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Ventilatory Responsiveness during Exercise and Performance Impairment in Acute Hypoxia

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Abstract

Introduction: An adequate increase in minute ventilation to defend arterial oxyhemoglobin saturation (SpO₂) 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 (TT).

Methods: Sixteen endurance-trained men ($\dot{V}O_{2peak}$, 62.5 ± 5.8 mL·kg⁻¹·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_IO₂ = 0.21) or hypoxic gas mixture (F_IO₂ = 0.16) in a randomized order.

Results: HVR_{EX} was significantly ($P < 0.001$) greater than HVR_{REST} (1.52 ± 0.47 and 0.22 ± 0.13 L·min⁻¹·%SpO₂⁻¹, respectively), and these measures were not correlated ($r = -0.16$, $P = 0.57$). TT was not correlated with HVR_{REST} ($P = 0.70$) or HVR_{EX} ($P = 0.54$), but differences in ventilation and end-tidal CO₂ between hypoxic and normoxic TT and the ventilatory equivalent for CO₂ during normoxic TT explained ~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

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to hypoxia, is essential for mitigating hypoxia-induced impairments in endurance cycling performance.

Keywords

PERIPHERAL CHEMORESPONSIVENESS; ARTERIAL OXYHEMOGLOBIN SATURATION; ALTITUDE; CYCLING; ATHLETES; EXERCISE

Large inter-individual variations exist in the extent to which maximal oxygen uptake ($\dot{V}O_{2\text{peak}}$) 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 afore-mentioned approach to measure resting HVR and to extend the outcomes to exercise ventilation. First, the responsiveness of peripheral chemoreceptors is augmented during exercise compared with rest (7,12,16), and second, isocapnia is not normally maintained under hypoxic conditions, and partial pressure of arterial CO_2 (P_aCO_2) 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_{EX}) will be greater than ventilatory responsiveness to progressive hypoxia at rest (HVR_{REST}). Second, we aimed to test the hypothesis that the degree of cycling performance impairment with acute exposure to moderate hypoxia ($F_iO_2 = 0.16$, ~2500 m of terrestrial altitude) will be inversely related to HVR_{EX} (i.e., those that increase minute ventilation [\dot{V}_E] enough to combat drops in SpO_2 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_{EX} , exercise \dot{V}_E , decline in S_pO_2 during exercise, and measures of an adequate hyperventilatory response during exercise (e.g., partial pressure of end-tidal CO_2 [$P_{et}CO_2$], $\dot{V}_E/\dot{V}O_2$, 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 ($\dot{V}O_{2peak}$, $62.5 \pm 5.8 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) 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^2) 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_iO_2 was reduced in a square-wave fashion (HVR_{SW} ; 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_iO_2 was reduced in a progressive, continuous manner (HVR_{REST} , see details below);

an exercise HVR test (HVR_{EX} , see details below); and a familiarization trial for the 10-km TT while breathing a hypoxic inspirate ($F_iO_2 = 0.18$, simulating an altitude of ~ 1500 m, subjects blinded), with 15 min of rest between the tests. This hypoxic level, i.e., a FiO_2 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 inspirate during the experimental TT. During the last two visits (visits 3 and 4), subjects performed a 10-km TT either in normoxia (TT_{NORM}) or in hypoxia (TT_{HYP} , $F_iO_2 = 0.16$, simulating an altitude of 2500 m). These final two visits were randomized and counterbalanced, and subjects were blinded to the inspirate.

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_{EX} (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 $\dot{V}O_{2peak}$ 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 ≥ 1.10 , and 3) a plateau in $\dot{V}O_2 \geq 150$ 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 $P_{\text{et}}CO_2$.

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 (ΔTT) between normoxia and hypoxia was calculated as a percentage difference in total time to complete the 10-km TT between TT_{NORM} and TT_{HYP} and is annotated in text with a “-TT” subscript. Thus, a positive ΔTT indicates performance during TT_{HYP} was worse (i.e., took more time to complete) than TT_{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 (Δ) in average values throughout the 10-km TT between the two conditions (e.g., $S_pO_{2\text{-TT}}$ and $P_{\text{et}}CO_{2\text{-TT}}$), where a negative Δ implies that values during TT_{NORM} were greater than TT_{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 ~ 40 mm Hg ($F_I O_2 = \sim 0.05$), 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_{REST}).—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 prefilled with room air. Slowly, 100% N_2 was added into the balloon reservoir to reduce the O_2 content in the inspired air over a 12- to 15-min time period. Real-time $P_{et}O_2$ values were used to guide the rate of addition of 100% N_2 into the balloon reservoir and ensure progressive hypoxia was induced. The test was concluded when S_pO_2 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_pO_2 and metabolic and ventilatory variables were taken from the last 30 s before the termination of the HVR_{REST} test and are annotated with a “-REST” subscript (e.g., SpO_{2-REST}).

Exercise HVR (HVR_{EX}).—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 inspirate with $F_I O_2 = 0.12$ (equivalent to ~ 4900 m). For HVR_{EX} , 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% O₂ for 5 min each. For safety reasons, if the subject's S_pO₂ reached ~70% or if P_{et}O₂ 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_{EX} and end-stage values. Values obtained from the last exercise stage (F_iO₂ = 0.12) are henceforth annotated with “-EX” (e.g., S_pO_{2-EX}).

Resting (square-wave) HVR (HVR_{SW}).—Because of differences in the specific fashion by which F_iO₂ was reduced during the HVR protocols for rest and exercise (i.e., a traditional protocol of continuous, progressive reduction during HVR_{REST} vs square-wave decreases during HVR_{EX}), we also implemented a resting HVR test where F_iO₂ was reduced in a square-wave manner (HVR_{SW}). Because HVR_{SW} 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% O₂ for 4 min. In series, the subject then breathed through three more meteorological balloon containing 15%, 12%, or 9% O₂ for 4 min each (hence, the total test time was 20 min). If the subject's S_pO₂ reached 70% or if P_{et}O₂ 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 (FEV₁), peak expiratory flow (PEF) and forced expiratory flow between 25% and 75% of the FVC (FEF₂₅₋₇₅), and a maximum voluntary ventilation (MVV) test. Each pulmonary test was performed in triplicate per ATS standards (28), and the largest FVC, FEV₁, PEF_R, FEF₂₅₋₇₅, 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_{REST}, HVR_{SW}, and HVR_{EX} and to determine differences in S_pO₂, HR, ventilatory, and metabolic variables at the multiple inspire levels during HVR_{EX}. Where a significant main effect was found, the Tukey *post hoc* test was performed. Because HVR_{EX} and HVR_{SW} were not normally distributed, a Spearman rank correlation was also performed in addition to Pearson's *r*. Within-test analyses for HVR_{REST} or HVR_{EX} 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 (TT, see details above) with HVR_{EX} 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 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. S_pO_2 during the GXT, performed in normoxia, was measured in 12 subjects, and of those, 5 demonstrated at least mild desaturation ($<95\% S_pO_2$ [30]). All participants had normal pulmonary function values (mean \pm SD; FVC = 5.8 ± 1.1 L, FEV_{1.0} = 4.8 ± 0.9 L, PEF = 10.2 ± 2.4 L·s⁻¹, FEF₂₅₋₇₅ = 5.2 ± 1.3 L·s⁻¹, MVV = 177.8 ± 43.1 L·min⁻¹).

Ventilatory responsiveness.

One subject was not able to complete more than two stages of HVR_{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 HVR_{EX} (1.60 ± 0.47 L·min⁻¹·%⁻¹) was greater than both HVR_{SW} (0.17 ± 0.12 L·min⁻¹·%⁻¹, $P < 0.001$) and HVR_{REST} (0.21 ± 0.15 L·min⁻¹·%⁻¹, $P < 0.001$). Because HVR_{SW} and HVR_{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 HVR_{SW} in this study was strictly performed as a validation test, only HVR_{REST} will be considered in further comparisons between, and discussion of, resting and exercise HVR. When 15 subjects were included in the analyses, HVR_{EX} (1.52 ± 0.47 L·min⁻¹·%⁻¹) was still significantly greater than HVR_{REST} (0.22 ± 0.13 L·min⁻¹·%⁻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).

HVR_{REST} .

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

HVR_{EX} .

Actual F_iO_2 levels were within $\pm 0.3\%$ of the target F_iO_2 for each stage. SpO_2 values at the end of the test ($F_iO_2 = 0.12$) ranged between 66.6% and 81.4%. HVR_{EX} ranged between 0.84 and 2.27 L·min⁻¹·%⁻¹ while subjects cycled at an average power output of 155 ± 25 W.

\dot{V}_E increased by <1.5% or <1.4 L·min⁻¹ between the third and the fifth minutes of the last stage of HVR_{EX}, confirming that a steady state was reached during this stage. As expected, there was a significant decrease in S_pO₂ and P_{et}O₂ throughout HVR_{EX} and between all stages (Table 2). A significant main effect for F_IO₂ level was also detected for P_{et}CO₂, \dot{V}_E , breathing frequency, $\dot{V}CO_2$, $\dot{V}_E/\dot{V}CO_2$, $\dot{V}_E/\dot{V}_{E_{max}}$, HR, and dyspnea (Table 2). Data obtained during each stage of HVR_{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 TT_{HYP} compared with TT_{NORM} (Δ : 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_{et}CO₂, S_pO₂, 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).

TT correlations.

As shown in Figure 3, TT between normoxia and hypoxia was not correlated with HVR_{REST} or HVR_{EX}. In addition, S_pO_{2-TT} ($r = -0.21$, $P = 0.55$) or average S_pO₂ values obtained during TT_{HYP} ($r = -0.11$, $P = 0.75$) and TT_{NORM} ($r = -0.28$, $P = 0.40$) were not correlated with TT. A significant negative correlation between \dot{V}_E -TT and TT (Fig. 3C) indicated higher (absolute) \dot{V}_E during TT_{NORM} compared with TT_{HYP} was associated with greater hypoxic performance impairments. By contrast, markers that indicate a more pronounced/exaggerated ventilatory response during TT_{HYP} relative to TT_{NORM} were also related to a greater impairment of 10 km cycle performance in hypoxia. Specifically, significant ($P < 0.05$) correlations between TT and P_{et}CO_{2-TT} (Fig. 3D) and $\dot{V}_E/\dot{V}O_{2-TT}$ (Fig. 3E), and an approaching significance correlation between TT and $\dot{V}_E/\dot{V}CO_{2-TT}$ ($P = 0.09$; Fig. 3F), would suggest hypoxic performance was impaired to a greater extent with an enhanced ventilatory response during TT_{HYP} compared with TT_{NORM}. Interestingly, subjects with markers of reduced ventilatory output during the normoxic TT such as P_{et}CO_{2-TTN} ($r = 0.72$, $P < 0.05$) 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 TT and mean P_{et}CO_{2-TTH} and $\dot{V}_E/\dot{V}CO_{2-TTH}$ during TT_{HYP} approached significance ($r = 0.56$, $P = 0.056$, and $r = -0.54$, $P = 0.07$, respectively).

Multiple regression analysis revealed \dot{V}_E -TT, P_{et}CO_{2-TT}, and $\dot{V}_E/\dot{V}CO_{2-TTN}$ as significant predictors of TT, and these variables explained 85% of the variance in performance impairment in acute hypoxia ($R^2_{adjusted} = 0.85$, $P < 0.001$, $TT = 8.47 - 0.25 \dot{V}_E/\dot{V}CO_{2-TTN} - 0.41 P_{et}CO_{2-TT} - 0.06 \dot{V}_E$ -TT). Although other independent variables (e.g., P_{et}CO_{2-TTN} and $\dot{V}_E/\dot{V}O_{2-TT}$) were also significantly correlated with TT, these factors were excluded from the final model due to collinearity and/or because their inclusion did not significantly improve the model.

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_{REST} and HVR_{EX} , implying that the gain of the ventilatory response to a given change in S_pO_2 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_{EX} . 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 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_{REST} or HVR_{EX}), is necessary for mitigating the expected hypoxia-induced impairments in endurance cycling performance. 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_aO_2 on \dot{V}_E , independent of P_aCO_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 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} and HVR_{EX} slopes (Fig. 1B), the normalized HVR slopes ($\dot{V}_E/\dot{V}CO_2$ vs S_pO_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 S_pO_2) would be correlated with TT. Our results, however, indicated that HVR_{EX} and degree of impairment in cycling performance in acute hypoxia were not correlated, despite 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 S_pO_2 during exercise, our results also do not support a relationship between ventilatory measures and any measure of exercise S_pO_2 or HVR_{EX} . It should be mentioned though that S_pO_{2-TT} values obtained in our study were within a narrow range (8.3%–10.9% reduction in S_pO_2 from normoxic to hypoxic TT), likely explaining why TT and S_pO_{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 S_pO_{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 $P_{et}CO_{2-TTN}$ and $P_{et}CO_{2-TTH}$ and lower $\dot{V}_E/\dot{V}CO_{2-TTN}$, $\dot{V}_E/\dot{V}CO_{2-TTH}$, and \dot{V}_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}_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 $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ and/or a decrease in $P_{et}CO_2$ 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 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 HVR_{REST} and HVR_{EX} , even when adjusting for exercise-induced increases in $\dot{V}CO_2$. By implementing a novel method to determine ventilatory responsiveness to progressive hypoxia during exercise, as an integrated process, we found that HVR_{REST} and HVR_{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 TT was correlated with percentage difference () in \dot{V}_E and $P_{et}CO_2$ between normoxic and hypoxic TT and $\dot{V}_E/\dot{V}CO_2$ during TT_{NORM} —which together explained 85% of the variance in TT—could provide valuable insight into the largely unknown mechanisms contributing to interindividual variations in hypoxic performance impairment.

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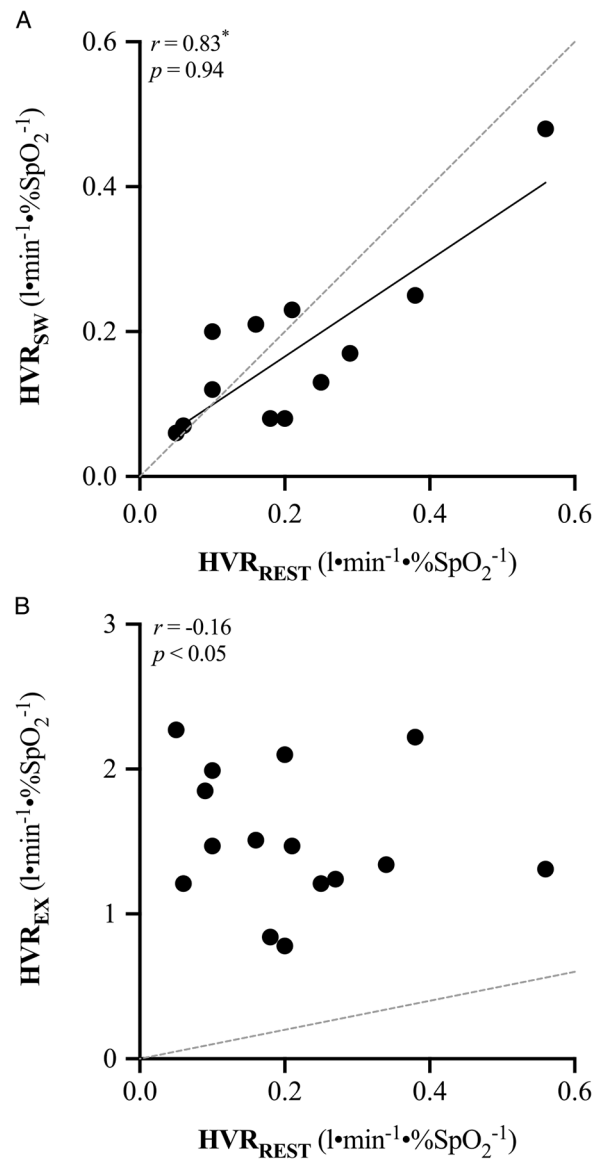


FIGURE 1—

Correlations between ventilatory responsiveness tests. A. Resting progressive (HVR_{REST}) vs resting square-wave (HVR_{SW}) HVR ($n = 12$); the slopes were not different and highly correlated $P < 0.05$. B. HVR_{REST} and exercise HVR (HVR_{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.

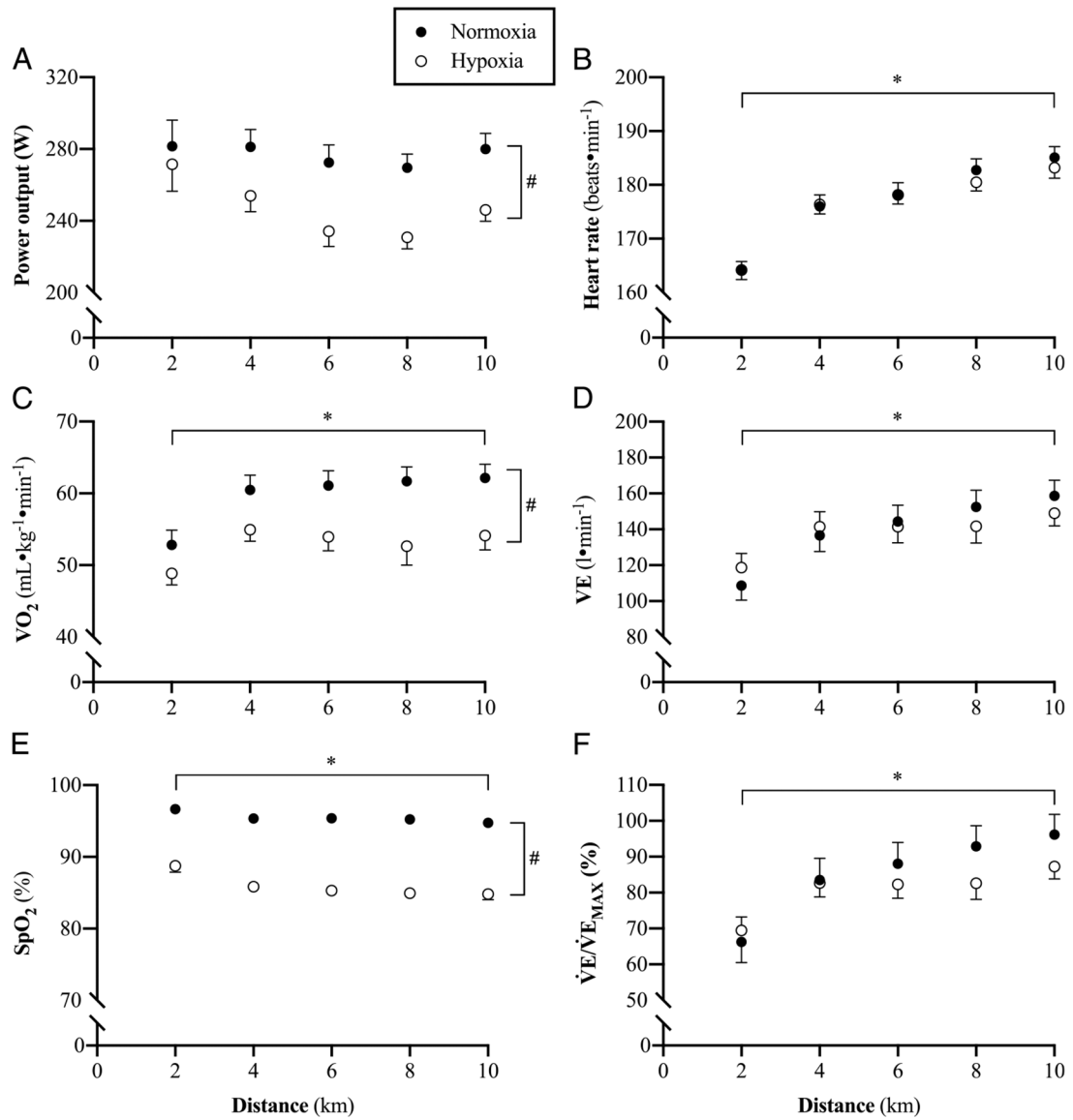


FIGURE 2—

Key measures obtained every 2 km during the 10-km TT performed in normoxia (closed circles) and hypoxia ($F_iO_2 = 0.16$; open circles). Power output (A); HR (B); O_2 consumption ($\dot{V}O_2$) (C); minute ventilation (\dot{V}_E) (D); arterial oxyhemoglobin saturation (S_pO_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 inspirate ($P < 0.05$). Values are presented as mean \pm SE.

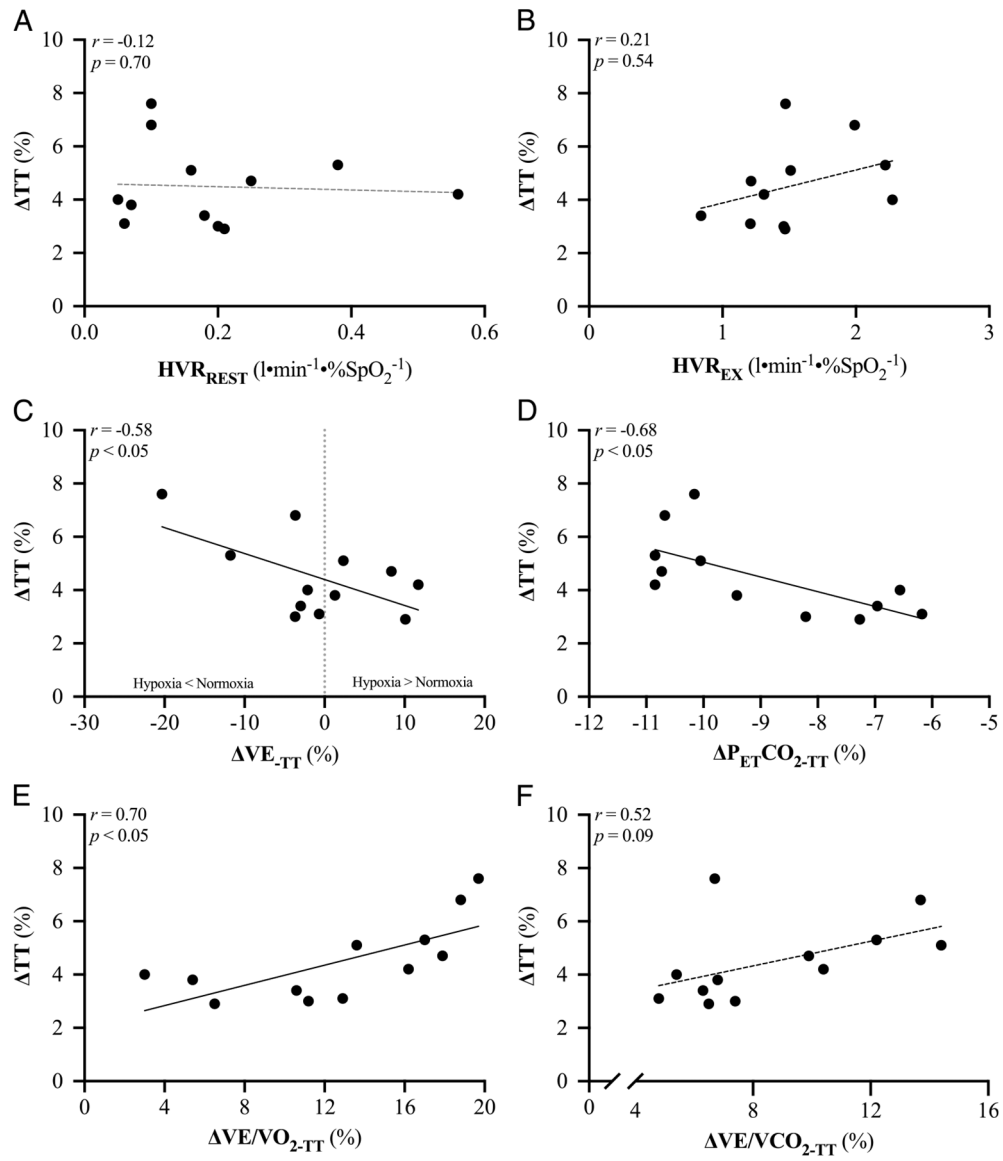
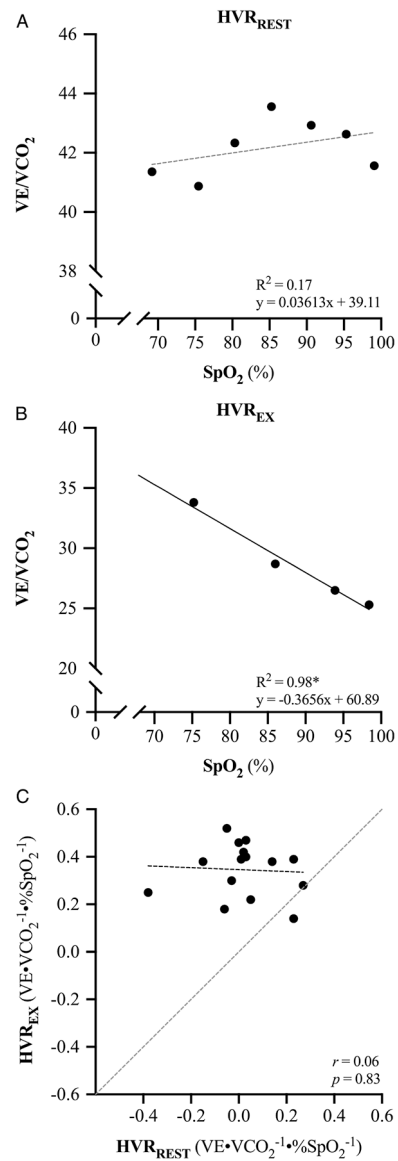


FIGURE 3— Relationships between degree of performance impairments in a 10-km TT from normoxia to hypoxia ($F_iO_2 = 0.16$; TT) and HVR at rest (HVR_{REST}) (A); HVR during exercise (HVR_{EX}) (B); minute ventilation (\dot{V}_{E-TT}) (C); partial pressure of end-tidal CO_2 ($P_{et}CO_{2-TT}$) (D); ventilatory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

**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 S_pO_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).

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

Age (yr)	24 ± 5
Height (m)	1.79 ± 5.7
Mass (kg)	71.3 ± 7.6
Body surface area (m ²)	1.91 ± 0.11
Graded exercise test—end exercise values	
Peak power output (W)	379 ± 42
$\dot{V}O_{2\text{peak}}$ (L·min ⁻¹)	4.4 ± 0.5
$\dot{V}O_{2\text{peak}}$ (mL·kg ⁻¹ ·min ⁻¹)	62.5 ± 5.8
$\dot{V}CO_{2\text{peak}}$ (L·min ⁻¹)	5.1 ± 0.6
$\dot{V}_{E\text{max}}$ (L·min ⁻¹)	173.2 ± 29.5
$\dot{V}_E/\dot{V}O_2$	39.2 ± 5.3
$\dot{V}_E/\dot{V}CO_2$	33.8 ± 4.1
RER	1.16 ± 0.06
$P_{\text{et}}CO_2$ (mm Hg)	35.2 ± 3.3
HR (bpm)	186 ± 9
S_pO_2 (%)	95.0 ± 2.2

Values are presented as mean \pm SD.

$\dot{V}O_{2\text{peak}}$, maximal O₂ consumption; $\dot{V}CO_{2\text{peak}}$, maximal CO₂ production; $\dot{V}_{E\text{max}}$, maximal exercise minute ventilation.

TABLE 2.

Ventilatory response tests—end test/stage values.

	HVR _{EX} (n = 15)				Interaction		
	HVR _{REST} (n = 16)	Stage 1 (F _I O ₂ = 0.21)	Stage 2 (F _I O ₂ = 0.18)	Stage 3 (F _I O ₂ = 0.15)	Stage 4 (F _I O ₂ = 0.12)	P	F
Slope (L·min ⁻¹ ·% ⁻¹)	0.22 ± 0.13	1.52 ± 0.47					
S _p O ₂ (%)	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 ⁻¹)	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 ⁻¹)	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 ⁻¹)	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 _e tO ₂ (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 _e tCO ₂ (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_IO₂ = 0.12).

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

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