longer periods of hypoxic exercise (2–12 min) (38). A specific oxygen-sensing transcription factor, the hypoxia-inducible factor-1α (HIF-1α), is expected to play a pivotal role for the functional adaptations to hypoxic training (1, 11, 47). Of note, the duration and intensity of the hypoxic exercise bouts included in the present IHT model are in good agreement with the properties of HIF-1α expression at the cellular level in humans. Not only does the half-time of the HIF-1α response to hypoxia fall in the range of 12–13 min (25), but also the magnitude of this response varies exponentially with the degree of Hyp in the physiological range (26). These observations further reinforce the necessity to combine a minimum duration and intensity of hypoxic exercise in IHT programs, to reduce oxygen pressure in the active muscle (37) and achieve a substantial HIF-1α response, resulting in peripheral muscle adaptations. Consequently, present and previous results suggest that the combination of sufficient hypoxic exercise intensity and duration within IHT programs is of paramount importance to obtain significant performance ameliorations in already trained athletes. An additional advantage of the hypoxic sessions in the present IHT design (i.e., 19% of the total training time in the present study) is the possibility to maintain the usual training load, which could also participate in the \( \dot{V}O_2_{max} \) improvement that we observed.

Some of our findings let us consider that peripheral adaptations might have been involved. We observed that \( O_2p_{max} \) improved in the Hyp group only after IHT. Because \( O_2p \) represents the product of stroke volume with \( \Delta(a-v)O_2 \), and because invasive experiments have shown that \( O_2p_{max} \) is largely determined by \( \Delta(a-v)O_2 \) (35, 42), \( O_2p_{max} \) is likely to have increased via an \( \Delta(a-v)O_2 \)-mediated mechanism after IHT, suggesting an enhanced tissue \( O_2 \) extraction. Because our study was not designed to investigate \( O_2 \) extraction, further studies are needed to verify this hypothesis. Nevertheless, several muscle changes have already been observed after hypoxic training programs in endurance-trained subjects, such as larger deoxygenation in active muscles (28) and, although not reaching significance, a 36% increase in capillary density (43), supporting the concept of an improved \( O_2 \) extraction after IHT. Moreover, modelization studies have suggested that exercising in Hyp may increase the relative contribution of peripheral factors (i.e., muscle perfusion, peripheral diffusion, and mitochondrial capacity) to \( O_2 \) delivery and utilization (14, 15, 19, 48). We believe that the intensity and duration of the hypoxic exercise bouts included in the present IHT program are sufficient to induce the signaling cascade initiated by HIF-1α, leading to molecular and tissue changes within the exercising skeletal muscles of our Hyp subjects (34). The results disclosed in the two companion papers of our study, appearing in the present issue, also support this concept, at least in part. Conversely, as far as \( O_2 \) transport is concerned, we observed that hemoglobin and Hct were similar in both groups, before vs. after training, in agreement with previous reports (22, 28, 34, 38, 43). Together with the unchanged maximum HR (HR\(_{max}\)), these results suggest that \( O_2 \) delivery capacity is unlikely to represent a major cause of the \( \dot{V}O_2_{max} \) improvement of the Hyp group after IHT.

\( T_{lim} \) at \( v\dot{V}O_2_{max} \) and Oxygen Kinetics

A major finding of the present study is that \( T_{lim} \) is specifically improved after IHT (+35%) but unchanged after normoxic training. Due to the exponential shape of the running velocity/time-to-fatigue relationship, our observed 3.7-min lengthening of \( T_{lim} \) suggests that larger improvements of endurance time at lower velocities may have occurred. Thus this observation can be considered as a hallmark of an enhanced performance capacity in middle and long-distance running events. Consequently, \( T_{lim} \) lengthening in the present study extends previous findings, demonstrating that 3 wk of IHT dramatically delayed fatigue during a submaximal constant-load test in elite triathletes (45).

To date, the mechanisms leading to \( T_{lim} \) improvement remain poorly understood. It has been proposed that normoxic training may lengthen the endurance time at a given absolute running velocity, due to increases of \( \dot{V}O_2_{max} \) and/or submaximal running velocity (velocity at the lactate threshold), reducing the relative running speed the subjects have to sustain (i.e., expressed in percentage of the posttraining \( \dot{V}O_2_{max} \)) (12, 23). In the present study, we did not find any correlation between \( T_{lim} \) changes and alterations of maximal (\( \dot{V}O_2_{max} \)) and sub-
maximal (ventilatory thresholds) \( V_{\text{O}_2} \) nor with their associated velocities (i.e., \( \nu V_{O_2 \text{max}} \), \( \nu V_{\text{T}2} \), and \( \nu V_{\text{T}1} \)). Therefore, it is unlikely that changes in \( O_2 \) fluxes (i.e., \( V_{O_2 \text{max}} \)) and/or running velocities (i.e., \( \nu V_{O_2 \text{max}} \)) are the major causes of the \( T_{\text{lim}} \) improvement that we observed. However, as \( V_{O_2 \text{max}} \) and ventilatory thresholds improved concomitantly with \( T_{\text{lim}} \) in the Hyp group, we cannot rule out the possible relevance of these changes, and this point warrants further investigations.

Alternatively, \( V_{O_2} \) kinetics have also been proposed as a determinant of \( T_{\text{lim}} \) that may be improved after normoxic training. To the best of our knowledge, the effect of hypoxic training on \( V_{O_2} \) kinetics has never been reported, especially in already trained athletes. A speeding of \( V_{O_2} \) adjustment has been proposed as a potential contributor of the delayed fatigue after high-intensity training at sea level (13). These changes are expected to reduce the reliance toward anaerobic metabolisms for energy provision, which have been reported to amount to \( \sim 15\% \) of energy expenditure during such \( T_{\text{lim}} \) testing (18). Nevertheless, we failed to observe such a mechanism, as illustrated by an unchanged fast component of \( V_{O_2} \) kinetics, leading to unaltered \( O_2 \) deficit in both experimental groups. Additionally, sea level training was often demonstrated to reduce the amplitude of the \( V_{O_2} \) slow component, thereby contributing to improve exercise tolerance and delay fatigue (20). Again, we recorded no alterations in the \( V_{O_2} \) slow component, even when expressed at consistent exercise time before vs. after IHT (A2old). Taken together, the unchanged fast and slow components of \( V_{O_2} \) kinetics suggest that the dynamic control of \( O_2 \) fluxes is not a likely contributor to \( T_{\text{lim}} \) changes after IHT in already trained athletes. Therefore, neither the rates of \( O_2 \) fluxes nor \( V_{O_2} \) kinetics significantly account for the \( T_{\text{lim}} \) lengthening that we observed, suggesting that IHT may improve \( T_{\text{lim}} \) by specific, hypoxic-related adaptations.

A 2.5 times longer \( T_{\text{lim}} \) at \( V_{O_2 \text{max}} \) was observed in the Hyp group after IHT, indicating an improved capacity to sustain high levels of \( O_2 \) fluxes close to or above pretraining \( V_{O_2 \text{max}} \), before exhaustion occurs. This observation appears, despite unchanged [La] values recorded at exhaustion during the all-out test after vs. before IHT. Collectively, these findings suggest either a slower rate of blood lactate accumulation and/or a better tolerance of high levels of blood lactate after IHT. This might be associated with a concomitant amelioration of metabolite exchange and/or removal, contributing to enhance cellular homeostasis, thereby delaying the time at which fatigue occurs. This idea has already been suggested by a previous study, demonstrating that \( T_{\text{lim}} \) is related to the capacity of lactate exchange and removal. Due to its coupled transport with \( H^+ \) (27), an improved lactate exchange and removal could have contributed to slow down the progressive lowering of muscle pH while running at pretraining \( \nu V_{O_2 \text{max}} \). Although purely speculative in the present study, additional supports for the peripheral hypothesis underlying the improvement of endurance performance capacity after IHT are presented in the two following papers appearing in this issue. The second companion paper of the present study suggests that IHT induces qualitative mitochondrial changes leading to an enhanced channeling of energy within the muscle cell, whereas the third companion paper shows that IHT training induces transcriptional changes, potentially mediated by HIF-1\( \alpha \), leading to enhanced metabolite exchanges and improved aerobic metabolism within the skeletal muscle cell.

**Limitations of the Study**

A limitation of the present study is related to the IHT design and management of training intensities. First, we speculated that \( V_{\text{T}2} \) might be more effective in IHT designs than lower (i.e., \( V_{\text{T}1} \)) or higher (i.e., \( \nu V_{O_2 \text{max}} \)) training intensities, because of the achievement of a unique combination of intensity and duration of the hypoxic training stimulus. Moreover, this protocol was chosen as it allowed the usual training load of athletes to be unaltered (Table 2). Nevertheless, we did not test this hypothesis in the present study by including additional experimental groups training at either lower or higher intensity during the hypoxic sessions. Therefore, it remains to be determined whether different hypoxic training intensities and durations elicit similar beneficial effects on endurance performance capacity in already trained athletes. Especially including a group trained at, or close to, \( V_{\text{T}1} \), would have been helpful and remains to be done.

Second, only the Hyp group required its laboratory running speed to be increased at the end of week 3 to maintain the initial HR level, raising the question as to whether the Hyp group may have trained harder than the Nor group. We believed that this possibility is not supported by the unchanged \( V_{\text{T}2} \) at the end vs. the beginning of training, when expressed in percentage of postraining \( \nu V_{O_2 \text{max}} \), indicating that both groups trained at the same relative intensity during the laboratory sessions (Table 3). Nevertheless, a different time course of training speed and \( \nu V_{O_2 \text{max}} \) improvements may have led to a transient increase (i.e., weeks 4 and 5) in relative training intensity, thereby potentially acting as a confounding factor in our results. We believe that this possibility should have been counterbalanced by the transient lower relative intensity that could be expected in the Hyp group just before training speed adjustments (i.e., weeks 2 and 3). Therefore, differences in relative training intensity, if present, may have probably played a minor role in the present study. Nevertheless, future studies need to incorporate serial \( V_{O_2 \text{max}} \) testing to completely eliminate this possibility.

On the same token, an additional \( T_{\text{lim}} \) test performed at the new \( \nu V_{O_2 \text{max}} \) after training (same relative intensity before vs. after training) could have been helpful to clarify the role of \( V_{O_2 \text{max}} \) and \( \nu V_{O_2 \text{max}} \) in the improvement of \( T_{\text{lim}} \) that we observed in the Hyp group (+35%). However, since both groups improved \( V_{O_2 \text{max}} \) in quite near proportions, the posttraining \( T_{\text{lim}} \) was performed at a similar relative intensity in both groups (96 vs. 97% of the postraining \( V_{O_2 \text{max}} \) in the Hyp and Nor group, respectively). Therefore, although not performed at 100% of postraining \( V_{O_2 \text{max}} \), the changes in relative testing intensity are unlikely to account for the \( T_{\text{lim}} \) improvements that we observed.

On a methodological standpoint, it can be argued from our relatively low maximum respiratory exchange ratio and maximum [La] values (Table 3) that \( V_{O_2 \text{max}} \) might have been underestimated. Nevertheless, 67–89% of the subjects reached a true \( V_{O_2} \) plateau (i.e., always at least 6 of 9 subjects in each test), and the \( \nu HR_{\text{max}} \) were close to (97%) the theoretical \( HR_{\text{max}} \). Moreover, \( V_{O_2 \text{max}} \) as well as \( HR_{\text{max}} \) were significantly higher.
on the treadmill than the ones previously obtained on the cycle ergometer at the time of subjects’ basal medical examination. Conversely, these parameters were similar between IET and Tlim testing. Therefore, we believe that true VO2 max has been at least closely approached. On the other hand, our RE values were estimated at moderate mainly aerobic (12 km/h) and high (18 and 15 km/h in normoxia and hypoxia, respectively) running speeds, yielding results consistent with previous reports (40, 41, 50). Nevertheless, since they were not measured at steady state during constant load exercise, these RE values must be interpreted with caution, until appropriate RE testing is done by further investigations.

In conclusion, the present study investigates the effects of a carefully calibrated IHT program, designed to avoid reduction in training load, by including high-intensity (VT2) and moderate-duration (24–40 min) hypoxic sessions, into the usual normoxic training of already trained athletes. Such an IHT model provides an original framework, in which the metabolic stimulus is enhanced through hypoxic sessions, without altering the mechanical component of the usual training load. Significant improvements of several indexes of aerobic performance capacity were observed not only at altitude but also at sea level, including VO2 max and Tlim. Additionally, IHT did not significantly modify VO2 kinetics such that Tlim lengthening was correlated neither with changes in the rate of VO2 adjustment nor with VO2 max and ventilatory thresholds. Collectively, these findings suggest that the enhanced endurance performance capacity obtained with IHT might be due to specific muscle adaptations to hypoxic training. This hypothesis is further explored in the two following companion papers of our study appearing in the present issue.

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