Variability of Erythropoietin Response to Sleeping at Simulated Altitude: A Cycling Case Study

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Living at moderate altitude (2000 to 3000 m) and training near sea level improves performance in some but not all athletes. Chapman et al reported that runners who improved their 5-km running performance after altitude exposure (ie, “responders”) displayed a greater altitude-induced increase in serum erythropoietin (sEPO) than “nonresponders.” The difference in sEPO between groups was statistically significant, although the mean sEPO concentration of the responders after 30 hours at 2500 m was only 3% greater than that of nonresponders (19.0 ± 4.6 vs 18.4 ± 7.3 mU/mL). These authors concluded that the slightly higher sEPO in responders was sufficient to increase red-cell volume, maximum aerobic capacity, and distance-running performance. Whether the improvement in running performance after living high and training low can be solely attributed to accelerated erythropoiesis has recently been debated.

A large individual variation in the sEPO response to hypoxia has been reported that might be attributable to differences in hypoxia-inducible factor 1-alpha (HIF-1α)—the ubiquitous controller of oxygen-regulated gene expression. It is also possible, however, that the training load preceding altitude exposure could influence the sEPO response. High-intensity exercise can stimulate increases in sEPO secondary to arterial hypoxemia. In similar findings, preliminary research at the Australian Institute of Sport has shown a tendency for oxyhemoglobin saturation while sleeping at simulated moderate altitude to be lower after heavy training days than after “recovery” days, with sleeping oxyhemoglobin saturation inversely related to daily training load (kJ) over 2 weeks (Gawthorn, unpublished observation).

We had the unique opportunity to work with one of the best cycling hill climbers in Australia, who allowed us to modifying his training volume to evaluate the influence of training load on the sEPO response to simulated altitude exposure.

Methods

We monitored a professional male cyclist over a 1-month period. The athlete provided informed consent before starting the study, which was approved by the human ethics committee of the Australian Institute of Sport. The study design...
(Figure 1[A]) was for duplicate measures of sEPO after sleeping for 2 nights (8 h/night) in simulated altitude (2800 m) after 2 “light” periods and 2 “heavy” periods of cycling training in and around Canberra, Australia (~600 m). Training distance, time, cadence, and power output were measured with an SRM power meter (Pro-
fessional Version, Jülich, Germany). Simulated normobaric altitude was created with an Air Dome II (AIS, Canberra, Australia/AirSep, Buffalo, NY) based on atmospheric air-compression and filtration principles. Oxyhemoglobin saturation and heart rate were recorded throughout the night using a portable pulse oximeter (Nellcor, Pleasanton, Calif).

Fasted, resting, venous blood samples were drawn in normoxic conditions, approximately 25 to 50 minutes after hypoxic exposure had ceased, at 6:30 AM on the 2 mornings before and 2 mornings after each exposure to simulated altitude. Whole blood was analyzed via a flow cytometer (ADVIA hematology analyzer, Bayer Diagnostics, Tarrytown, NY) for hematocrit (Hct) and hemoglobin concentration (Hb) within 12 hours of collection. These parameters were monitored to assess plasma volume shifts in response to heavy training to allow corrections to sEPO. Serum samples were frozen at –80°C. Within 8 weeks of blood collection, sEPO was measured in duplicate using an Immulite EPO assay (Diagnostic Products, Los Angeles, Calif).

The cyclist’s maximum aerobic power (VO\text{2\,max}) was measured 1 week after the completion of the case study using an automated, custom-built indirect calorimetry system based on the Douglas-bag principle. A double-baseline measure of hemoglobin mass was taken during the first week of testing using the recently validated carbon-monoxide-rebreathing technique.\textsuperscript{7} Both of these parameters were quantified only to characterize the athlete.

## Results

### Physical Characteristics

The cyclist was 29.0 years of age and 1.75 m tall with a body mass of 65 kg. His VO\text{2\,max} and hemoglobin mass were 85 mL · kg\textsuperscript{–1} · min\textsuperscript{–1} and 15.3 g/kg, respectively.

### Training

Daily training distance ranged from 72 to 118 km/d in the light periods to 182 to 224 km/d in the heavy periods. The mean (± SD) total training distance for the 3 days before altitude exposure was 287 ± 6 km and 604 ± 2 km for the light and heavy periods, respectively (Figure 1[A]). The mean power output for each ride ranged from 142 to 173 W (including time at 0 W), averaging 161 W on the light days and 169 W on the heavy days (~45% maximum aerobic power). Training rides were performed over semimountainous terrain with infrequent climbs (<4 to 6 and <10 to 15 minutes duration). Interim training followed the cyclist’s normal pattern of training with a daily distance of approximately 100 km. Time spent at simulated altitude averaged 8.4 ± 1.0 h/night, ranging from 7.5 to 9.8 hours. Complete pulse-oximeter data were only available for 4 nights of exposure as a result of equipment malfunction (light 2, heavy 2). For the 4 nights of data recorded, average sleeping percentage oxyhemoglobin saturation and heart rate were 94% ± 0% (range 90% to 99%) and 43 ± 2 beats/min (range 41 to 47 beats/min), respectively.

### Blood Measures

Compared with prealtitude values, the cyclist’s Hct and Hb remained similar throughout the month of training (Figure 1[B]). The mean Hct was 43% (range
41% to 44%), and mean Hb was 14.5 g/dL (range 14.4 to 14.7 g/dL). Neither Hct nor Hb was consistently influenced by training or altitude exposure.

Repeatability of the assay for quantifying sEPO was acceptable with 24/32 results within 0.5 mU/mL (5%) and the remaining 5 of the 16 pairs differing by 8% to 17%. The intra-assay coefficients of variation for sEPO for 14 of the 16 pairs were 8% or less and for the remaining pairs were 10% and 12%. Resting sEPO before altitude exposure was ~10 mU/mL but ranged from 7.3 to 14.4 mU/mL over the 4-week period. The sEPO response to simulated altitude showed substantial variation from week to week (Figure 1B). A minimal sEPO response was observed after the first light block (8.9 vs 8.8 mU/mL). After the first heavy training period, sEPO increased by 24% (9.8 vs 12.2 mU/mL) after the first night of altitude exposure but decreased to 8.8 mU/mL 1 night later, such that the net effect of these 2 measures was a 7% increase (mean prealtitude = 9.8, mean postaltitude = 10.5 mU/mL). After the second light period sEPO consistently increased postaltitude by 38% (8.5 vs 11.8 mU/mL). Resting sEPO was highest preceding altitude in the second period of heavy training (13.3 mU/mL), decreasing by 11% after the last altitude exposure (11.8 mU/mL). No clear pattern was observed between training volume and the sEPO response to simulated altitude (light change = 18% ± 28%, heavy change = 7% ± 25%).

Discussion

Over a 1-month period, we observed a variable EPO response (~11% to +38%) to sleeping at simulated altitude (2800 m) in a professional male road cyclist. This response was not consistently modulated by training volume. More specifically, heavy and light training volumes before altitude exposure were associated with a minimal EPO response on 1 occasion, varying increases on 2 occasions, and a decrease on the other occasion. Furthermore, the 2 heavy-training periods resulted in opposite trends, with marked increases and decreases in sEPO over the first 3 measurements of the first and second periods, respectively. These results document that in at least one elite cyclist the sEPO response to simulated altitude is not a stable trait, as has been assumed by previous researchers.\(^1\)\(^3\)

Ge et al\(^3\) reported that although interindividual variation in the sEPO response to acute altitude was large, each subject’s response to a number of different altitudes (1780 to 2800 m) was consistent, with those showing the greatest sEPO response at low altitudes also showing the greatest response at higher altitudes. Although those researchers did not use athletes as subjects, they speculated that an individual’s sEPO response to altitude might be genetically predetermined. Our results bring into question this hypothesis and reveal that the sEPO response to sleeping repeatedly at ~2800 m in an elite cyclist can be quite variable.

Although our experimental design consisted of 4 separate periods of altitude exposure, it is possible that the altitude exposure preceding each trial might have influenced subsequent results. The highest prealtitude sEPO was observed before the final altitude trial, following a 10-night period of altitude exposure. The elevated resting sEPO at the end of our study is in contrast to previous research documenting a blunted sEPO response to altitude after multiple nights of exposure.\(^2\) Heinicke et al have shown, however, that “finely controlled regulation of EPO expression still
occurs after up to 22 years of weekly exposure to altitude, thereby indicating that prior intermittent altitude exposure might not down-regulate the sEPO response to subsequent acute bouts of exposure.

Residual fatigue might also offer an explanation for the elevated sEPO commencing during the final phase of monitoring and for its decrease in response to the last 2 nights of simulated altitude exposure. The preceding training blocks were usually followed by 4 days of “normal” training, equating to ~100 km/d, which was designed to act as a washout period and lessen the risk of fatigue accumulating. The final heavy training block, however, followed 10 consecutive nights of altitude exposure and training with only 2 days of washout, so residual fatigue might have influenced both the starting sEPO and the athlete’s response to simulated altitude. Inflammation can also influence the athlete’s sEPO response, and although white blood cell counts across the whole study period were not indicative of any viral or bacterial infections (data not shown), a training-induced skeletal-muscle inflammatory response cannot be ruled out.

Our results indicate that the sEPO response of an individual athlete to simulated altitude is not consistent, although the exact reason for the observed variation cannot be elucidated. In addition to providing an adequate dose of hypoxia (>2200 m for >12 h/d for >21 days), the training history and state in which an athlete presents before altitude exposure might need to be considered to maximize any possible hematological benefits of living high and training low. Further research on larger samples of athletes is required to clarify the reproducibility of the sEPO response of elite athletes to simulated altitude and the importance of elevated sEPO on subsequent performance changes when following the live high:train low approach to altitude training.

References