

# Ventilatory Responsiveness during Exercise and Performance Impairment in Acute Hypoxia

KEREN CONSTANTINI<sup>1</sup>, ANNA C. BOUILLET<sup>1</sup>, CHAD C. WIGGINS<sup>2</sup>, BRUCE J. MARTIN<sup>3</sup>,  
and ROBERT F. CHAPMAN<sup>1</sup>

<sup>1</sup>Department of Kinesiology, Indiana University, Bloomington, IN; <sup>2</sup>Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN; and <sup>3</sup>Indiana University School of Medicine, Bloomington, IN

## ABSTRACT

CONSTANTINI, K., A. C. BOUILLET, C. C. WIGGINS, B. J. MARTIN, and R. F. CHAPMAN. Ventilatory Responsiveness during Exercise and Performance Impairment in Acute Hypoxia. *Med. Sci. Sports Exerc.*, Vol. 53, No. 2, pp. 295–305, 2021. **Introduction:** An adequate increase in minute ventilation to defend arterial oxyhemoglobin saturation ( $SpO_2$ ) during hypoxic exercise is commonly viewed as an important factor contributing to large inter-individual variations in the degree of exercise performance impairment in hypoxia. Although the hypoxic ventilatory response (HVR) could provide insight into the underpinnings of such impairments, it is typically measured at rest under isocapnic conditions. Thus, we aimed to determine whether 1) HVR at rest and during exercise are similar and 2) exercise HVR is related to the degree of impairment in cycling time trial (TT) performance from normoxia to acute hypoxia ( $\Delta TT$ ). **Methods:** Sixteen endurance-trained men ( $\dot{V}O_{2peak}$ ,  $62.5 \pm 5.8 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) performed two poikilocapnic HVR tests: one during seated rest ( $HVR_{REST}$ ) and another during submaximal cycling ( $HVR_{EX}$ ). On two separate visits, subjects ( $n = 12$ ) performed a 10-km cycling TT while breathing either room air ( $F_{iO_2} = 0.21$ ) or hypoxic gas mixture ( $F_{iO_2} = 0.16$ ) in a randomized order. **Results:**  $HVR_{EX}$  was significantly ( $P < 0.001$ ) greater than  $HVR_{REST}$  ( $1.52 \pm 0.47$  and  $0.22 \pm 0.13 \text{ L} \cdot \text{min}^{-1} \cdot \%SpO_2^{-1}$ , respectively), and these measures were not correlated ( $r = -0.16$ ,  $P = 0.57$ ).  $\Delta TT$  was not correlated with  $HVR_{REST}$  ( $P = 0.70$ ) or  $HVR_{EX}$  ( $P = 0.54$ ), but differences in ventilation and end-tidal  $CO_2$  between hypoxic and normoxic TT and the ventilatory equivalent for  $CO_2$  during normoxic TT explained  $\sim 85\%$  of the variance in performance impairment in acute hypoxia ( $P < 0.01$ ). **Conclusion:** We conclude that 1) HVR is not an appropriate measure to predict the exercise ventilatory response or performance impairments in acute hypoxia and 2) an adequate and metabolically matched increase in exercise ventilation, but not the gain in the ventilatory response to hypoxia, is essential for mitigating hypoxia-induced impairments in endurance cycling performance. **Key Words:** PERIPHERAL CHEMORESPONSIVENESS, ARTERIAL OXYHEMOGLOBIN SATURATION, ALTITUDE, CYCLING, ATHLETES, EXERCISE

Large inter-individual variations exist in the extent to which maximal oxygen uptake ( $\dot{V}O_{2peak}$ ) and endurance performance are impaired with acute exposure to hypoxia (1–3); yet, the specific mechanisms leading to these vast differences between athletes are not entirely understood. With more sporting events taking place at altitude (4) and an increase in the popularity of chronic hypoxic exposure methods to enhance sea-level athletic performance, identifying factors that could help determine how the individual athlete responds to exercise in hypoxic conditions has strong practical applications. Ventilatory-related measures, such as ventilatory equivalents to  $O_2$  consumption ( $\dot{V}_E/\dot{V}O_2$ ) and  $CO_2$  production ( $\dot{V}_E/\dot{V}CO_2$ ) and reductions in arterial oxyhemoglobin saturation

( $S_pO_2$ ), have been thought to play a key role in performance impairment observed during hypoxic exercise (2,5,6). However, the literature remains equivocal as to whether these ventilatory factors are related to the gain in the ventilatory response to progressive hypoxia (7–11). Furthermore, the relationship between measures of exercise ventilation, the hypoxic ventilatory response (HVR), and a true endurance performance measures has not been determined.

First described by Weil et al. (12), the HVR test has been extensively used to better understand the complex process and determinants of ventilatory control at rest and during exercise. When this test is performed at rest, and typically under conditions of isocapnia, it is thought to represent the “isolated” response of peripheral chemoreceptors to hypoxia, which has long been suggested to contribute to overall ventilatory control (13). Thus, the isocapnic HVR test is well suited for identifying the specific effects of changes in arterial  $O_2$  tension ( $P_aO_2$ ) on minute ventilation, and it has been repeatedly used to better understand ventilatory control at rest and ventilatory responses during exercise, both in normoxia and in hypoxia (7,9,10,14,15). In our view, two problems arise with the aforementioned approach to measure resting HVR and to extend the outcomes to exercise ventilation. First, the responsiveness of peripheral chemoreceptors is augmented during exercise

Address for Correspondence: Robert F. Chapman, Ph.D., Department of Kinesiology, School of Public Health, Indiana University, 112, 1025 E. 7th St., Bloomington, IN 47405; E-mail: rfchapma@indiana.edu.

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compared with rest (7,12,16), and second, isocapnia is not normally maintained under hypoxic conditions, and partial pressure of arterial CO<sub>2</sub> (P<sub>a</sub>CO<sub>2</sub>) deviates (decreases) further from normal during exercise in hypoxia (17,18). Thus, it could be argued that relying on *resting isocapnic* HVR measures to predict ventilatory responses and patterns during exercise may be insufficient, specifically under hypoxic exercise conditions and/or during a true endurance performance task. To address these issues, few previous studies have quantified HVR during exercise (8,14,16,19), and some even performed the test under poikilocapnic conditions (20,21). Nevertheless, of the studies that have used an exercise HVR test, the only “performance” measure reported was climbing abilities of mountaineers on Mount Everest (14)—a challenging task no doubt, but one that requires a combination of different athletic as well as cognitive skills and abilities than those of endurance athletes completing continuous high-intensity aerobic tasks at low to moderate altitudes. To the best of our knowledge, the relationship between the overall integrated ventilatory response to progressive hypoxia *during exercise* and the degree of impairment in a true performance measure (e.g., cycling time trial [TT]) in acute hypoxia remains unknown.

Therefore, the purpose of our study in a cohort of endurance-trained athletes was threefold. First, we aimed to test the hypothesis that poikilocapnic ventilatory responsiveness to progressive hypoxia during exercise (HVR<sub>EX</sub>) will be greater than ventilatory responsiveness to progressive hypoxia at rest (HVR<sub>REST</sub>). Second, we aimed to test the hypothesis that the degree of cycling performance impairment with acute exposure to moderate hypoxia (F<sub>i</sub>O<sub>2</sub> = 0.16, ~2500 m of terrestrial altitude) will be inversely related to HVR<sub>EX</sub> (i.e., those that increase minute ventilation [ $\dot{V}_E$ ] enough to combat drops in SpO<sub>2</sub> will better preserve performance in hypoxia) in a group of highly trained endurance cyclists. Finally, we aimed to identify ventilatory-related factors that could explain the variance in cycling TT performance impairment in acute hypoxia, including HVR<sub>EX</sub>, exercise  $\dot{V}_E$ , decline in S<sub>p</sub>O<sub>2</sub> during exercise, and measures of an adequate hyperventilatory response during exercise (e.g., partial pressure of end-tidal CO<sub>2</sub> [P<sub>et</sub>CO<sub>2</sub>],  $\dot{V}_E/\dot{V}O_2$ , and  $\dot{V}_E/\dot{V}CO_2$ ).

## METHODS

### Ethical Approval

Before participation in the study, all subjects were advised orally, and in writing, as to the nature of the experiments and gave written, informed consent to the study protocol, which was approved by Indiana University’s Institutional Review Board (IRB no. 1707471144) for the Protection of Human Subjects and conformed to the standards set by the Declaration of Helsinki, except for registration in a database.

### Subjects

Sixteen highly endurance-trained men ( $\dot{V}O_{2peak}$ , 62.5 ± 5.8 mL·kg<sup>-1</sup>·min<sup>-1</sup>) volunteered to participate in the study. Because of the potential effects of progesterone on exercise  $\dot{V}_E$

(22) and the multiple laboratory visits required, we chose to examine only men in this study. Of the 16 subjects recruited, only the 12 who were highly trained cyclists were included in the part of the study that included a cycling TT, designed to test the second hypothesis (see details below). Subjects were healthy, without any pulmonary, cardiovascular, or metabolic disease, and had normal pulmonary function. Body surface area (in m<sup>2</sup>) was calculated using Mosteller’s (23) equation.

### Experimental Design

Subjects attended the laboratory on two ( $n = 4$ ) or four ( $n = 12$ ) different occasions, separated by a minimum of 48 h between visits. The first visit, which served to screen subjects, consisted of resting pulmonary function tests, a resting HVR test where F<sub>i</sub>O<sub>2</sub> was reduced in a square-wave fashion (HVR<sub>SW</sub>; see details below) and a graded maximal exercise test (GXT) in normoxia on a cycle ergometer to volitional exhaustion, with appropriate and standardized rest between tests. Visit 2 consisted of a resting HVR test where F<sub>i</sub>O<sub>2</sub> was reduced in a progressive, continuous manner (HVR<sub>REST</sub>; see details below); an exercise HVR test (HVR<sub>EX</sub>; see details below); and a familiarization trial for the 10-km TT while breathing a hypoxic inspire (F<sub>i</sub>O<sub>2</sub> = 0.18, simulating an altitude of ~1500 m, subjects blinded), with 15 min of rest between the tests. This hypoxic level, i.e., a F<sub>i</sub>O<sub>2</sub> midway between the normoxic and the hypoxic trials performed on visits 3 and 4, was chosen to make it more difficult for the subjects to identify whether they were breathing a hypoxic or normoxic inspire during the experimental TT. During the last two visits (visits 3 and 4), subjects performed a 10-km TT either in normoxia (TT<sub>NORM</sub>) or in hypoxia (TT<sub>HYP</sub>, F<sub>i</sub>O<sub>2</sub> = 0.16, simulating an altitude of 2500 m). These final two visits were randomized and counterbalanced, and subjects were blinded to the inspire.

Before the laboratory visits, subjects were asked to abstain from caffeine consumption for 12 h (visits 1 and 2), avoid alcohol consumption for 24 h, be 10–12 h postprandial (visits 1 and 2) or at least 3–4 h postprandial (visits 3 and 4), and avoid high-intensity exercise during the 24 h leading to each visit. Visits 1 and 2 were performed first thing in the morning, and subjects arrived at the laboratory fasted and within 1 h of waking up. Subjects were also asked to consume a similar diet the night before visits 1 and 2. Training logs were kept in the days before visit 3 and replicated along with food and water intake before visit 4. Visits 3 and 4 were performed at the same time of day in attempt to mitigate diurnal variations in TT performance (24).

### Cycling Tests

The GXT (visit 1) and the HVR<sub>EX</sub> (visit 2) were performed on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands), and the performance trials (10-km TT) were performed on a Velotron® Cycle Ergometer (RacerMate Inc., Seattle, WA). The seat and handlebars setting of the ergometers were recorded for each subject on

their first and second visits and replicated for subsequent testing. During all exercise tests, heart rate (HR; Model FT1; Polar, Stamford, CT) and  $S_pO_2$  (Nellcor N600x; Medtronic Inc., Minneapolis, MN) using a noninvasive infrared sensor affixed on the subject's forehead were continuously monitored and recorded. Ventilatory and metabolic measurements were collected using breath-by-breath analysis (Vmax-Encore System; CareFusion, Yorba Linda, CA) while subjects breathed through an oronasal face mask (7450 Series; Hans Rudolph, Kansas, MO) attached to a mass flow sensor that measured inspired and expired flow and  $O_2$  and  $CO_2$  concentrations. The  $O_2$  and  $CO_2$  analyzers were calibrated before each test with room air and calibration gases within the physiological range, and the mass flow sensor was calibrated at varying flow ( $30\text{--}360\text{ L}\cdot\text{min}^{-1}$ ) using a 3.0-L syringe. During all trials, the mass flow sensor was attached to a two-way non-rebreathing valve (2700 Series, Hans Rudolph).

## GXT

Subjects performed a ramped incremental cycling test to volitional exhaustion for the determination of  $\dot{V}O_{2\text{peak}}$  and peak power output. After a brief warm-up at a self-selected intensity, the GXT began with 2 min at 100 W; thereafter, power output was continuously increased by 1 W every other second ( $30\text{ W}\cdot\text{min}^{-1}$ ). Subjects were instructed to maintain their self-selected cadence (90–110 rpm) until exhaustion. The test was terminated when cadence dropped  $>10$  rpm below the subject's preferred cadence despite strong verbal encouragement, or when the subject voluntarily ended the test.  $\dot{V}O_{2\text{peak}}$  was determined as the highest 30-s average  $O_2$  uptake ( $\dot{V}O_2$ ) achieved during exercise while meeting two of the following three criteria: 1) an HR  $\geq 90\%$  age-predicted maximum, 2) an RER  $\geq 1.10$ , and 3) a plateau in  $\dot{V}O_2 \leq 150\text{ mL}$  with increased workload (25). Maximal ventilation ( $\dot{V}_{E\text{max}}$ ) was determined as the highest pulmonary ventilation ( $\dot{V}_E$ ) value for 30-s bin-averaged data measured during the GXT, and peak power output was determined as the final work rate attained during the test. Peak values for the remaining dependent variables were determined as the highest 30-s averages observed during the test or the lowest 30-s averages for  $S_pO_2$  and  $P_{et}CO_2$ .

## 10-km TT

Each TT was preceded by a warm-up period that consisted of 5 min of cycling at 100 W and 3 min where subjects freely select their cycling intensity. Subjects could select and change gears and cadence throughout the trial and were instructed to complete the distance in as short a time as possible. Distance completed was shown to the subjects continuously and in real time on a computer monitor and announced verbally every 2 km. Subjects were blinded to the time elapsed during the trial, power output during the test, time to completion, and the inspirate. During the TT, the two-way non-rebreathing valve attached to the mass flow sensor was connected through a hose on the inspired side to a three-way valve with one opening to room air and one opening leading to a balloon reservoir

(850 L). Hypoxic inspirate was delivered using a portable nitrogen generator (CAT-12 model; Colorado Altitude Training Systems, Boulder, CO).

Every other kilometer during the TT, subjects were asked to rate their perceived breathlessness (dyspnea) on a scale of 0–10 (modified Borg scale [26]). Subjects were familiarized with this scale before each test and were told that 0 implied “no noticeable breathing effort above what occurs at rest” and 10 indicated “maximal ventilatory effort.” In addition, at the end of each cycling test subjects were asked to rate their overall rate of perceived exertion (6–20 modified Borg scale where 6 indicated “no effort” and 20 indicated “maximal effort” [26]).

Completion time, average power output,  $S_pO_2$ , HR, and metabolic and ventilatory variables were averaged for every 2 km and analyzed using a custom script (The MathWorks, Inc., Natick, MA). Mean values during the 10-km TT are annotated with a “-TTN” or “-TTH” subscript for the normoxic and hypoxic trials, respectively. Change in TT performance ( $\Delta TT$ ) between normoxia and hypoxia was calculated as a percentage difference in total time to complete the 10-km TT between  $TT_{\text{NORM}}$  and  $TT_{\text{HYP}}$  and is annotated in text with a “-TT” subscript. Thus, a positive  $\Delta TT$  indicates performance during  $TT_{\text{HYP}}$  was worse (i.e., took more time to complete) than  $TT_{\text{NORM}}$ . This method [i.e.,  $(TT_{\text{HYP}} - TT_{\text{NORM}})/(TT_{\text{NORM}} \times 100)$ ] was also used for other dependent variables to calculate percentage difference ( $\Delta$ ) in average values throughout the 10-km TT between the two conditions (e.g.,  $\Delta S_pO_{2\text{-TT}}$  and  $\Delta P_{et}CO_{2\text{-TT}}$ ), where a negative  $\Delta$  implies that values during  $TT_{\text{NORM}}$  were greater than  $TT_{\text{HYP}}$ .

## Ventilatory Response Tests

**General procedures.** For the ventilatory responsiveness trials, the two-way non-rebreathing valve attached to the mass flow sensor was connected through a hose on the inspired side to a three-way valve with one opening to room air and one opening leading to a balloon reservoir.  $P_{et}CO_2$  was not adjusted throughout the HVR tests to mimic conditions that more closely match those that exist during high-intensity exercise and hypoxic exposure (i.e., all tests were performed under poikilocapnic conditions). Accordingly, alveolar  $PCO_2$  (and thus  $P_{et}CO_2$ ) levels during the ventilatory response tests were not clamped and, consequentially, were lower than resting levels (i.e., hypocapnia induced by hypoxic hyperventilation). Because the Vmax-Encore system is not sensitive to  $PO_2$  values lower than  $\sim 40\text{ mm Hg}$  ( $F_iO_2 = \sim 0.05$ ), partial pressure of end-tidal  $O_2$  ( $P_{et}O_2$ ) was also continuously measured using a separate  $O_2$  analyzer (Model 17625; Vacumed, Ventura, CA) and recorded using data acquisition software (DasyLab Version 12; Measurement Computing Corporation, Norton, MA). The analyzer was calibrated before each test with room air and a calibration gas (8%  $O_2$ , balance  $N_2$ ). Ventilatory responsiveness is represented by the slope of the line for the linear regression relating  $\dot{V}_E$  and  $S_pO_2$  determined by plotting  $\dot{V}_E$  and  $S_pO_2$  measurements against each other. A negative linear relationship is expected, and by convention HVR values are reported

as a positive number in liters per minute per percent (i.e., the slope of the relationship).

### Resting hypoxia ventilatory response (HVR<sub>REST</sub>).

For this test, a slight modification of the (traditional) methods to determine HVR described by Weil et al. (12) was used. Briefly, upon arrival to the laboratory, subjects rested quietly for at least 15 min on a comfortable chair to ensure true measure of resting  $\dot{V}_E$ . After breathing room air for 5 min, a three-way valve was adjusted so that the subject breathed the air contained in a meteorological balloon (100 L) that was pre-filled with room air. Slowly, 100% N<sub>2</sub> was added into the balloon reservoir to reduce the O<sub>2</sub> content in the inspired air over a 12- to 15-min time period. Real-time P<sub>et</sub>O<sub>2</sub> values were used to guide the rate of addition of 100% N<sub>2</sub> into the balloon reservoir and ensure progressive hypoxia was induced. The test was concluded when S<sub>p</sub>O<sub>2</sub> dropped below 65%, or when the subject terminated the test by voluntarily removing the face mask (12). Thirty-second bin averages were used to calculate the HVR slope (see above). End-test values reported for S<sub>p</sub>O<sub>2</sub> and metabolic and ventilatory variables were taken from the last 30 s before the termination of the HVR<sub>REST</sub> test and are annotated with a “-REST” subscript (e.g., SpO<sub>2-REST</sub>).

**Exercise HVR (HVR<sub>EX</sub>).** Ventilatory responsiveness during exercise was determined using a 20-min cycling bout where subjects cycled at a low exercise intensity equivalent to 40% of power at  $\dot{V}O_{2peak}$  in normoxia (27), an intensity that does not affect the ventilatory response to hypoxia during exercise at simulated altitudes up to 4800 m (20). This exercise intensity was also chosen to ensure subjects were exercising below their gas exchange threshold and reached a steady state even when breathing a hypoxic inspire with F<sub>I</sub>O<sub>2</sub> = 0.12 (equivalent to ~4900 m). For HVR<sub>EX</sub>, subjects were instructed to maintain a constant self-selected cadence. During the first 5 min of exercise, subjects breathed room air. Then the three-way valve on the inspiratory side was adjusted so that, in series and in a stepwise manner, the subject breathed air from one of three large meteorological balloons containing 18%, 15%, and 12% O<sub>2</sub> for 5 min each. For safety reasons, if the subject's S<sub>p</sub>O<sub>2</sub> reached ~70% or if P<sub>et</sub>O<sub>2</sub> reached 40 mm Hg, the test was terminated. During the last 15 s of the each hypoxic stage/inspire, subjects were asked to rate their dyspnea (0–10 modified Borg scale [26]). For this test, average data from the last 60 s (average of 2 × 30 s) of each stage/inspire level were used for the calculation of HVR<sub>EX</sub> and end-stage values. Values obtained from the last exercise stage (F<sub>I</sub>O<sub>2</sub> = 0.12) are henceforth annotated with “-EX” (e.g., SpO<sub>2-EX</sub>).

**Resting (square-wave) HVR (HVR<sub>SW</sub>).** Because of differences in the specific fashion by which F<sub>I</sub>O<sub>2</sub> was reduced during the HVR protocols for rest and exercise (i.e., a traditional protocol of continuous, progressive reduction during HVR<sub>REST</sub> vs square-wave decreases during HVR<sub>EX</sub>), we also implemented a resting HVR test where F<sub>I</sub>O<sub>2</sub> was reduced in a square-wave manner (HVR<sub>SW</sub>). Because HVR<sub>SW</sub> served as a validation test, only 12 subjects performed it. This additional test allowed us to assess whether the manner by which hypoxia was induced affected the primary outcome variables.

After resting quietly for 15 min while breathing normal room air through a face mask for an additional 4 min, a three-way valve was adjusted so that the subject breathed the air from a 100-L bag containing 18% O<sub>2</sub> for 4 min. In series, the subject then breathed through three more meteorological balloons containing 15%, 12%, or 9% O<sub>2</sub> for 4 min each (hence, the total test time was 20 min). If the subject's SpO<sub>2</sub> reached 70% or if P<sub>et</sub>O<sub>2</sub> reached 40 mm Hg, the test was terminated.

### Resting Pulmonary Function Tests

All resting pulmonary function tests were performed using the Vmax® Encore Metabolic Cart after the subjects have been seated and rested for at least 5 min (28). Measurements consisted of forced vital capacity (FVC) maneuvers to determine forced expired volume in 1 s (FEV<sub>1</sub>), peak expiratory flow (PEF) and forced expiratory flow between 25% and 75% of the FVC (FEF<sub>25–75</sub>), and a maximum voluntary ventilation (MVV) test. Each pulmonary test was performed in triplicate per ATS standards (28), and the largest FVC, FEV<sub>1</sub>, PEF, FEF<sub>25–75</sub>, and MVV were selected. Subjects breathed through a rubber mouthpiece (CareFusion) and wore a nose clip during all pulmonary function tests.

### Statistical Analyses

All data are presented as mean ± SD unless otherwise noted. Statistical analyses were performed using R version 1.0.143 (29), and statistical significance was set at  $\alpha = 0.05$ . Normality was assessed using the Shapiro–Wilk test and normal distribution plots. A one-way repeated-measures ANOVA was used to compare the HVR slopes from HVR<sub>REST</sub>, HVR<sub>SW</sub>, and HVR<sub>EX</sub> and to determine differences in S<sub>p</sub>O<sub>2</sub>, HR, ventilatory, and metabolic variables at the multiple inspire levels during HVR<sub>EX</sub>. Where a significant main effect was found, the Tukey *post hoc* test was performed. Because HVR<sub>EX</sub> and HVR<sub>SW</sub> were not normally distributed, a Spearman rank correlation was also performed in addition to Pearson's *r*. Within-test analyses for HVR<sub>REST</sub> or HVR<sub>EX</sub> were assessed with Pearson correlations.

Finally, a 2 × 5 (inspire [NORM, HYP] × distance [2, 4, 6, 8, 10 km]) repeated-measures ANOVA was used to determine differences in each of the dependent variables during the 10-km TT, and where a significant main effect was found, a Tukey's *post hoc* test was performed. Pearson's *r* was used to correlate the degree of impairment in a 10-km TT performance ( $\Delta$ TT, see details above) with HVR<sub>EX</sub> and other metabolic and ventilatory outcome variables. A stepwise multiple regression was used to predict factors that could explain the variance in 10-km TT performance impairment in acute hypoxia. Based on the Pearson correlations mentioned above, only independent variables that significantly correlated with  $\Delta$ TT were included in the multiple regression analysis.

## RESULTS

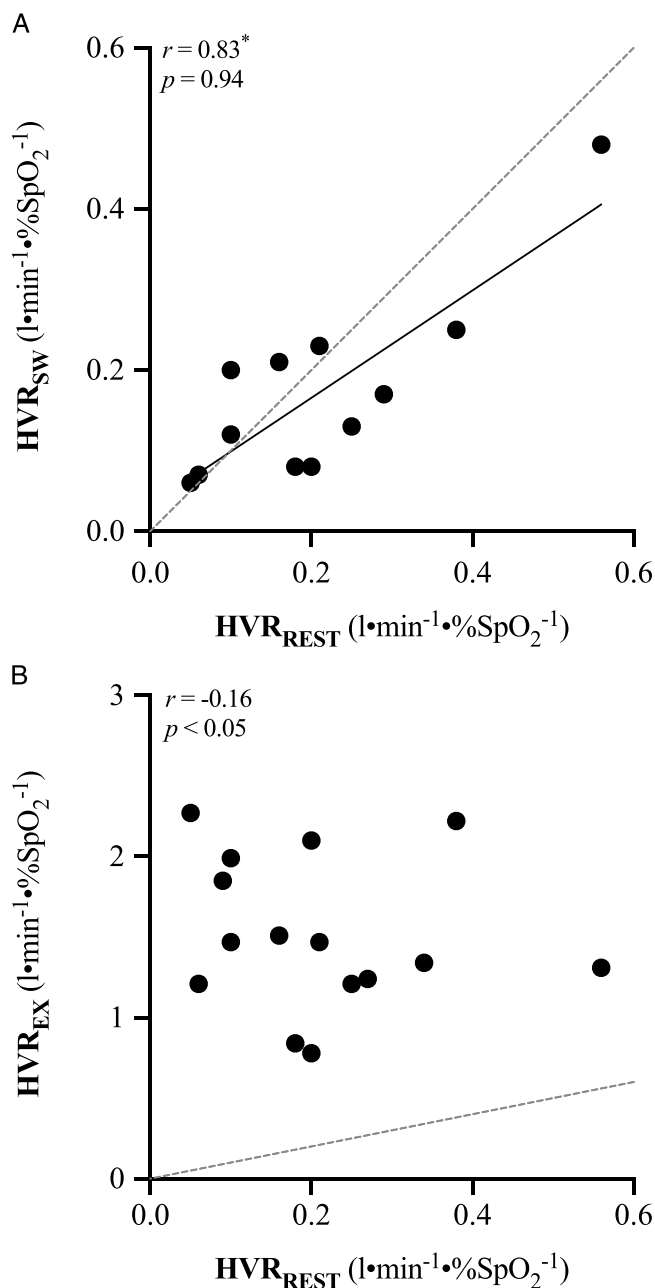
**Subject characteristics.** Descriptive data, including subject characteristics and peak values from the GXT, are presented

in Table 1.  $\text{SpO}_2$  during the GXT, performed in normoxia, was measured in 12 subjects, and of those, 5 demonstrated at least mild desaturation ( $<95\%$   $\text{SpO}_2$  [30]). All participants had normal pulmonary function values (mean  $\pm$  SD;  $\text{FVC} = 5.8 \pm 1.1$  L,  $\text{FEV}_{1.0} = 4.8 \pm 0.9$  L,  $\text{PEF} = 10.2 \pm 2.4$   $\text{L}\cdot\text{s}^{-1}$ ,  $\text{FEF}_{25-75} = 5.2 \pm 1.3$   $\text{L}\cdot\text{s}^{-1}$ ,  $\text{MVV} = 177.8 \pm 43.1$   $\text{L}\cdot\text{min}^{-1}$ ).

**Ventilatory responsiveness.** One subject was not able to complete more than two stages of  $\text{HVR}_{\text{EX}}$  and, therefore, was not included in any analyses concerning this test. A main effect ( $F = 91.05$ ,  $P < 0.001$ ) was detected when comparing the slopes of all three HVR tests ( $n = 11$ ). Specifically, the mean slope for  $\text{HVR}_{\text{EX}}$  ( $1.60 \pm 0.47$   $\text{L}\cdot\text{min}^{-1}\cdot\%^{-1}$ ) was greater than both  $\text{HVR}_{\text{SW}}$  ( $0.17 \pm 0.12$   $\text{L}\cdot\text{min}^{-1}\cdot\%^{-1}$ ,  $P < 0.001$ ) and  $\text{HVR}_{\text{REST}}$  ( $0.21 \pm 0.15$   $\text{L}\cdot\text{min}^{-1}\cdot\%^{-1}$ ,  $P < 0.001$ ). Because  $\text{HVR}_{\text{SW}}$  and  $\text{HVR}_{\text{REST}}$  were not different ( $P = 0.94$ ) and highly correlated ( $n = 12$ ; Pearson:  $r = 0.83$ ,  $P < 0.001$ ; Spearman rank:  $\rho = 0.72$ ,  $P < 0.01$ ; Fig. 1A), and because  $\text{HVR}_{\text{SW}}$  in this study was strictly performed as a validation test, only  $\text{HVR}_{\text{REST}}$  will be considered in further comparisons between, and discussion of, resting and exercise HVR. When 15 subjects were included in the analyses,  $\text{HVR}_{\text{EX}}$  ( $1.52 \pm 0.47$   $\text{L}\cdot\text{min}^{-1}\cdot\%^{-1}$ ) was still significantly greater than  $\text{HVR}_{\text{REST}}$  ( $0.22 \pm 0.13$   $\text{L}\cdot\text{min}^{-1}\cdot\%^{-1}$ ;  $P < 0.001$ ), and the two measures were not correlated (Pearson:  $r = -0.16$ ,  $P = 0.57$ ; Spearman rank:  $\rho = -0.21$ ,  $P = 0.46$ ; Fig. 1B).

**$\text{HVR}_{\text{REST}}$ .**  $\text{HVR}_{\text{REST}}$  ranged from 0.05 to 0.56  $\text{L}\cdot\text{min}^{-1}\cdot\%^{-1}$  ( $n = 16$ ), and the test lasted, on average,  $720 \pm 128$  s. None of the subjects reported experiencing any adverse symptoms.  $\text{HVR}_{\text{REST}}$  was significantly ( $P < 0.05$ ) correlated with body surface area ( $P < 0.01$ ,  $r = 0.71$ ), but not with  $\dot{\text{V}}\text{O}_{2\text{peak}}$  ( $r = -0.16$ ,  $P = 0.56$ ) or any other measures obtained at maximal exercise during the GXT. End-test values obtained during  $\text{HVR}_{\text{REST}}$  are presented in Table 2 and are annotated with a “-REST” subscript in text (e.g.,  $\text{P}_{\text{etCO}_2\text{-REST}}$ ).

**$\text{HVR}_{\text{EX}}$ .** Actual  $\text{F}_i\text{O}_2$  levels were within  $\pm 0.3\%$  of the target  $\text{F}_i\text{O}_2$  for each stage.  $\text{SpO}_2$  values at the end of the test ( $\text{F}_i\text{O}_2 = 0.12$ ) ranged between 66.6% and 81.4%.  $\text{HVR}_{\text{EX}}$  ranged between 0.84 and 2.27  $\text{L}\cdot\text{min}^{-1}\cdot\%^{-1}$  while subjects cycled at an average power output of  $155 \pm 25$  W.  $\dot{\text{V}}_{\text{E}}$  increased by  $<1.5\%$  or  $<1.4$   $\text{L}\cdot\text{min}^{-1}$  between the third and the fifth



**FIGURE 1—Correlations between ventilatory responsiveness tests. A.** Resting progressive ( $\text{HVR}_{\text{REST}}$ ) vs resting square-wave ( $\text{HVR}_{\text{SW}}$ ) HVR ( $n = 12$ ); the slopes were not different and highly correlated  $P < 0.05$ . **B.**  $\text{HVR}_{\text{REST}}$  and exercise HVR ( $\text{HVR}_{\text{EX}}$ ) were significantly different and not correlated ( $n = 15$ ). Dashed line: line of identity. \*Significant correlation,  $P < 0.05$ ;  $P$  values on figure refer to significance level of  $t$ -test.

minutes of the last stage of  $\text{HVR}_{\text{EX}}$ , confirming that a steady state was reached during this stage. As expected, there was a significant decrease in  $\text{SpO}_2$  and  $\text{P}_{\text{etO}_2}$  throughout  $\text{HVR}_{\text{EX}}$  and between all stages (Table 2). A significant main effect for  $\text{F}_i\text{O}_2$  level was also detected for  $\text{P}_{\text{etCO}_2}$ ,  $\dot{\text{V}}_{\text{E}}$ , breathing frequency,  $\dot{\text{V}}\text{CO}_2$ ,  $\dot{\text{V}}_{\text{E}}/\dot{\text{V}}\text{CO}_2$ ,  $\dot{\text{V}}_{\text{E}}/\dot{\text{V}}_{\text{Emax}}$ , HR, and dyspnea (Table 2). Data obtained during each stage of  $\text{HVR}_{\text{EX}}$  are presented in Table 2.

**10-km TT.** As expected, time to complete the 10-km TT was significantly ( $P < 0.01$ ) longer during  $\text{TT}_{\text{HYP}}$  compared

**TABLE 1.** Subject characteristics, maximal values from graded exercise test ( $n = 16$ ).

Age (yr)	24 $\pm$ 5
Height (m)	1.79 $\pm$ 5.7
Mass (kg)	71.3 $\pm$ 7.6
Body surface area ( $\text{m}^2$ )	1.91 $\pm$ 0.11
Graded exercise test—end exercise values	
Peak power output (W)	379 $\pm$ 42
$\dot{\text{V}}\text{O}_{2\text{peak}}$ ( $\text{L}\cdot\text{min}^{-1}$ )	4.4 $\pm$ 0.5
$\dot{\text{V}}\text{O}_{2\text{peak}}$ ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	62.5 $\pm$ 5.8
$\dot{\text{V}}\text{CO}_{2\text{peak}}$ ( $\text{L}\cdot\text{min}^{-1}$ )	5.1 $\pm$ 0.6
$\dot{\text{V}}_{\text{Emax}}$ ( $\text{L}\cdot\text{min}^{-1}$ )	173.2 $\pm$ 29.5
$\dot{\text{V}}_{\text{E}}/\dot{\text{V}}\text{O}_2$	39.2 $\pm$ 5.3
$\dot{\text{V}}_{\text{E}}/\dot{\text{V}}\text{CO}_2$	33.8 $\pm$ 4.1
RER	1.16 $\pm$ 0.06
$\text{P}_{\text{etCO}_2}$ (mm Hg)	35.2 $\pm$ 3.3
HR (bpm)	186 $\pm$ 9
$\text{SpO}_2$ (%)	95.0 $\pm$ 2.2

Values are presented as mean  $\pm$  SD.

$\dot{\text{V}}\text{O}_{2\text{peak}}$ , maximal  $\text{O}_2$  consumption;  $\dot{\text{V}}\text{CO}_{2\text{peak}}$ , maximal  $\text{CO}_2$  production;  $\dot{\text{V}}_{\text{Emax}}$ , maximal exercise minute ventilation.

TABLE 2. Ventilatory response tests—end test/stage values.

	HVR <sub>REST</sub> (n = 16)	HVR <sub>EX</sub> (n = 15)				Interaction	
		Stage 1 (F <sub>i</sub> O <sub>2</sub> = 0.21)	Stage 2 (F <sub>i</sub> O <sub>2</sub> = 0.18)	Stage 3 (F <sub>i</sub> O <sub>2</sub> = 0.15)	Stage 4 (F <sub>i</sub> O <sub>2</sub> = 0.12)	P	F
Slope (L·min <sup>-1</sup> ·% <sup>-1</sup> )	0.22 ± 0.13	1.52 ± 0.47					
S <sub>p</sub> O <sub>2</sub> (%)	69.9 ± 4.1	98.4 ± 1.3*	93.9 ± 2.5*	85.8 ± 4.0*	74.7 ± 4.9	<0.001	326.30
$\dot{V}_E$ (L·min <sup>-1</sup> )	17.4 ± 5.1	58.4 ± 9.2*	65.9 ± 11.2*	75.7 ± 12.5*	95.3 ± 16.7	<0.001	65.83
fb (breaths per minute)	14.5 ± 3.0	26.1 ± 4.6*	28.5 ± 5.8*	31.7 ± 6.9*	36.7 ± 10.6	<0.001	26.94
TV (L per breath)	1.20 ± 0.21	2.27 ± 0.30	2.35 ± 0.33	2.42 ± 0.33	2.49 ± 0.42		
$\dot{V}CO_2$ (L·min <sup>-1</sup> )	0.4 ± 0.1	2.3 ± 0.5*	2.5 ± 0.6	2.7 ± 0.5	2.9 ± 0.5	<0.01	9.04
$\dot{V}O_2$ (L·min <sup>-1</sup> )	0.2 ± 0.1	2.6 ± 0.5	2.7 ± 0.6	2.7 ± 0.6	2.7 ± 0.5		
$\dot{V}_E/\dot{V}CO_2$	42.1 ± 4.8	25.2 ± 2.8*	26.4 ± 2.7*	28.7 ± 2.6*	33.4 ± 3.8	<0.001	56.17
P <sub>a</sub> O <sub>2</sub> (mm Hg)	29.0 ± 5.0	95.7 ± 6.4*	79.1 ± 5.8***	64.5 ± 6.1***	53.4 ± 4.1	<0.001	454.50
P <sub>a</sub> CO <sub>2</sub> (mm Hg)	32.7 ± 3.5	44.5 ± 4.9*	42.6 ± 4.2*	39.3 ± 4.1*	33.5 ± 4.1	<0.001	52.03
$\dot{V}_E/\dot{V}_{E_{max}}$ (%)	10.2 ± 3.1	35.1 ± 6.0*	39.6 ± 7.4*	45.5 ± 8.0*	54.1 ± 15.0	<0.001	59.35
HR (bpm)	83 ± 11	129 ± 11*	138 ± 12*	149 ± 12**	158 ± 13	<0.001	48.27
Dyspnea (0–10)	—	2.5 ± 0.7*	3.2 ± 0.9*	4.2 ± 0.9***	6.0 ± 1.4	<0.001	84.29

Values are presented as mean ± SD.

\*Significantly ( $P < 0.05$ ) different from stage 4 (F<sub>i</sub>O<sub>2</sub> = 0.12).

\*\*Significantly ( $P < 0.05$ ) different from previous inspirate level/stage.

fb, breathing frequency; TV, tidal volume;  $\dot{V}_{E_{max}}$ , maximal exercise minute ventilation from graded exercise test.

with TT<sub>NORM</sub> ( $\Delta$ : 5% ± 1%, range: 3%–8%), which corresponded to a significant ( $P < 0.01$ ) reduction of 11% ± 3% in mean power output (range: 6%–18%). Further statistical analyses were performed to determine the effect of inspirate (i.e., normoxia vs hypoxia) and distance (average of every 2 km) on key outcome variables. There was a significant ( $P < 0.01$ ) main effect for both inspirate and distance for  $\dot{V}O_2$ ,  $\dot{V}CO_2$ ,  $\dot{V}_E/\dot{V}O_2$ ,  $\dot{V}_E/\dot{V}CO_2$ , P<sub>a</sub>CO<sub>2</sub>, S<sub>p</sub>O<sub>2</sub>, and dyspnea (Fig. 2). A significant ( $P < 0.01$ ) main effect for inspirate only was detected for power output and time, whereas a significant ( $P < 0.01$ ) main effect was found for distance for HR,  $\dot{V}_E$ , and  $\dot{V}_E/\dot{V}_{E_{max}}$  (Fig. 2).

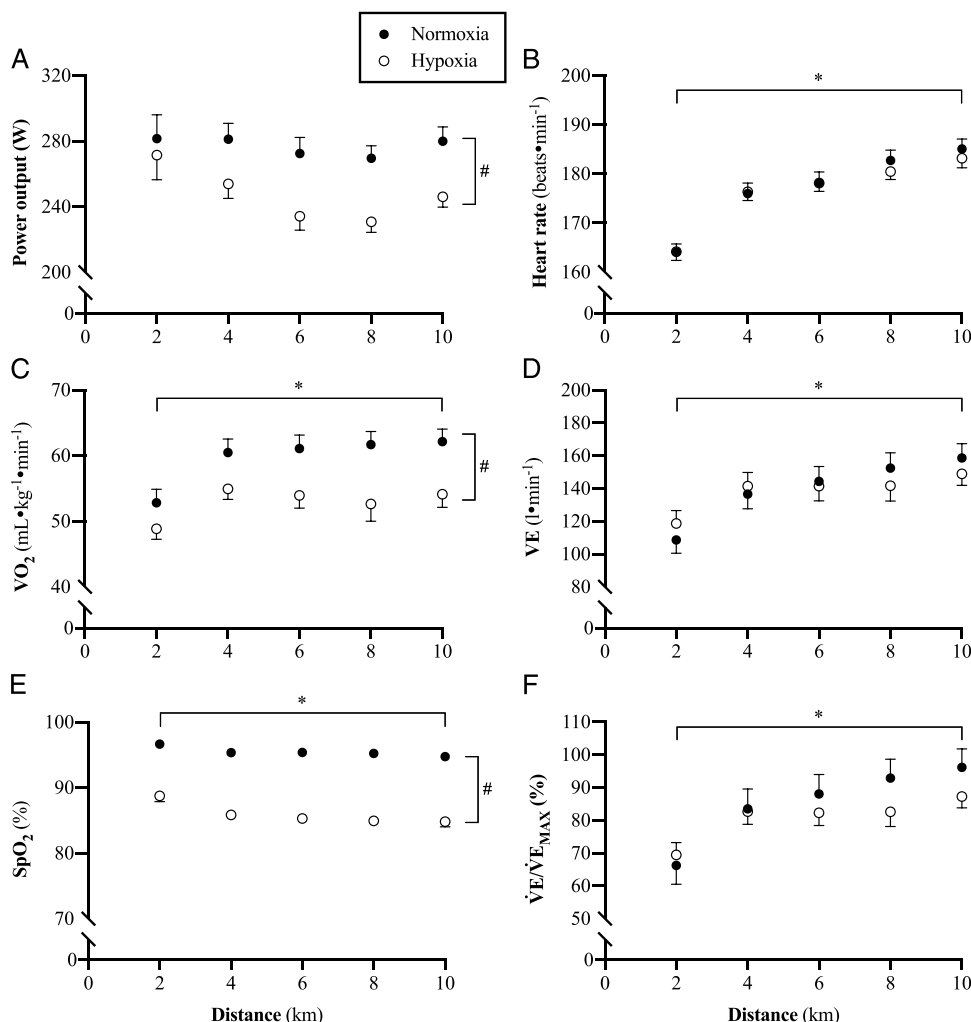
**$\Delta$ TT correlations.** As shown in Figure 3,  $\Delta$ TT between normoxia and hypoxia was not correlated with HVR<sub>REST</sub> or HVR<sub>EX</sub>. In addition,  $\Delta$ S<sub>p</sub>O<sub>2-TT</sub> ( $r = -0.21$ ,  $P = 0.55$ ) or average S<sub>p</sub>O<sub>2</sub> values obtained during TT<sub>HYP</sub> ( $r = -0.11$ ,  $P = 0.75$ ) and TT<sub>NORM</sub> ( $r = -0.28$ ,  $P = 0.40$ ) were not correlated with  $\Delta$ TT. A significant negative correlation between  $\Delta\dot{V}_{E-TT}$  and  $\Delta$ TT (Fig. 3C) indicated higher (absolute)  $\dot{V}_E$  during TT<sub>NORM</sub> compared with TT<sub>HYP</sub> was associated with greater hypoxic performance impairments. By contrast, markers that indicate a more pronounced/exaggerated ventilatory response during TT<sub>HYP</sub> relative to TT<sub>NORM</sub> were also related to a greater impairment of 10 km cycle performance in hypoxia. Specifically, significant ( $P < 0.05$ ) correlations between  $\Delta$ TT and  $\Delta$ P<sub>a</sub>CO<sub>2-TT</sub> (Fig. 3D) and  $\Delta\dot{V}_E/\dot{V}O_{2-TT}$  (Fig. 3E), and an approaching significance correlation between  $\Delta$ TT and  $\Delta\dot{V}_E/\dot{V}CO_{2-TT}$  ( $P = 0.09$ ; Fig. 3F), would suggest hypoxic performance was impaired to a greater extent with an enhanced ventilatory response during TT<sub>HYP</sub> compared with TT<sub>NORM</sub>. Interestingly, subjects with markers of reduced ventilatory output during the normoxic TT such as P<sub>a</sub>CO<sub>2-TTN</sub> ( $r = 0.72$ ,  $P < 0.05$ ) and  $\dot{V}_E/\dot{V}CO_{2-TTN}$  ( $r = -0.70$ ,  $P < 0.05$ ) had the largest worsening of performance in hypoxia. Correlation between  $\Delta$ TT and mean P<sub>a</sub>CO<sub>2-TTH</sub> and  $\dot{V}_E/\dot{V}CO_{2-TTH}$  during TT<sub>HYP</sub> approached significance ( $r = 0.56$ ,  $P = 0.056$ , and  $r = -0.54$ ,  $P = 0.07$ , respectively).

Multiple regression analysis revealed  $\Delta\dot{V}_{E-TT}$ ,  $\Delta$ P<sub>a</sub>CO<sub>2-TT</sub>, and  $\dot{V}_E/\dot{V}CO_{2-TTN}$  as significant predictors of  $\Delta$ TT, and these variables explained 85% of the variance in performance

impairment in acute hypoxia ( $R^2_{adjusted} = 0.85$ ,  $P < 0.001$ ,  $\Delta$ TT =  $8.47 - 0.25\dot{V}_E/\dot{V}CO_{2-TTN} - 0.41\Delta$ P<sub>a</sub>CO<sub>2-TT} - 0.06\Delta\dot{V}\_{E-TT}). Although other independent variables (e.g., P<sub>a</sub>CO<sub>2-TTN</sub> and  $\Delta\dot{V}_E/\dot{V}O_{2-TT}$ ) were also significantly correlated with  $\Delta$ TT, these factors were excluded from the final model due to collinearity and/or because their inclusion did not significantly improve the model.</sub>

## DISCUSSION

The first aim of this study was to determine whether the integrative ventilatory response to progressive hypoxia is similar at rest and during exercise in a group of highly trained individuals. As hypothesized, the HVR slope was greater during exercise than it was at rest, and there was no correlation between HVR<sub>REST</sub> and HVR<sub>EX</sub>, implying that the gain of the ventilatory response to a given change in S<sub>p</sub>O<sub>2</sub> is not comparable under these distinct conditions. The second aim of the study was to determine whether the degree of impairment in cycling TT performance with acute exposure to moderate hypoxia could be determined substantially by HVR<sub>EX</sub>. Contrary to our initial hypothesis, our results indicate that ventilatory responsiveness to progressive hypoxia, *per se*, may predict very little of the degree of hypoxic performance impairments. Nevertheless, various measures of ventilatory “output” were significantly correlated with, and explained a large portion (~85%) of, the variance in  $\Delta$ TT, such that hypoxic TT performance was impaired to a lesser extent in athletes whose  $\dot{V}_E$  during high-intensity exercise in hypoxia exceeded (or matched)  $\dot{V}_E$  in normoxia. Interestingly though, our findings also imply that to minimize performance decrements in hypoxia, exercise  $\dot{V}_E$  should remain proportional to the reduced metabolic requirements during hypoxic, compared with normoxic, exercise because of varying degrees of the downregulation of power output in hypoxia. Based on these results, we conclude that an adequate and metabolically matched increase in exercise  $\dot{V}_E$ , but not the gain in the ventilatory response to progressive hypoxia (i.e., HVR<sub>REST</sub> or HVR<sub>EX</sub>), is necessary for mitigating the expected hypoxia-induced impairments in endurance cycling performance.



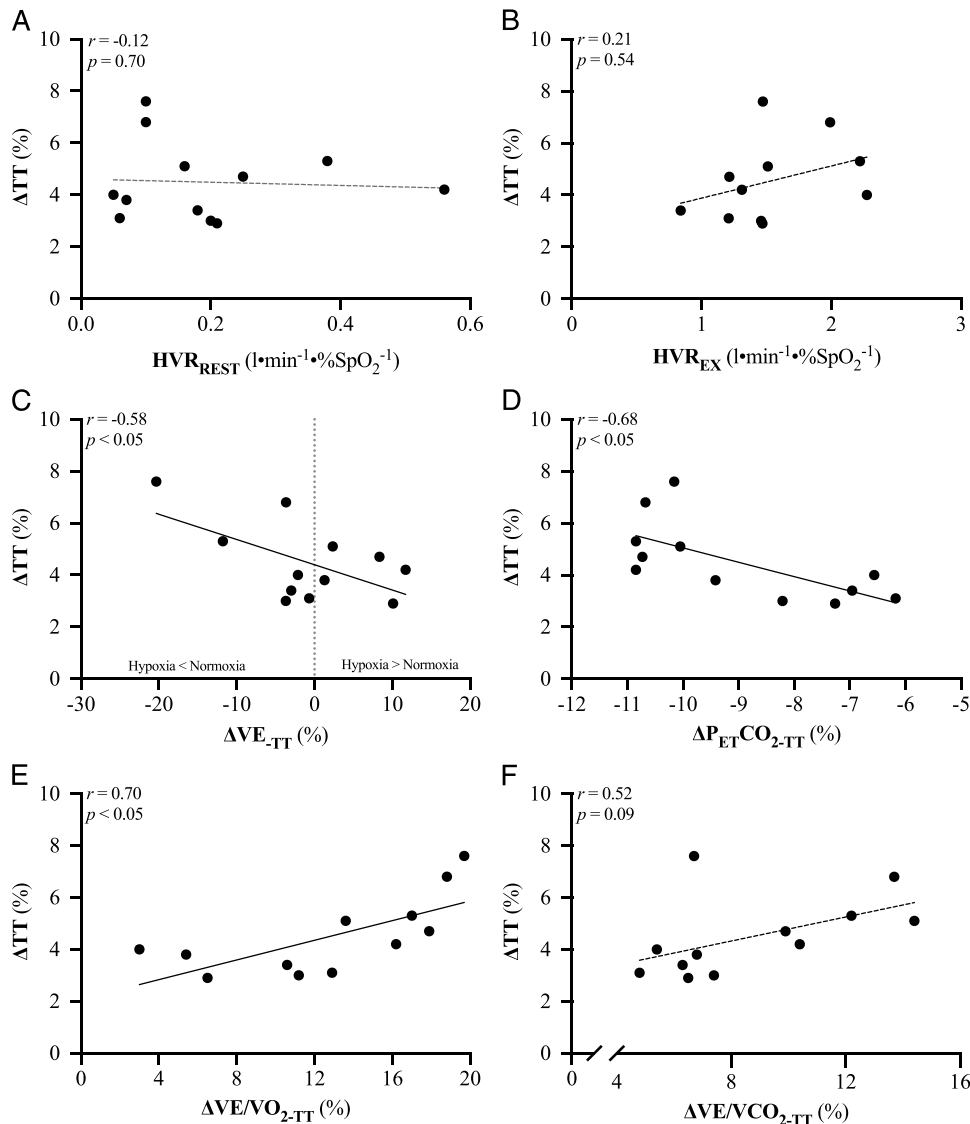
**FIGURE 2**—Key measures obtained every 2 km during the 10-km TT performed in normoxia (closed circles) and hypoxia ( $F_{I}O_2 = 0.16$ ; open circles). Power output (A); HR (B);  $O_2$  consumption ( $\dot{V}O_2$ ) (C); minute ventilation ( $\dot{V}_E$ ) (D); arterial oxyhemoglobin saturation ( $SpO_2$ ) (E);  $\dot{V}_E$  as a percentage of maximal exercise minute ventilation from graded exercise test ( $\dot{V}_E/\dot{V}_{E_{MAX}}$ ) (F). \*Significant main effect for distance ( $P < 0.05$ ). #Significant main effect for hypoxia ( $P < 0.05$ ). Values are presented as mean  $\pm$  SE.

In addition, it may be possible to identify individual athletes who are more susceptible to large performance impairments in hypoxic conditions based on key ventilatory measures obtained during high-intensity TT exercise in normoxia and hypoxia.

Historically, ventilatory responsiveness to hypoxia has been measured predominantly under isocapnic conditions, as this method is ideal for isolating the role of peripheral chemoreceptors and identifying the effects of changing levels of  $P_{a}O_2$  on  $\dot{V}_E$ , independent of  $P_{a}CO_2$ . Similar to Richalet et al. (20,21), to more closely mimic conditions that are encountered during exercise and/or acute hypoxia and to attempt to study the *integrated* ventilatory response to progressive hypoxia,  $P_{et}CO_2$  levels were not clamped during  $HVR_{REST}$  or  $HVR_{EX}$  in our study. As a result,  $P_{et}CO_2$  levels fell concomitantly because of the hyperventilation associated with reductions in  $F_{I}O_2$ , and this resultant hypocapnia may have weakened/attenuated the ventilatory response (12), especially during  $HVR_{EX}$  (31). Because acute changes in  $P_{et}CO_2$  could affect HVR (12), this measure may in turn be overestimated when  $P_{et}CO_2$  is artificially

held constant during isocapnic HVR tests. Thus, although any increases in ventilation observed under hypoxic, poikilocapnic conditions are likely to be reduced compared with isocapnia, we believe the former provides a better and truer estimate of the integrated ventilatory response to real-world exercise tasks performed in normoxia or hypoxia.

**HVR at rest and during exercise.** Compared with rest, exercise induces an increase in the influx of cues and inputs that allow the respiratory control system to provide an appropriate and adequate ventilatory response—one that matches the increased metabolic needs and prevents extreme perturbation in homeostasis. Nevertheless, over the last few decades, researchers have mostly studied *resting* (isocapnic) HVR, and whether the conclusions favored a relationship between resting HVR and exercise ventilation or not, exercise HVR has been largely ignored. Our results indicate that ventilatory responsiveness to progressive hypoxia is different at rest than during exercise. In a recent study of young, untrained men, Lhuissier et al. (19) have shown greater intra-individual variability



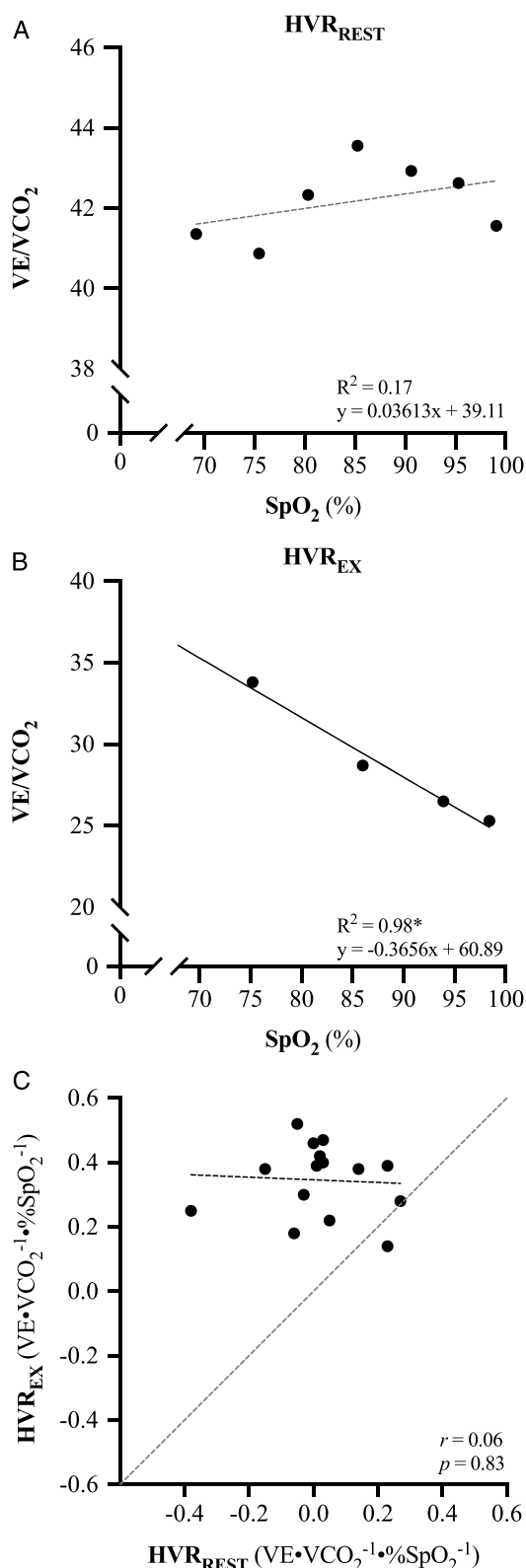
**FIGURE 3**—Relationships between degree of performance impairments in a 10-km TT from normoxia to hypoxia ( $F_iO_2 = 0.16$ ;  $\Delta TT$ ) and HVR at rest ( $HVR_{REST}$ ) (A); HVR during exercise ( $HVR_{EX}$ ) (B); minute ventilation ( $\dot{V}_{E-TT}$ ) (C); partial pressure of end-tidal  $CO_2$  ( $P_{ET}CO_{2-TT}$ ) (D); ventilatory equivalents for  $O_2$  consumption ( $\dot{V}_E/\dot{V}O_{2-TT}$ ) (E); ventilatory equivalents for  $CO_2$  production ( $\dot{V}_E/\dot{V}CO_{2-TT}$ ) (F).  $\Delta$ , percentage change between normoxic and hypoxic TT [(TT<sub>HYP</sub> – TT<sub>NORM</sub>)/(TT<sub>NORM</sub>)  $\times$  100]. \*Significant correlation ( $P < 0.05$ ).

for resting, compared with exercise HVR. In support of this,  $HVR_{REST}$  in our study in highly trained athletes was not related to any metabolic or ventilatory measure obtained during maximal exercise, which conforms to some (9,11) but not all previous work (7,10). It should also be mentioned that—although impossible to completely control for—large day-to-day variations in HVR (~26% for between-day measurements [32]) may have affected our finding that  $HVR_{REST}$  and  $HVR_{EX}$  were not correlated.

It could be argued that the exaggerated increase in ventilation and steeper  $\dot{V}_E/S_pO_2$  slopes seen during  $HVR_{EX}$  compared with  $HVR_{REST}$  were driven by exercise-induced increases in  $CO_2$  production during  $HVR_{EX}$ . To account for higher  $\dot{V}CO_2$  values during  $HVR_{EX}$  compared with  $HVR_{REST}$  that may have affected  $\dot{V}_E$ , we calculated, *post hoc*, a “normalized HVR slope” representing the relationship between  $\dot{V}_E/\dot{V}CO_2$  and  $S_pO_2$

(Fig. 4). Although  $\dot{V}_E/\dot{V}CO_2$  did not increase in any predictable or consistent fashion along with the fall in  $S_pO_2$  during  $HVR_{REST}$ ,  $\dot{V}_E/\dot{V}CO_2$  increased linearly as  $F_iO_2$  was reduced during  $HVR_{EX}$ , and there was a strong negative correlation between  $\dot{V}_E/\dot{V}CO_2$  and  $S_pO_2$  (Fig. 4). This finding suggests that during low and moderate exercise in hypoxia, the increase in ventilation is dependent on the combined effect of the drop in  $S_pO_2$  and metabolic rate (i.e.,  $\dot{V}CO_2$ ), where there is a disproportionate ventilatory response to  $\dot{V}CO_2$  as  $S_pO_2$  falls with increased hypoxia. Furthermore, the relationship between  $\dot{V}_E/\dot{V}CO_2$  and  $S_pO_2$  (i.e., the normalized slope for  $HVR_{EX}$ ) was significantly lower than the original  $\dot{V}_E/S_pO_2$  slope ( $0.35 \pm 0.11 \text{ L}\cdot\%^{-1}$  vs  $1.52 \pm 0.47 \text{ L}\cdot\text{min}^{-1}\cdot\%^{-1}$ , respectively), implying that  $\dot{V}CO_2$  mediates, at least in part, the ventilatory response during exercise in hypoxia. It could also be noticed in Figure 4 that similar to the “original”  $HVR_{REST}$





**FIGURE 4—Hypoxic ventilatory response (HVR) normalized for  $CO_2$  production ( $\dot{V}CO_2$ ); HVR was calculated as the slope of the line for the linear regression relating ventilatory equivalents for  $\dot{V}CO_2$  ( $\dot{V}_E/\dot{V}CO_2$ ) and  $SpO_2$ . A, Resting HVR ( $HVR_{REST}$ ),  $n = 16$ . B, Exercise HVR ( $HVR_{EX}$ ),  $n = 15$ . C, Relationship between the normalized slopes for  $HVR_{REST}$  and  $HVR_{EX}$  ( $r = 0.06$ ,  $P = 0.83$ ). Note that for 93% of subjects, normalized  $HVR_{EX}$  was greater than, or equal to  $HVR_{REST}$ , as demonstrated by the data points lying above the line of identity (dashed gray line).**

and  $HVR_{EX}$  slopes (Fig. 1B), the normalized HVR slopes ( $\dot{V}_E/\dot{V}CO_2$  vs  $SpO_2$ ) were significantly different ( $P < 0.01$ ) and not correlated, and in all but one of the subjects, the normalized  $HVR_{EX}$  slope was greater than that obtained during  $HVR_{REST}$ . Thus, regardless of metabolic rate, ventilatory responsiveness to progressive hypoxia is augmented during exercise, perhaps due to changes in the sensitivity of the ventilatory system to other stimuli that are unique to exercise conditions (e.g., augmentation of locomotor afferent feedback, exercise-related changes in temperature, and accumulation of metabolic by-products).

**Ventilatory responsiveness to progressive hypoxia, performance, and exercise ventilation.** The literature remains equivocal as to whether isocapnic resting and/or exercise HVR are truly related to and/or predictive of various exercise outcomes such as aerobic capacity (i.e.,  $\dot{V}O_{2peak}$  [10,31]), exercise  $\dot{V}_E$  and inadequate hyperventilation in athletes (7–11), exercise-induced arterial hypoxemia (9,10), climbing abilities in mountaineers (14,33), and endurance performance (6). It appears though that higher exercise  $\dot{V}_E$  and HVR appear to be both positive and negative for exercise performance in acute hypoxia. For example, augmented HVR was suggested to be advantageous, and perhaps necessary, for extreme hypoxic “performance” (i.e., better climbing abilities) in mountaineers (33), whereas an adequate increase in exercise ventilation also appears to be important for mitigating decrements in aerobic capacity and cycling performance in hypoxia (5,6,14).

One mechanism by which enhanced exercise hyperventilation could benefit endurance performance in hypoxic conditions is better defense against arterial oxyhemoglobin desaturation during heavy and maximal exercise (2,10,34,35). Thus, we hypothesized that  $HVR_{EX}$  (i.e., the increase in exercise ventilation in response to a progressive decline in  $SpO_2$ ) would be correlated with  $\Delta TT$ . Our results, however, indicated that  $HVR_{EX}$  and degree of impairment in cycling performance in acute hypoxia were not correlated, despite  $\Delta TT$  being related to various other measures of ventilation (see below). Similar to Hopkins and McKenzie (9) who have shown that HVR is not correlated with exercise ventilation or maintenance of  $SpO_2$  during exercise, our results also do not support a relationship between ventilatory measures and any measure of exercise  $SpO_2$  or  $HVR_{EX}$ . It should be mentioned though that  $\Delta SpO_{2-TT}$  values obtained in our study were within a narrow range (8.3%–10.9% reduction in  $SpO_2$  from normoxic to hypoxic TT), likely explaining why  $\Delta TT$  and  $\Delta SpO_{2-TT}$  were not correlated. Thus, although this finding is in contrast to what Chapman et al. (2) observed in highly trained runners, it should be interpreted with caution due to the narrow range of  $\Delta SpO_{2-TT}$  values and perhaps the mode of exercise performed in our study.

Despite the potential benefits an adequate hyperventilatory response could offer during exercise and/or under hypoxic conditions, it has been suggested that endurance athletes “breathe less” relative to their metabolic needs (i.e., lower  $\dot{V}_E/\dot{V}O_2$  and  $\dot{V}_E/\dot{V}CO_2$ ) compared with others with lower levels of fitness (8,14,31). Although we did not make any comparisons between trained and untrained individuals, our results indicate that in our cohort of endurance-trained athletes, TT performance in acute

moderate hypoxia was impaired to a greater extent in athletes who had markers of inadequate hyperventilation during normoxic and hypoxic exercise (i.e., higher  $P_{\text{et}}\text{CO}_{2\text{-TTN}}$  and  $P_{\text{et}}\text{CO}_{2\text{-TTH}}$  and lower  $\dot{V}_{\text{E}}/\dot{V}\text{CO}_{2\text{-TTN}}$ ,  $\dot{V}_{\text{E}}/\dot{V}\text{CO}_{2\text{-TTH}}$ , and  $\Delta\dot{V}_{\text{E-TT}}$ ). Our data also suggest that during hypoxic TT exercise, where pace/power is self-selected, it is essential that the increase in  $\dot{V}_{\text{E}}$  closely matches, or is proportional to, the specific metabolic requirements of hypoxic exercise (Fig. 2). In other words, there appears to be a “sweet spot” for exercise ventilation, where too large of an increase in  $\dot{V}_{\text{E}}/\dot{V}\text{O}_2$  and  $\dot{V}_{\text{E}}/\dot{V}\text{CO}_2$  and/or a decrease in  $P_{\text{et}}\text{CO}_2$  during exercise in hypoxia compared with normoxia is associated with a greater degree of TT performance impairment in hypoxia (Fig. 3). It is possible that further augmentation of ventilation during hypoxic exercise (compared with normoxia) would require more respiratory muscle work and amplify the respiratory muscle metaboreflex response (36,37). If so, this scenario would ultimately result in decreased  $\text{O}_2$  delivery to the exercising muscles, and consequentially greater performance impairments (36). However, this judicious speculation would need to be confirmed with direct measures.

## CONCLUSION

This is the first study to investigate the relationship between the poikilocapnic HVR at rest and during exercise, exercise ventilation, and a true performance measure at a moderate altitude more commonly experienced by endurance athletes in competition and training. Our results indicated that in a group

of highly trained individuals, ventilatory responsiveness to progressive hypoxia was greater during exercise than at rest, and there was no correlation between  $\text{HVR}_{\text{REST}}$  and  $\text{HVR}_{\text{EX}}$ , even when adjusting for exercise-induced increases in  $\dot{V}\text{CO}_2$ . By implementing a novel method to determine ventilatory responsiveness to progressive hypoxia during exercise, as an integrated process, we found that  $\text{HVR}_{\text{REST}}$  and  $\text{HVR}_{\text{EX}}$  were not correlated with the change in TT performance between normoxia and hypoxia. Thus, the gain in the ventilatory response to progressive hypoxia (at rest or during exercise) does not appear to be a significant factor in hypoxic exercise performance impairment. Nevertheless, a sufficient, but not exaggerated, hyperventilatory response during exercise is likely essential for mitigating impairments in performance in acute hypoxia. Specifically, our findings that  $\Delta\text{TT}$  was correlated with percentage difference ( $\Delta$ ) in  $\dot{V}_{\text{E}}$  and  $P_{\text{et}}\text{CO}_2$  between normoxic and hypoxic TT and  $\dot{V}_{\text{E}}/\dot{V}\text{CO}_2$  during  $\text{TT}_{\text{NORM}}$ —which together explained 85% of the variance in  $\Delta\text{TT}$ —could provide valuable insight into the largely unknown mechanisms contributing to interindividual variations in hypoxic performance impairment.

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The authors declare no conflict of interest. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

## REFERENCES

- Wehrin JP, Hallén J. Linear decrease in  $\dot{V}\text{O}_{2\text{max}}$  and performance with increasing altitude in endurance athletes. *Eur J Appl Physiol*. 2006;96(4):404–12.
- Chapman RF, Stager JM, Tanner DA, Stray-Gundersen J, Levine BD. Impairment of 3000-m run time at altitude is influenced by arterial oxyhemoglobin saturation. *Med Sci Sports Exerc*. 2011;43(9):1649–56.
- Lawler J, Powers SK, Thompson D. Linear relationship between  $\dot{V}\text{O}_{2\text{max}}$  and  $\dot{V}\text{O}_{2\text{max}}$  decrement during exposure to acute hypoxia. *J Appl Physiol*. 1988;64(4):1486–92.
- Burtscher M, Niedermeier M, Burtscher J, Pesta D, Suchy J, Strasser B. Preparation for endurance competitions at altitude: physiological, psychological, dietary and coaching aspects. A narrative review. *Front Physiol*. 2018;9:1504.
- Gavin TP, Derchak PA, Stager JM. Ventilation's role in the decline in  $\text{O}_{2\text{max}}$  and  $\text{SaO}_2$  in acute hypoxic exercise. *Med Sci Sports Exerc*. 1998;30(2):195–9.
- Townsend NE, Gore CJ, Ebert TR, Martin DT, Hahn AG, Chow CM. Ventilatory acclimatisation is beneficial for high-intensity exercise at altitude in elite cyclists. *Eur J Sport Sci*. 2016;16(8):895–902.
- Martin BJ, Weil JV, Sparks KE, McCullough RE, Grover RF. Exercise ventilation correlates positively with ventilatory chemoresponsiveness. *J Appl Physiol Respir Environ Exerc Physiol*. 1978;45(4):557–64.
- Martin BJ, Sparks KE, Zwillich CW, Weil JV. Low exercise ventilation in endurance athletes. *Med Sci Sports*. 1979;11(2):181–5.
- Hopkins SR, McKenzie DC. Hypoxic ventilatory response and arterial desaturation during heavy work. *J Appl Physiol* (1985). 1989; 67(3):1119–24.
- Harms CA, Stager JM. Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia. *J Appl Physiol*. 1995;79(2):575–80.
- Guenette JA, Diep TT, Koehle MS, Foster GE, Richards JC, Sheel AW. Acute hypoxic ventilatory response and exercise-induced arterial hypoxemia in men and women. *Respir Physiol Neurobiol*. 2004;143(1):37–48.
- Weil JV, Byrne-Quinn E, Sodal IE, et al. Hypoxic ventilatory drive in normal man. *J Clin Invest*. 1970;49(6):1061–72.
- Whipp BJ. Peripheral chemoreceptor control of exercise hyperpnea in humans. *Med Sci Sports Exerc*. 1994;26(3):337–47.
- Schoene RB, Lahiri S, Hackett PH, et al. Relationship of hypoxic ventilatory response to exercise performance on Mount Everest. *J Appl Physiol Respir Environ Exerc Physiol*. 1984;56(6):1478–83.
- Townsend NE, Gore CJ, Hahn AG, et al. Hypoxic ventilatory response is correlated with increased submaximal exercise ventilation after live high, train low. *Eur J Appl Physiol*. 2005;94(1–2): 207–15.
- Weil JV, Byrne-Quinn E, Sodal IE, Kline JS, McCullough RE, Filley GF. Augmentation of chemosensitivity during mild exercise in normal man. *J Appl Physiol*. 1972;33(6):813–9.
- Weil JV. Ventilatory control at high altitude [Internet]. *Compr Physiol*. 1986; available from: <http://onlinelibrary.wiley.com/doi/10.1002/cphy.cp030221/full>.
- Wasserman K, Whipp BJ, Casaburi R. Respiratory control during exercise. *Compr Physiol*. 2011;595–619.
- Bärtsch P, Swenson ER, Paul A, Jülg B, Hohenhaus E. Hypoxic ventilatory response, ventilation, gas exchange, and fluid balance in acute mountain sickness. *High Alt Med Biol*. 2002;3(4):361–76.
- Lhuissier FJ, Brumm M, Ramier D, Richalet JP. Ventilatory and cardiac responses to hypoxia at submaximal exercise are independent of altitude and exercise intensity. *J Appl Physiol* (1985). 2012; 112(4):566–70.

21. Richalet JP, Larmignat P, Poitrine E, Letournel M, Canouï-Poitrine F. Physiological risk factors for severe high-altitude illness: a prospective cohort study. *Am J Respir Crit Care Med*. 2012;185(2):192–8.
22. Dempsey JA, Olson EB, Skatrud JB. *Hormones and Neurochemicals in the Regulation of Breathing*. Bethesda (MD): American Physiological Society; 1986. pp. 181–222.
23. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098.
24. Atkinson G, Todd C, Reilly T, Waterhouse J. Diurnal variation in cycling performance: influence of warm-up. *J Sports Sci*. 2005;23(3):321–9.
25. Howley ET, Bassett DR Jr, Welch HG. Criteria for maximal oxygen uptake: review and commentary. *Med Sci Sports Exerc*. 1995;27(9):1292–301.
26. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14(5):377–81.
27. McConnell AK, Semple ES, Davies CT. Ventilatory responses to exercise and carbon dioxide in elderly and younger humans. *Eur J Appl Physiol Occup Physiol*. 1993;66(4):332–7.
28. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–38.
29. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna (Austria): R Foundation for statistical Computing; 2015. Available from: <http://www.R-project.org/>.
30. Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. *J Appl Physiol*. 1999;87(6):1997–2006.
31. Byrne-Quinn E, Weil JV, Sodal IE, Filley GF, Grover RF. Ventilatory control in the athlete. *J Appl Physiol*. 1971;30(1):91–8.
32. Zhang S, Robbins PA. Methodological and physiological variability within the ventilatory response to hypoxia in humans. *J Appl Physiol*. 2000;88(5):1924–32.
33. Schoene RB. Control of ventilation in climbers to extreme altitude. *J Appl Physiol*. 1982;53(4):886–90.
34. Dempsey JA, Hanson PG, Henderson KS. Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J Physiol*. 1984;355:161–75.
35. Amann M, Eldridge MW, Lovering AT, Stickland MK, Pegelow DF, Dempsey JA. Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans. *J Physiol*. 2006;575(3):937–52.
36. Harms CA, Babcock MA, McClaran SR, et al. Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* (1985). 1997;82(5):1573–83.
37. Dominelli PB, Molgat-Seon Y, Griesdale DEG, et al. Exercise-induced quadriceps muscle fatigue in men and women: effects of arterial oxygen content and respiratory muscle work. *J Physiol*. 2017; 595(15):5227–44.