Living high-training low increases hypoxic ventilatory response of well-trained endurance athletes

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VENTILATORY ACCLIMATIZATION is defined as “a time-dependent change in ventilatory magnitude resulting from exposure to a changed environment” (7). On acute exposure to hypoxia, one of the earliest and most consistent physiological responses is an increase in minute ventilation (V̇E), mediated primarily by hypoxic stimulation of the peripheral chemoreceptors (7). Ventilatory acclimatization to chronic hypoxic exposure, however, displays a triphasic response. The initial, rapid increase in V̇E is followed by ventilatory depression after 20–30 min of hypoxia (8), and then over a period of hours to days, there is a gradual and progressive, time-dependent increase in V̇E (1, 9, 20).

Ventilatory acclimatization to altitude is facilitated by increased sensitivity of the peripheral chemoreceptors to hypoxia, estimated by the hypoxic ventilatory response (HVR) in humans (3). The HVR has been reported to correlate with the magnitude of increase in V̇E on arrival at altitude (19), and several studies have demonstrated an increase in the HVR during natural altitude acclimatization (31, 33, 39) or intermittent hypoxic exposure (11, 21). An enhancement of the HVR during acclimatization is viewed as a positive adaptation, because an increase in V̇E improves alveolar O2 pressure and raises arterial oxygenation while at altitude (19). An increase in the HVR allows ventilatory acclimatization to altitude to proceed, despite an inhibitory influence of respiratory alkalosis (7) and a decrease in the original hypoxic stimulus.

In contrast to altitude acclimatization, endurance training appears to decrease the HVR. Endurance-trained athletes demonstrate a blunted HVR compared with untrained, healthy individuals (4, 34), and a decrease in the HVR has been observed after endurance training in previously untrained subjects (22). Furthermore, when endurance training was conducted during 1 wk of an intermittent hypoxic exposure protocol (30 min/day, 4,500-m simulated altitude) that did increase the HVR in nontraining control subjects, no
change in the HVR was reported (21). Therefore, endurance training and adaptation to hypoxia appear to have opposing effects on the HVR.

Altitude training is commonly used by athletes for specific competition preparation or to provide an alternative physiological stress at some other point in the training macrocycle. Additionally, discontinuous hypoxic exposure in the form of “living-high-training low” (LHTL) is a popular practice among athletes because this strategy allows exposure to hypoxia with concurrent maintenance of training intensity at or near sea level (14). The time course of ventilatory acclimatization to altitude is well documented in healthy, untrained individuals (3, 7), but the effect of discontinuous hypoxic exposure on ventilatory acclimatization in well-trained endurance athletes has received little attention. In this study, we hypothesized that athletes undergoing LHTL at a simulated altitude of 2,650 m while training at 600 m would exhibit ventilatory acclimatization and an augmented HVR. Previous observations have indicated that not all athletes respond to the hypoxic stimulus of altitude in a uniform manner (5); therefore, we also hypothesized that athletes would exhibit substantial individual variation in ventilatory acclimatization and enhancement of the HVR in response to LHTL. Finally, it has been suggested that individual differences in ventilatory acclimatization to altitude could be the result of differences in the preexisting HVR (29), which is known to vary markedly between individuals (16). Consequently, we hypothesized that athletes with a higher HVR would demonstrate a greater degree of ventilatory acclimatization during the early stages of LHTL.

METHODS

Subjects. Thirty-three male endurance-trained athletes (9 triathletes and 24 cyclists) gave written informed consent to participate in the study, which was approved by the Australian Institute of Sport Ethics Committee. Subjects were divided into three groups matched for initial maximal O2 consumption. It was not possible to initially randomize all subjects into the three groups, because the altitude house could accommodate only eight people at any one time. Accordingly, the experimental design necessitated four independent waves of testing to study 33 subjects. The three groups comprised an LHTL consecutive (LHTLc) group (n = 12), an LHTL intermittent (LHTLi) group (n = 10), and a control (Con) group (n = 11). Normal lung function (13) was verified in all subjects using a spirometer (model AS600, Minato Medical Science, Osaka, Japan). Subject characteristics for each group are presented in Table 1.

Subjects maintained their own training during the study and kept a daily log of duration, mode, and frequency of training beginning ≥1 wk before and continuing throughout the experimental period.

Overview of experimental design. The LHTLc group spent 8–10 h/day for 20 consecutive nights in a room enriched with N2, simulating an altitude of 2,650 m in normobaric hypoxia (16.3% inspired O2, ~710 Torr ambient barometric pressure). The LHTLi group also spent a total of 20 nights sleeping in hypoxia at a simulated altitude of 2,650 m, comprising 4 “blocks” of 5 nights in hypoxia, with each block interspersed by 2 nights of sleep in normoxia at a natural altitude of 600 m above sea level.

Table 1. Physiological and anthropometric characteristics of subject population

<table>
<thead>
<tr>
<th>Con</th>
<th>LHTLc</th>
<th>LHTLi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, cm</td>
<td>177.6 ± 5.4</td>
<td>181.0 ± 8.0</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>71.3 ± 6.0</td>
<td>73.8 ± 10.7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>26.2 ± 4.5</td>
<td>27.2 ± 5.7</td>
</tr>
<tr>
<td>VO2max, l/min</td>
<td>4.75 ± 0.22</td>
<td>4.66 ± 0.48</td>
</tr>
<tr>
<td>ml·kg⁻¹·min⁻¹</td>
<td>67.0 ± 4.3</td>
<td>64.8 ± 7.9</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>5.39 ± 0.55</td>
<td>6.34 ± 1.04</td>
</tr>
<tr>
<td>FEV1.0, liters</td>
<td>4.54 ± 0.84</td>
<td>4.97 ± 0.72</td>
</tr>
</tbody>
</table>

Values are means ± SD. Con, control; LHTLc and LHTLi, live high-train low consecutive and intermittent, respectively; VO2max, maximal O2 uptake; FVC, forced vital capacity; FEV1.0, forced expiratory volume in 1 s.

(Canberra, Australia). Details of the altitude house operation have been described in detail previously (2). The Con group slept in dormitory-style accommodation under Canberra ambient conditions during the entire experimental protocol. Daytime hours were spent in ambient conditions.

Each subject completed a baseline resting HVR test (Pre) within 2 wk before hypoxic exposure, with the HVR remeasured on the morning after 1 (N1), 3 (N3), 10 (N10), and 15 (N15) nights of hypoxia. A final measurement was taken 2 days after the 20th night of hypoxia (Post). Baseline HVR measures were repeated in 24 subjects to determine the typical error of measurement (TEM) for the HVR (18).

HVR. The HVR was determined using a modification of the method of Weil et al. (38), with all tests conducted in a fasted state, in normobaric normoxia, within 2 h of waking. No alcohol or caffeine was consumed for 12 h preceding an HVR test. Immediately before the test, subjects rested in a chair for 10 min. Throughout the test, subjects were given reading material and listened to quiet music to minimize behavioral influences on resting breathing patterns. At the start of the test, subjects breathed room air for 5 min through a two-way respiratory valve (model R2700, Hans Rudolph, Kansas City, MO) while wearing a nose clip, and Ve was measured using a 0–100 l/min heated pneumotachometer (model 3719, Hans Rudolph) coupled to a proprietary pneumotach system (model RSS 100HR, Hans Rudolph). The pneumotachometer was calibrated before every test with a 1-liter volumetric syringe. Expired O2 and CO2 were sampled continuously from a mouth port and measured using an Ametek S-3A O2 analyzer and CD-3A CO2 analyzer, respectively (Applied Electrochemistry, Pittsburgh, PA). Immediately before each test, gas analyzers were calibrated with three precision-grade gases (BOC Gases, Sydney, Australia) containing 18.16, 14.51, and 8.96% O2 and 5.50, 2.49, and 0.00% CO2, respectively. Heart rate (HR) and blood O2 saturation (SpO2) were estimated by finger-tip pulse oximetry (model 505-US, Criticare Systems, Waukesha, WI). Analog output signals from the pneumotach system, the gas analyzers, and the pulse oximeter were sampled at 50 Hz and time synchronized using custom data acquisition software.

After the subjects breathed room air, 100% N2 was gradually added to the inspired gas mixture over 6–9 min. The test was terminated when SpO2 remained at or below 75% for three successive breaths. During the test, small amounts of 100% CO2 were added to maintain isocapnia at the resting, eucapnic end-tidal PCO2 (PetCO2) determined immediately before each test. The manual addition of N2 and CO2 to the inspired gas mixture was facilitated by real-time display of O2 and CO2 fractions on a computer monitor linked to the analog outputs of the gas analyzers.

J Appl Physiol • VOL 93 • OCTOBER 2002 • www.jap.org
HVR data analysis. To allow time for stable resting ventilatory patterns to be achieved, only the last 60 s of room air breathing were used for calculation of the HVR, resting Ve, and PETCO2. Ventilatory data were initially expressed as individual breath-by-breath values. The average SpO2 during each breath was calculated, and end-tidal Po2 (PETO2) and PETCO2 were determined for each breath. In cases of ventilatory instability (e.g., swallowing and coughing) where abnormal Ve values were observed, three successive breaths were averaged. All data points were then smoothed using a rolling average with an interval of five breaths. Linear regression was conducted on the Ve-SpO2 relationship, and the slope of the line (HVRlin, 1 min⁻¹, %⁻¹) was calculated. A least squares curve fit was applied to the Ve-PETO2 relationship using Prism software (GraphPad Software, San Diego, CA) according to the following hyperbolic equation

\[ V_E = V_0 + \left[ A/(PETO2 - B) \right] \]

where \( V_0 \) is the derived horizontal asymptote when PETO2 approaches infinity, A is the hyperbolic “shape” parameter (HVRhyp), such that the greater the value of A, the greater the vertical asymptote for Ve when PETO2 is low. For the constant B, a value of 26 Torr, instead of 32 Torr as originally described by Weil et al. (38), was chosen, because our criteria for termination of the HVR test allowed PETO2 to consistently fall 5–6 Torr below that of Weil et al., who used 40 Torr as their termination criterion. The use of 26 Torr, rather than 32 Torr, for the constant B was found to be justified, since on numerous occasions PETO2 values fell below 32 Torr toward the end of the HVR test. In these cases, using 32 Torr as the nadir for PETO2 resulted in a negative value for parameter A and a poor curve fit (\( r < 0.05 \)). A mean \( r = 0.88 \) across all trials was found for the hyperbolic curve fit relating Ve and PETO2 when B was 26 Torr.

Ventilatory acclimatization. The change in resting PETCO2 (\( \Delta PETCO2 \)) from Pre to N1, N3, N10, and N15 was determined for each subject and used as an index of ventilatory acclimatization (29).

Statistical analysis. Values are means ± SD. Each dependent variable was analyzed using a two-way analysis of variance (ANOVA) with repeated measures over time (group × day). For subjects who completed dual baseline HVR measures, only results from the second test were included in the two-way ANOVA. Significant main effects and interactions were subsequently analyzed using Tukey’s honestly significant difference post hoc procedure. To examine the specific effect of return to normoxia on the HVR, data were pooled for LHTLc and LHTLi, and N15 was compared with Post using a paired t-test. This procedure was considered appropriate, because both groups were exposed to the hypoxic stimulus and the pooling maximized statistical power. For each subject, HVRlin and HVRhyp were each plotted against time, from Pre to N15, and linear regression was performed on the relationship to produce an “HVR slope.” Therefore, units for the linear response slope are change in the HVR (expressed as 1 min⁻¹, %⁻¹) for HVRhyp per day (ΔHVR/day). Differences in the mean response slope between groups were examined with a one-way ANOVA, as were differences in mean training volume (h/wk). The within-group SD for the response slope was compared between LHTLc and Con and between LHTLi and Con using a t-test for independent samples. Individual responders vs. nonresponders were determined by significant deviation of the HVR slope from zero using a standard F test. Strong responders were defined as those subjects whose response slopes were greater than zero (\( P < 0.05 \)) for HVRlin and HVRhyp variables. Moderate responders were defined as those subjects whose response slopes were greater than zero (\( P < 0.05 \)) for HVRlin or HVRhyp or were greater than zero (\( P < 0.1 \)) for both variables. Nonresponders were defined as subjects whose response slopes for HVRlin and HVRhyp variables were not significantly (\( P > 0.1 \)) different from zero. Relationships between variables were examined using linear regression. Statistical significance was accepted at \( P < 0.05 \), and all analyses were completed using Statistica software version 5.0 (StatSoft, Tulsa, OK).

HVR typical error and internal validity. The within-subject SD, also called TEM, was determined from the dual baseline values for HVRlin and HVRhyp variables, resting Ve, and PETCO2. Additionally, linear regression was conducted on the relationship between HVRlin and HVRhyp for each time point during the experimental protocol.

Treatment of outliers. In 3 of the 222 HVR tests conducted (1 occasion each in 3 subjects), HVRlin values were above the group upper quartile by >1.5 times the interquartile range of the group. These scores were defined as outliers according to standard statistical procedure (36), and on each occasion, those subjects whose response slopes were greater than zero, despite HVRlin values within the acceptable range. The error in these three tests was most likely due to technical error in the measurement of SpO2. Accordingly, data for two tests conducted at N15 and one at N3 were corrected by fitting a fourth-order polynomial to the PETO2-PETO2 curve obtained from their tests recorded at N10 and N1, respectively. The PETO2 values recorded during the outlier tests were then used to estimate the SpO2 values, and the HVRlin slope was recalculated using these corrected SpO2 values. One test recorded at N3 yielded a raw value of 2.14 1 min⁻¹, %⁻¹ and was corrected to 0.91 1 min⁻¹, %⁻¹, and two tests recorded at N15 yielded raw values of 3.52 and 3.17 1 min⁻¹, %⁻¹ and were corrected to 1.23 and 1.28 1 min⁻¹, %⁻¹, respectively.

RESULTS

HVRlin. The mean HVRlin values at Pre were not significantly different between groups (Fig. 1A), indicating similar baseline hypoxic chemosensitivity in all groups. However, there was a significant group × day interaction (\( P < 0.001 \)). In LHTLc, the HVRlin was increased above Pre at N3, N10, N15, and Post (\( P < 0.05 \)) and greater than Con at N1, N3, N10, N15, and Post (\( P < 0.05 \)). Additionally, HVRlin was greater in LHTLc than in LHTLi at N15 (\( P < 0.05 \)). In contrast, for LHTLi, HVRlin was increased above Pre only at N15, where it was also greater than Con (\( P < 0.05 \)). For pooled LHTLc and LHTLi data, HVRlin was lower (\( P = 0.04 \)) at Post than at N15 (0.68 ± 0.40 vs. 0.85 ± 0.39 1 min⁻¹, %⁻¹).

HVRhyp. There was a significant group × day interaction (\( P < 0.001 \)) for HVRhyp (Fig. 1B). Post hoc analysis revealed no significant difference between groups at Pre, but in LHTLc, HVRhyp was elevated above Pre and was greater than Con at N10, N15, and Post (\( P < 0.05 \)). For LHTLi, HVRhyp was greater than Pre and Con only at N15 (\( P < 0.05 \)). For pooled LHTLc and LHTLi data, HVRhyp was lower (\( P = 0.004 \)) at Post than at N15 (203 ± 99 vs. 294 ± 142 parameter A units).
for HVR hyp variable, the mean response for HVR lin (Fig. 1) was significant between HVR lin and HVR hyp. The mean HVR hyp slope for LHTLi (13.3 ± 3.7 h/wk) was significantly different from Con at N1, N3, N10, N15, and Post (P < 0.05). Within groups, PET CO2 was lower in LHTLi than Con at N1, N3, N10, N15, and Post (P < 0.05). Within groups, PET CO2 was lower than Pre at N3 and N10 for LHTLi and LHTLc (P < 0.05). At N15 it was lower than Pre in LHTLi (P < 0.05) and tended to be lower in LHTLc (P = 0.07). No differences were observed between or within groups over time for resting VE at any point during the study.

Effect of HVR on ventilatory acclimatization. When LHTLi and LHTLc data were pooled, the Pre HVR lin was correlated (r = -0.44, P = 0.04) with ΔPET CO2 from Pre to N1 (Fig. 4A) and with ΔPET CO2 from Pre to N3 (r = -0.47, P = 0.03; Fig. 4B). However, this relationship was not significant thereafter.

Training volume. Average training volume was higher in LHTLc than in Con (15.8 ± 3.7 vs. 11.0 ± 3.0 h/wk, P < 0.05), but neither differed significantly from LHTLi (13.3 ± 3.7 h/wk).

Correlation between HVR lin and HVR hyp. The correlation between HVR lin and HVR hyp was significant at all time points (0.70 < r < 0.90, P < 0.001).

HVR slope. The group main effect for the HVR slope was significant for HVR lin (P < 0.001) and HVR hyp (P < 0.001). The mean HVR lin slope was greater in LHTLc than in LHTLi and Con [0.047 ± 0.039 vs. 0.016 ± 0.014 (P < 0.05) and 0.0028 ± 0.0079 ΔHVR/day (P < 0.05)]. For the HVR hyp variable, the mean response slopes for LHTLc and LHTLi (11.21 ± 6.55 and 7.75 ± 6.04 ΔHVR/day, respectively) were greater than for Con (0.63 ± 3.12 ΔHVR/day, P < 0.05). However, LHTLc was not significantly different from LHTLi.

Responders vs. nonresponders. The SD of the HVR lin slopes was greater for LHTLc than for Con (SD = 0.019 vs. 0.008 ΔHVR/day, P = 0.01). The SD of the HVR lin slopes tended to be greater for LHTLi (SD = 0.014) than for Con; however, the difference was not significant (P = 0.08). Similar results were obtained for the HVR hyp slope [SD = 6.35 ΔHVR/day for LHTLc, 3.12 ΔHVR/day for Con (P = 0.03), and 6.04 ΔHVR/day for LHTLi (P = 0.051)]. Seven subjects responded strongly to the experimental treatment, seven responded moderately, and eight did not respond (Fig. 2). For the LHTLc group, 5 of 12 subjects were strong responders, 4 were moderate responders, and 3 were nonresponders. For the LHTLi group, 2 of 10 subjects were strong responders, 3 were moderate responders, and 5 were nonresponders. One subject in the Con group displayed a significant response; however, the magnitude of his response was lower than that of any subject defined as a responder in either treatment group. Additionally, a significant correlation between the HVR hyp and the HVR lin slope (LHTLc and LHTLi subjects only) was observed (r = 0.84, P < 0.001).

Resting PET CO2 and VE. A significant group × day interaction (P < 0.001) was observed for resting PET CO2 (Fig. 3). Post hoc analysis did not reveal a significant difference between groups at Pre. However, resting PET CO2 was lower in LHTLc and LHTLi than Con at N1, N3, N10, N15, and Post (P < 0.05). Within groups, PET CO2 was lower than Pre at N3 and N10 for LHTLc and LHTLi (P < 0.05). At N15 it was lower than Pre in LHTLi (P < 0.05) and tended to be lower in LHTLc (P = 0.07). No differences were observed between or within groups over time for resting VE at any point during the study.
The rate of change in the HVR is likely to be influenced by the strategy of hypoxic exposure employed and endurance training. Our results are the first to demonstrate that the strategy of LHTL (8–10 h/day, 2,650-m simulated altitude) can enhance the HVR within 10 days in endurance-trained athletes. In nontraining subjects, an increased HVR was found after 6 days of intermittent hypoxic exposure (30 min/day, 4,500 m simulated altitude). However, when the same hypoxic protocol was combined with simultaneous endurance training, there was no increase in the HVR (21), suggesting that endurance training may attenuate the increase in HVR with hypoxia. When 2 wk of an identical intermittent hypoxic training protocol was conducted, a trend toward an increased HVR was observed (22), and after 5 wk of a similar protocol (45 min/day, 5 days/wk, 2,500-m simulated altitude) the HVR increased significantly (25). When nontraining subjects lived at a natural altitude of 3,810 m, a significant increase in the HVR was observed within 2–4 days (10, 31, 32, 39), but when a hypoxic stimulus of similar magnitude (3,800-m simulated altitude) was administered for only 2 h/day, a significant increase in the HVR required 5 days (11). Therefore, we observed an earlier increase in the HVR than in studies where subjects engaged in endurance training were exposed to intermittent hypoxia for up to 45 min/day (22, 25) but a slower increase than in nontraining subjects exposed to a greater hypoxic stimulus, and especially when hypoxia was continuous in nature (10, 21, 31, 32, 22).

The main findings of this study were that, in well-trained endurance athletes, 1) the HVR increased during 20 nights of LHTL exposure at a simulated altitude of 2,650 m, with the overall response being more pronounced during consecutive nightly exposure than intermittent block exposure; 2) individual increases in the HVR were variable, with stronger individual responses tending to occur during consecutive nightly exposure; 3) PETCO2 decreased progressively during the first 3 nights of hypoxia, and this was related to the magnitude of the Pre HVR; and 4) resting VE remained at baseline levels, despite the decrease in PETCO2.

**Effect of LHTL on HVR.** In the present study, augmentation of the HVR was found for the linear slope of the VE-SpO2 regression and parameter A in the treatment groups only. Therefore, our results support the general consensus that hypoxic exposure induces an increase in the HVR, as reported during natural altitude acclimatization (10, 31, 32, 39), after intermittent hypoxic exposure (11, 21, 25), or after 8 h of mild hypoxia (9). The increase in the HVR observed in this study occurred despite previous findings that short-term endurance training depresses the HVR (22, 23) and endurance-trained athletes display blunted hypoxic chemoresponsiveness (4, 34). Furthermore, the HVR was enhanced, even though the LHTLc group completed a greater weekly training volume than the Con group.

**DISCUSSION**

The absolute TEM of the HVRlin method was 0.13 l/min⁻¹·%⁻¹ or 35.4% of the mean (%TEM). The TEM of the HVRhyp method was 51.8 parameter A units or 46.2% of the mean. The TEM of resting VE was 1.24 l/min, and the TEM of resting PETCO2 was 1.38 Torr, which were equivalent to %TEM values of 16.7 and 3.6%, respectively.
39). Hence, endurance training and/or shorter daily periods of hypoxia may attenuate the rate of increase in peripheral chemosensitivity, but a greater hypoxic stimulus might induce faster gains in the HVR.

The notion that hypoxia-induced enhancement of the HVR may be attenuated by returning to normoxia is supported by the finding that the mean HVRin slope was lower in LHTLi than LHTLc. The attenuation in LHTLi could have been an effect of the 2 nights of sleep in normoxia after each block of hypoxic exposure, since a decrease in the HVR was observed at Post. Evidence of a diminished HVR on return to sea level was also observed several days after altitude sojourns at 3,810 m lasting 6 days (10, 31, 32, 39) or 12 days (31). In contrast, Forster et al. (10) observed an elevated HVR 45 days after return to sea level from an altitude of 3,100 m for 45 days and were not engaged in endurance training. Additionally, these investigators did not employ the same HVR technique used in the present study, making direct comparisons between studies difficult. Overall, the available evidence suggests that a depression of the HVR does occur within several days of return to normoxic conditions.

Previous investigators have reported low chemoresponsiveness in endurance athletes (4, 34), and the mean Pre HVRin (0.39 ± 0.25 l·min⁻¹·%⁻¹) and HVRin (117.4 ± 78.1 parameter A units) values in our study were lower than those previously reported for healthy, untrained individuals (16, 21, 38, 40). However, our subjects also displayed high interindividual variability of the HVR, as previously reported in healthy untrained individuals (30). Therefore, despite the endurance-trained status of our subjects, low hypoxic chemosensitivity does not appear to be a uniform trait among this population.

Responders vs. nonresponders. Previous research indicates that all endurance athletes do not respond positively to LHTL (5). The variability of the HVR slopes was significantly greater in LHTLc and tended to be greater in LHTLi than in Con. This indicates that individual variation in the HVR due to endurance training alone is exacerbated by the addition of nightly hypoxic exposure. The greater incidence of strong responders in the LHTLc group provides additional support for the notion that consecutive nightly exposure is a greater stimulus to enhance the HVR than intermittent block-style exposure.

Ventilatory acclimatization to hypoxia. PETCO₂ has been described as “a well-defined index of effective ventilation and acclimatization” (29). In the present study, we found a decrease in PETCO₂ after 1 night (~8–10 h) at a simulated altitude of 2,650 m, indicative of an increased V̇E during the overnight hypoxic exposure. Previous studies have reported that PETCO₂ decreases during acute altitude exposure and also declines progressively over several days to weeks (1, 19, 29). Similar evidence of a progressive decrease in PETCO₂ during the first 3 nights of LHTL was found in the present study, suggesting that repeated nightly exposure to hypoxia induced hyperventilation, which had a cumulative effect on depletion of CO₂ body stores. PETCO₂ was not further depressed at N10 than at N3; hence, ventilatory acclimatization to 2,650 m was probably attained after 3 consecutive nights of exposure to hypoxia. However, peak values for HVR were not obtained until after 15 nights of hypoxia. The magnitude of depression in PETCO₂ at all points during LHTL was less than that reported for equivalent periods of continuous altitude exposure at 4,300 m (1, 29), but in these studies, sea-level residents required ~10 days at altitude to achieve ventilatory acclimatization. Therefore, ventilatory acclimatization to 2,650 m simulated altitude appeared to have been achieved more rapidly than in nontraining subjects residing at 4,300 m natural altitude, but the absolute magnitude of depression in PETCO₂ required to achieve ventilatory acclimatization was less in the present study. The effect of training per se on the time course of ventilatory acclimatization at a given altitude remains to be elucidated.

An important finding was the significant (although only moderate) correlation between Pre HVRin and ΔPETCO₂ after 1 and 3 nights of hypoxic exposure. After 10 nights of exposure to hypoxia, even subjects with low initial HVR scores displayed some depression of PETCO₂; hence, the correlation between Pre HVRin and ΔPETCO₂ at N10 (and N15) was not significant. This suggests that the rate of ventilatory acclimatization was more rapid in those subjects with greater initial hypoxic chemosensitivity. Our results are consistent with the findings of Huang et al. (19), who reported a significant positive correlation between baseline HVR and resting V̇E after 4 days at 4,300 m, and Reeves et al. (29), who reported a significant positive correlation between sea-level HVR and arterial O₂ saturation after 1 day at 4,300 m. In each of these studies, the magnitude of the correlation was only moderate, but, collectively, the results indicate that at least part of the variability in ventilatory acclimatization to hypoxia is related to the magnitude of the preexisting HVR.

It is well known that hypocapnia attenuates the ventilatory response to hypoxia (28, 38) and blunts the increase in resting V̇E on arrival at altitude (19). During each HVR measurement, we maintained PETCO₂ at the eucapnic level determined at the onset of each test, and since PETCO₂ for the LHTLc and LHTLi groups was diminished during the experimental period, the true increase in HVR may have been greater than observed. Interestingly, we found little change in resting V̇E within 2 h of return to normoxia, suggesting that the depression of PETCO₂ was likely a result of ventilatory acclimatization during overnight hypoxia leading to decreased CO₂ body stores, and not a short-term effect of elevated V̇E during the HVR test itself. Because resting V̇E in normoxia was not blunted, some consequence of hypoxic exposure must have led to a stimulation of V̇E, such that the inhibitory effect of hypocapnia was balanced out. At least two factors could have led to such an effect: I) increased sympathetic activation as a result of hypoxic exposure, which has been shown to contribute to increased resting metabolic rate

J Appl Physiol • VOL. 93 • OCTOBER 2002 • www.jap.org
(27), which in turn contributes to increased $V_E$ (20), and 2) a change in the $PCO_2$ set point of the respiratory control mechanism (6). A limitation of the present study is that we did not assess sympathetic activation, nor did we measure basal metabolic rate or hypercapnic ventilatory response.

**Methodological considerations.** We employed two distinct methods of analyzing data collected from the HVR technique developed by Weil et al. (38): 1) the linear relationship of $\Delta V_E$ vs. $\Delta P_{O_2}$ (HVR$_{lin}$) and 2) the hyperbolic relationship of $\Delta V_E$ vs. $\Delta P_{ETCO_2}$, the so called “shape parameter A” (HVR$_{hyp}$). The %TEM for the HVR$_{lin}$ and HVR$_{hyp}$ variables was large compared with measures such as maximal $O_2$ uptake ($\text{L/min}$; TEM = 2.2%) or blood lactate at threshold (mmol/L; TEM = 13.3%) (12). Two studies that examined variability of the HVR also reported relatively high coefficients of variation for between-day comparisons, with values of 19.4% (30) and 36% (40). Hopkins (18) states that a realistic threshold for assessing whether a real change has occurred is nearly twice the TEM. In the present study, we observed an increase in the mean HVR$_{in}$ up to 4.3 times TEM in the LHTLi group and 2.1 times TEM in the LHTLi group. The mean HVR$_{hyp}$ was increased by up to 3.6 and 2.4 times TEM in the LHTLi and LHTLi groups, respectively. Therefore, despite the relatively high between-day variance in the HVR, we were still able to detect significant differences, since the increase in the HVR in the treatment groups, and, in particular, the LHTLi group was much greater than the imprecision of measurement.

The isocapnic HVR technique developed by Weil et al. (38) has been widely used as an index of hypoxic chemoresponsiveness in humans, reported as parameter A (16, 26, 30, 37) or the slope of the $V_E$-$P_{O_2}$ linear regression line (15, 17, 19, 21–24, 29, 31, 32, 39). Few studies have reported both (28, 35, 38), and no studies were located that tracked changes in both variables over time. This study was the first to investigate changes in linear slope and parameter A during hypoxic acclimatization. The correlation between parameter A and the slope of the $V_E$-$P_{O_2}$ regression line reported by van Klaveren and Demedts (35) was $r = -0.41$. We found substantially higher correlation coefficients of 0.71–0.89 over the course of the experiment (we have presented the HVR slope by convention as a positive value; therefore, the correlation between parameter A and linear slope was positive). Additionally, a strong correlation ($r = 0.84$) was observed between the HVR$_{hyp}$ and HVR$_{in}$ slopes. Therefore, the hyperbolic and linear methods of analysis display high internal validity and track changes in the HVR over time within individuals, also with a high degree of internal validity. We observed slightly different results between the HVR$_{in}$ and HVR$_{hyp}$ variables, but this result was largely due to the presence of one atypical subject in the LHTLi group who displayed high parameter A scores relative to the slope.

**Conclusions.** This study provides strong evidence that well-trained endurance athletes exhibit ventilatory acclimatization and an enhancement of the HVR during consecutive nightly and intermittent block models of LHTL. The results were consistent whether the HVR data were analyzed as a linear function of the $V_E$-$P_{O_2}$ relationship or as a hyperbolic function of the $V_E$-$P_{ETCO_2}$ relationship. Consecutive nightly exposure to hypoxia was associated with a stronger response than intermittent LHTL exposure. The preexisting HVR level displayed high interindividual variability and was positively correlated with the magnitude of ventilatory acclimatization during the first 3 nights of hypoxic exposure. An important finding was that resting $V_E$ remained unchanged on return to normoxia, despite a decrease in $P_{ETCO_2}$ after hypoxic exposure. This suggests that as little as 1 night of mild hypoxic exposure is sufficient to induce changes in the respiratory control system.

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