



Rapidity of responding to a hypoxic challenge during exercise

Authors

Blair D. Johnson · Trent Joseph · Glenn Wright · **Rebecca A. Battista** · Christopher Dodge · Alecia Balweg · Jos J. de Koning · Carl Foster

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The ability to modify power output (PO) in response to a changing stimulus during exercise is crucial for optimizing performance involving an integration system involving a performance template and feedback from peripheral receptors. The rapidity with which PO is modified has not been established, but would be of interest relative to understanding how PO is regulated. The objective is to determine the rapidity of changes in PO in response to a hypoxic challenge, and if change in PO is linked to changes in arterial O₂ saturation (SaO₂). Well-trained cyclists performed randomly ordered 5-km time trials. Subjects began the trials breathing room air and switched to hypoxic (HYPOXIC, FIO₂ = 0.15) or room (CONTROL, FIO₂ = 0.21) air at 2 km, then to room air at 4 km. The time delay to begin decreasing SaO₂ and PO and to recover SaO₂ and PO on to room air was compared, along with the half time (t_{1/2}) during the HYPOXIC trial. Mean SaO₂ and between 2 and 4 km were significantly different between CONTROL and HYPOXIC (94 ± 2 vs. 83 ± 2% and 285 ± 16 vs. 245 ± 19 W, respectively). There was no difference between the time delay for SaO₂ (31.5 ± 12.8 s) and in PO (25.8 ± 14.4 s) or the recovery of SaO₂ (29.0 ± 7.7 s) and PO (21.5 ± 12.4 s). The half time for decreases in SaO₂ (56.6 ± 14.4 s) and in PO (62.7 ± 20.8 s) was not significantly different. Modifications of PO due to the abrupt administration of hypoxic air are related to the development of arterial hypoxemia, and begin within »30 s.

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decreases in S_aO_2 (56.6 + 14.4 s) and in PO (62.7 + 20.8 s) was not significantly different. Modifications of PO due to the abrupt administration of hypoxic air are related to the development of arterial hypoxemia, and begin within »30 s.

Keywords Cycling · Altitude · Pacing · Hypoxia

Introduction

Many athletic competitions involve the use of pacing strategies, which can be defined as an organized plan to optimize the use of energetic resources in order to improve performance and delay fatigue (Ansley et al. 2004; Foster et al. 2003, 2004; Joseph et al. 2008; St Clair Gibson et al. 2006). Pacing strategies appear to be somewhat unique to each athlete, competitive distance and type of event (e.g., air resisted, water resisted, gravity resisted). Prior experience with competition and practice is probably essential to developing a template or general pacing plan (Lambert et al. 2004; Noakes and St Clair Gibson 2004) which may be modified in response to a variety of internal and external stimuli including changes in weather, substrate availability, fitness level, and mental state (Ulmer 1996; Craig 2002). Eston et al. (2007) have presented evidence that the growth of the rating of perceived exertion (RPE) is scalar (e.g., grows in a pattern which is proportional to the relative time to fatigue). Recent evidence from our laboratory (Joseph et al. 2008) has indicated that the growth of RPE during time trials is related to the relative proportion of the event completed. These data support the concept that athletes are continually asking themselves how fatigued they feel at any particular moment compared to how fatigued they expected to feel at that point, and actively adjust their power output

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(PO) if the momentary level of fatigue (or sense of effort) is different than anticipated.

Given that muscular PO will be downregulated in the presence of factors that accelerate the growth of fatigue, we know very little about how developing fatigue signals its presence and how rapidly the exerciser can sense and respond to disruptive stimuli. Exercise performance changes predictably with changes in FiO_2 , improving in hyperoxia and deteriorating in hypoxia (Amann et al. 2006a, b; Peltonen et al. 1995, 2001; Tucker et al. 2007). While there is evidence of peripheral fatigue, evidenced by increases in the iEMG/PO as exercise proceeds (Amann et al. 2006a, b; Tucker et al. 2007) and reductions in stimulated muscle force output (Amann et al. 2006a, b), there is also evidence that iEMG and PO change during exercise in response to changes in FiO_2 , supporting the concept of a centrally mediated regulation. Because of the possibility of blinding subjects to manipulations in normobaric FiO_2 , such a challenge represents a convenient experimental model to explore how disruptive stimuli are sensed. Most previous studies in which FiO_2 has been manipulated have required that the subject breathe a given FiO_2 from the beginning of exercise (Amann et al. 2006a, b; Lundby et al. 2001; Peltonen et al. 1995, 2001; Tucker et al. 2007; Wehrlin and Hallen 2006). Thus, the nature of the acute response of PO to changes in FiO_2 are unknown. Previous studies have shown that subjects begin time trial exercise at a common PO and may take some time (30–60 s) to downregulate PO in the presence of a reduced FiO_2 (Amann et al. 2006a, b; Tucker et al. 2007). We felt that it might be instructive to determine how rapidly PO changed in response to square wave changes in FiO_2 during the midst of an exercise bout. Accordingly, the purpose of this study was to determine how rapidly PO changes after FiO_2 was experimentally changed and to test the hypothesis that the decrease in power output was related to changes in S_aO_2 .

Methods

Ten well-trained cyclists (Table 1) provided written informed consent. The university human subjects committee approved the research protocol. The subjects were informed that hypoxia might be employed during some trials. Each subject completed an incremental exercise test to determine maximal exercise responses, a practice 5-km time trial designed to habituate the subjects to the equipment and time trial distance, and then randomly ordered CONTROL (room air) and HYPOXIC (experimental) 5-km time trials.

The incremental test was performed on an electrically braked cycle ergometer (Lode Excalibur, Groningen, The Netherlands) beginning at 25 W and increasing 25 W every

Table 1 Descriptive statistics and responses at maximal exercise during the incremental exercise test (mean \pm SD)

| Variable | Males (n = 7) | Females (n = 3) | Total (n = 10) |
|---|------------------|--------------------|-------------------|
| Age (years) | 23.9 \pm 6.1 | 30.0 \pm 7.2 | 25.7 \pm 6.7 |
| Mass (kg) | 78.4 \pm 9.9 | 59.2 \pm 7.6* | 72.6 \pm 12.8 |
| $\text{VO}_{2\text{max}}$ (L min^{-1}) | 4.80 \pm 0.60 | 3.02 \pm 0.40* | 4.27 \pm 1.00 |
| HR_{max} (beats min^{-1}) | 189 \pm 11 | 189 \pm 7 | 189 \pm 9 |
| PO_{max} (W) | 357 \pm 62 | 267 \pm 29* | 330 \pm 69 |

* Significantly different versus males, $P < 0.05$

2 min until volitional fatigue. Respiratory gas exchange was measured using a mixing chamber based open circuit spirometry system (AEI Technologies, Pittsburgh, PA). RPE were recorded using the category ratio RPE scale (Borg 1998) at the end of each stage. Heart rate (HR) was monitored using radiotelemetry (Polar Vantage XL, Polar Instruments, Port Washington, NY). Ventilatory threshold was defined and highest continuously recorded 30-s oxygen consumption ($\text{VO}_{2\text{max}}$), power output (PO_{max}), and heart rate (HR_{max}) were recorded (Foster and Cotter 2006).

Time trials

Randomly ordered CONTROL and HYPOXIC 5-km time trials were used to determine the rapidity of sensing the changes in PO and S_aO_2 induced by changes in FiO_2 . In the HYPOXIC trial the subjects breathed hypoxic air ($\text{F}_i\text{O}_2 = 0.15$) between 2 and 4 km from bags. An F_iO_2 of 0.15 was chosen since, given the average barometric pressure of our laboratory (740 mmHg), it represents an inspired pO_2 approximating an altitude of 2,300 m, which is the highest altitude at which Olympic level competition has been organized. During the CONTROL trial, the subjects performed the same protocol except that the bags contained normoxic air ($\text{F}_i\text{O}_2 = 0.209$). The bags were attached to a mixing chamber and hoses that contained a volume of 7 L. F_iO_2 in the bags was measured prior to each time trial to verify the experimental conditions; however, our respiratory analysis system would not allow continuous measurement of FiO_2 during the time trial. The subjects were not informed about the duration of hypoxia or at what point in the trial they were to breathe from the bags. The location of the bags was somewhat behind the subject, so other than being aware of laboratory personnel moving around the laboratory equipment, they had no possibility of determining when their air source was switched to the bags, or the composition of air in the bags. The bags, with a pre-exercise volume of $\gg 600$ L, were pre-filled, connected in series and did not require filling during the time trial.

Time trials were performed on an electronically braked cycle ergometer (Velotron, Racermate Inc, Seattle, WA).

Prior to each time trial, subjects performed a 10-min warm-up at two workloads (5 min each) requiring 50 and 90% of the PO at the ventilatory threshold. Following a 3-min recovery period at $\gg 25$ W following the warm-up, a Wngertip blood sample was taken to measure blood lactate concentration [BL] (Accusport, Hawthorne, NY). The time trial was begun 4 min after completion of the warm-up. During the time trials, feedback was available to the subjects via the ergometer monitor regarding distance completed, elapsed time, momentary velocity, PO, and HR, just as they might have during competition using many commercially available cycle computers. Ventilation (V_E) was measured using open circuit spirometry during each time trial and was averaged every 500 m. Because we were not able to continuously measure F_iO_2 and F_eO_2 during the HYPOXIC trials, we did not compute VO_2 during the time trials. PO and velocity were recorded at 31 Hz and integrated every 100 m. Arterial oxygen saturation (S_aO_2) was measured by a fingertip pulse oximeter (Allegiance Oximeter 2000, Allegiance Health Care, McGraw Park, IL), recorded every second and averaged every 100 m. The oximeter has a manufacturer designated 2-s delay, which was adjusted in the data array prior to analysis. RPE was recorded using the category ratio scale (Borg 1998) every 500 m using hand signals. A 3-min post time trial [BL] was measured in a fingertip blood sample.

A habituation 5-km time trial was used to orient the subjects to the equipment, procedures, and distance prior to the experimental trials. Throughout this trial the subjects breathed room air from the bag system while wearing the respiratory apparatus as in the experimental trials. This was done in order to become familiar with the slightly increased inspiratory resistance associated with the breathing apparatus and serial bag arrangement. The bag system contained $\gg 600$ L of gas mixed to the specified concentration by adding N_2 to room air. The bags were connected in series to the subjects via a mixing chamber and hose containing $\gg 7$ L of dead space. The subject drew this air through the turbine for measuring ventilation directly into the respiratory mouthpiece.

Statistical analyses

Repeated measures ANOVA was used to compare differences between CONTROL and HYPOXIC for time trial performance (time) and mean S_aO_2 , PO, V_E , HR, velocity, and [BL]. A value of $P < 0.05$ was accepted as significantly significant. Additionally, the correlation between time markers of changes in S_aO_2 and PO was computed to provide evidence of the strength of the hypothesized temporal relationship. We chose to include both time delay and $t_{1/2}$ markers of the response during the HYPOXIC trial and the return to normoxia in order to have enough range in the data to allow for appropriate use of correlation statistics.

To compare the effects of breathing abruptly administered low F_iO_2 air, we calculated the variation of PO and S_aO_2 in the 60 s prior to the transition from normoxia to hypoxia (at 2 km), and from hypoxia to normoxia (at 4 km), and in the 80 s following each transition. The change in PO and S_aO_2 was individually fitted to curves in the stable period before switching to the hypoxic gas mixture and to the period after switching. The intersection of the individual curves was accepted as the time delay. This allows calculation of the time delay before S_aO_2 and PO began to decrease after the transition from normoxia to hypoxia at 2 km and before S_aO_2 and PO began to increase after the transition from hypoxia to normoxia at 4 km. From the individual curve *watts*, the $t_{1/2}$ of changes in PO and S_aO_2 following the transition to breathing low F_iO_2 air was calculated for each subject. Because the PO response from hypoxia to normoxia after 4 km was confounded by the end spurt, stable values of PO were never observed, and kinetic variables could not be calculated. However, for comparative purposes, the $t_{1/2}$ for recovery of S_aO_2 was calculated. Statistical significance was accepted when $P < 0.05$.

Results

The experimental condition produced a significant decrement in time trial performance as evidenced by a longer time required to complete the 5-km time trial (CONTROL 478.9 \pm 37.5 s vs. HYPOXIC 490.1 \pm 33.8 s). Table 2 displays the mean values for S_aO_2 , PO, HR, V_E , and velocity over various segments of the CONTROL and HYPOXIC trials, from which it is evident that the decrement in performance was related to the period during which the subjects were breathing low F_iO_2 air. Pre and post [BL] changed significantly within each condition (CONTROL pre 3.1 \pm 1.3 mmol L^{-1} vs. post 8.9 \pm 3.0 mmol L^{-1} and HYPOXIC pre 2.9 \pm 1.0 mmol L^{-1} vs. post 8.6 \pm 2.9 mmol L^{-1}), but were not significantly different between CONTROL versus HYPOXIC conditions.

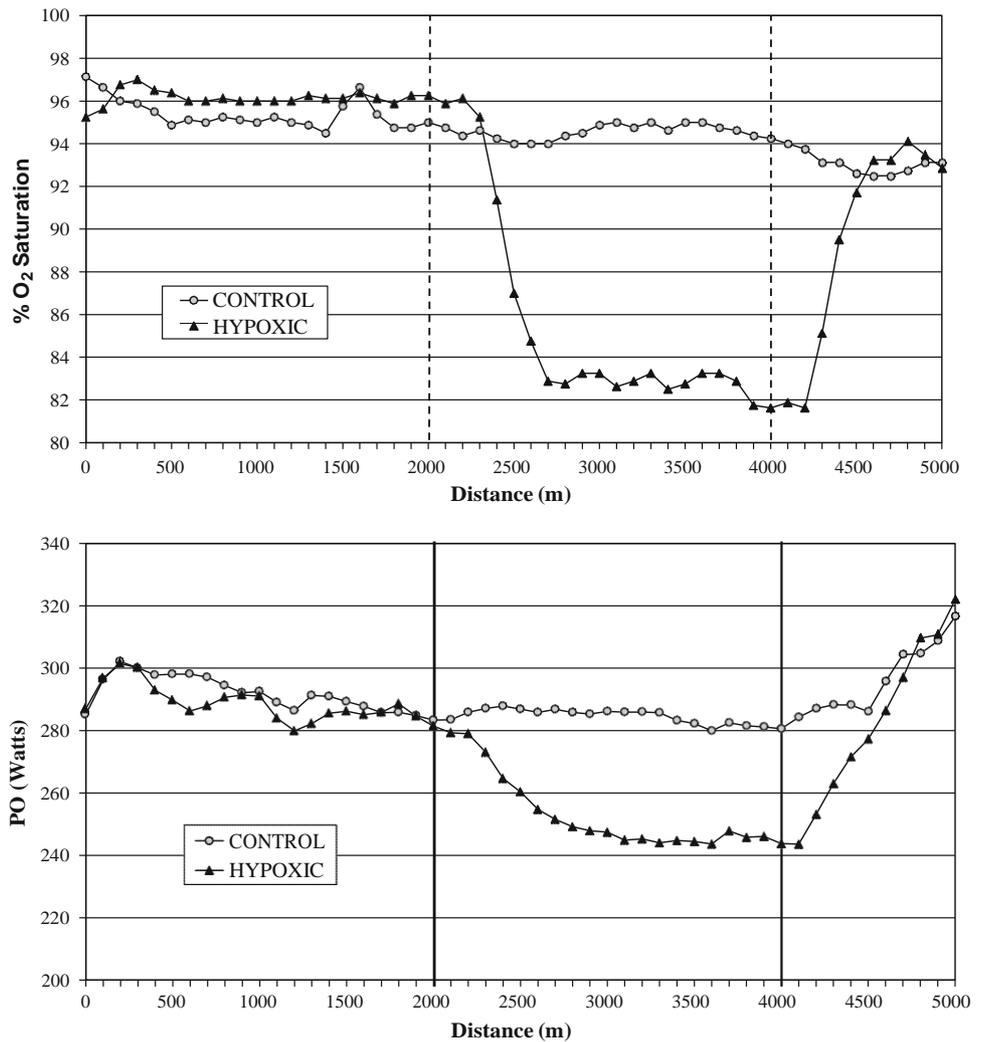
Mean values for each 100 m for S_aO_2 are presented in Fig. 1 (top). During the CONTROL ride there was not a systematic variation in S_aO_2 , other than a general tendency toward mild desaturation which has been reported previously (Dempsey and Wagner 1999). S_aO_2 was relatively stable over the first 2,000 m of the HYPOXIC trial then decreased rapidly during the period of breathing low F_iO_2 air, and reached a relatively stable level after $\gg 700$ m hypoxic administration. Upon returning to breathing room air, S_aO_2 recovered to control values quickly. During the CONTROL ride, PO was relatively stable except for the end spurt beginning at approximately 90% of the full distance, which has been reported previously (Amann et al. 2006a; Foster et al. 2003, 2004; Joseph et al. 2008; Rauch et al. 2005; Tucker et al.

Table 2 Mean responses over various segments of the CONTROL and HYPOXIC trials (mean \pm SD)

| Variable | CONTROL | | | HYPOXIC | | |
|-------------------------|----------------|------------------|------------------|-----------------|------------------|------------------|
| | 0–2,000 m | 2,000–4,000 m | 4,000–5,000 m | 0–2,000 m | 2,000–4,000 m | 4,000–5,000 m |
| S_aO_2 (%) | 95 \pm 4 | 94 \pm 4 | 93 \pm 4 | 95 \pm 4 | 84 \pm 8* | 89 \pm 8 |
| PO (W) | 284 \pm 59 | 277 \pm 60 | 290 \pm 62 | 281 \pm 56 | 246 \pm 50* | 276 \pm 62 |
| HR (beats min^{-1}) | 172 \pm 11 | 184 \pm 9 | 189 \pm 9 | 170 \pm 11 | 182 \pm 9 | 185 \pm 9 |
| V_E (L min^{-1}) | 94 \pm 27.8 | 129.2 \pm 28.0 | 141.8 \pm 35.0 | 94.1 \pm 25.2 | 123.9 \pm 23.2 | 129.5 \pm 28.2 |
| Velocity (km h^{-1}) | 37.9 \pm 2.9 | 37.6 \pm 3.0 | 38.2 \pm 3.0 | 37.8 \pm 2.8 | 36.0 \pm 2.7* | 37.5 \pm 3.1 |

* $P < 0.05$ versus CONTROL

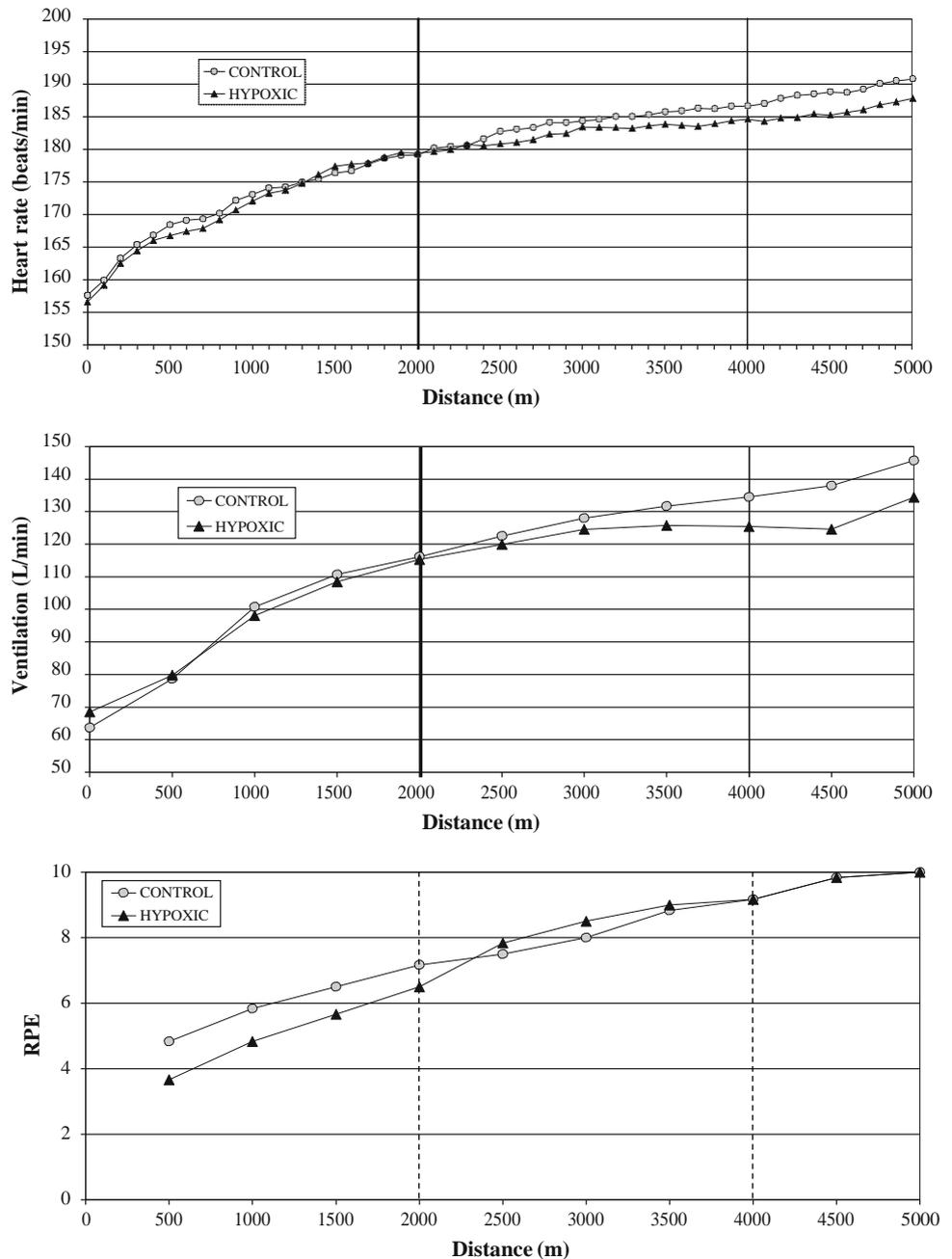
Fig. 1 Top arterial oxygen saturation during HYPOXIC and CONTROL trials. Dashed lines enclose the period of breathing hypoxic or room air from a bag. Bottom power output during HYPOXIC and CONTROL trials. Dashed lines enclose the period of breathing hypoxic or room air from a bag



2007), and occurred after the experimental portion of the ride (Fig. 1, bottom). PO was relatively stable over the first 2,000 m of the HYPOXIC trial, then decreased rapidly during the period of breathing low FiO_2 air, and reached a relatively stable level after \gg 1,000-m administration of low FiO_2 air. Upon returning to breathing room air, PO recovered toward CONTROL values quickly. With the onset of breathing low FiO_2 air, the time delay for beginning the decrease in

PO (25.8 + 14.4 s) was not significantly different than the time delay for decreasing S_aO_2 (31.5 + 12.8 s). With the return to breathing room air, the time delay for beginning the recovery of PO (21.5 + 12.4 s) was not significantly different than the time delay for recovering S_aO_2 (29.0 + 7.7 s). The $t_{1/2}$ for decreasing S_aO_2 during breathing low FiO_2 air (56.6 + 14.4 s) was not significantly different than the $t_{1/2}$ for decreasing PO (62.7 + 20.8 s).

Fig. 2 Heart rate, ventilation, and RPE during HYPOXIC and CONTROL trials. *Dashed lines* enclose the period of breathing hypoxic or room air from a bag



Mean values for each 100 m for HR and V_E , and for each 500 m for RPE are presented in Fig. 2. There were no statistically significant differences during the HYPOXIC and CONTROL rides, although there was a tendency for HR and V_E to be reduced during the period of breathing low F_{iO_2} air, consistent with the reduction in PO. There were no differences between HYPOXIC and CONTROL rides for RPE.

We questioned the subjects after the conclusion of both trials, and only 3 of 10 could correctly identify which trial was the HYPOXIC trial, and none was consciously aware of great differences. In response to questioning about why

they were going slower during the period of breathing low F_{iO_2} air, they replied that they just thought they were having a 'bad patch'.

Discussion

We tested the hypothesis that a modification in PO in trained cyclists, due to an abrupt and blinded change in F_{iO_2} , would be related to the decrease in S_aO_2 . We induced large changes in S_aO_2 by the experimental treatment, and found that changes in PO were significant, of similar

magnitude ($\gg 85\%$ of CONTROL values) and temporally linked. The recovery of PO and S_aO_2 following the hypoxic challenge were nearly simultaneous. Accordingly, the hypothesis that changes in PO would be related to changes in S_aO_2 is supported. This suggests that arterial hypoxemia may be a direct signaling mechanism for the control of PO during exercise, although without information about intramuscular conditions we cannot definitively isolate the location of the signal for disturbed homeostasis that leads to decreases in PO. It is probably reasonable to assume that the decrease in PO was attributable to a decrease in iEMG (Amann et al. 2006a, b, Tucker et al. 2007), since the only time iEMG increases while PO is decreasing is during profound fatigue (Hettinga et al. 2006). Based on the recovery of PO, once the subject returned to breathing room air, it also seems reasonable to assume that the subjects were not profoundly fatigued during the experimental period of the study. However, without direct measurement factors of iEMG (Amann et al. 2006a, b; Hettinga et al. 2006; Tucker et al. 2007), EEG (St Clair Gibson et al. 2006), muscle metabolites (Karlsson and Saltin 1970) or muscle O_2 saturation (Foster et al. 1999) it is impossible to determine whether the decrease in PO during HYPOXIA was attributable to a directly mediated decrease in central motor output or to feedback to the central nervous system from increased disturbances in the exercising muscles. Nevertheless, the present results suggest that this type of temporary hypoxic challenge might be a useful experimental model for subsequent studies with more definitive technology.

Because the subjects experienced the same respiratory resistance during the CONTROL and HYPOXIC trials, and because the density of each gas mixture was equal, the decrease in PO cannot be explained by an increase in respiratory resistance or change in air density. This is supported by the tendency to decrease V_E during the HYPOXIC trial. In hypobaric hypoxia, as would occur during high altitude exercise, V_E is often increased secondary to the reduction in air density. Since V_E essentially followed the momentary PO, there is little likelihood that changes in V_E could serve as a signaling mechanism for the presence of hypoxia and trigger the decrease in PO.

We were successful in our attempt to create hypoxemia in our subjects through the abrupt and blinded administration of low FiO_2 air. However, there were large variations between subjects' time delay to desaturation (20–41 s), which could be attributed to several causes. We were not able to coordinate the hypoxic air exposure with the stage of the subjects' respiratory cycle. Subjects with a high residual volume at the moment of breathing the hypoxic air (e.g., end inspiration) would take longer to desaturate than the subjects with a low residual volume (e.g., end expiration). Additionally, the subjects had different values for V_E , ranging from 79 to 144 L min^{-1} when they were introduced

to the low FiO_2 air. Due to the constant 7-L dead space in the system, this could account for delays in hypoxic air reaching subjects' mouth ranging from 2 to 5 s. This value, combined with reasonable estimates of the time for pulmonary gas exchange (2–5 s) and circulatory time (5–10 s) is of the appropriate order of magnitude as the observed time delay for decreasing PO with the onset of breathing low FiO_2 air (25.8 \pm 14.4) or with the return to breathing room air (21.5 \pm 12.9). Unfortunately, as it was not possible to continuously measure FiO_2 at the mouthpiece during the HYPOXIC trial particularly with a metabolic system designed for mixing chamber use with a design not optimal to measuring rapid changes in FiO_2 , we lack definitive evidence regarding how "square" the square wave changes in FiO_2 actually was. We assume that it occurred within <5 s.

Previous studies from Eston et al. (2007), Joseph et al. (2008) and Tucker et al. (2007) have indicated that the growth of RPE during exhaustive exercise is scaled to the relative effort or relative percent of distance completed. Recent evidence from Tucker et al. (2007) has suggested that performance is improved in hyperoxia by an upregulation of motor unit recruitment, but without a change in RPE. These data have suggested that the effort is regulated in a manner designed to protect the perceived effort relative to the anticipated perceived effort (St Clair Gibson et al. 2006). The present results support this concept in that the downregulation of PO during the period of breathing low FiO_2 air was sufficient to almost perfectly match the growth of RPE during the HYPOXIC trial to that observed during the CONTROL trial. Rauch et al. (2005) have shown similar precision of control of PO related to relative muscle glycogen depletion, which seems unlikely to be relevant here. Albertus et al. (2005) have shown that the growth of perceived effort is related to the percent of perceived task completed, suggesting that such regulation is related to the subject's expectations as well as to objective physiologic responses. It is unclear what signaling mechanisms might allow such precise regulation of a gross parameter like RPE. Nevertheless, regardless of whether they are based on expectations, intramuscular sensations or direct feedback from central chemoreceptors, they appear to act with both rapidity and precision.

In conclusion, we were able to administer an unobvious hypoxic gas mixture that caused a decrease S_aO_2 and decrease in PO in our subjects. In support of our hypothesis, the timing and sequence of the changes in PO and S_aO_2 suggested that change in S_aO_2 is at least one of the signaling mechanisms that lead to the decreases in PO. Previous work from our laboratory (Hettinga et al. 2006) has demonstrated that PO is potentially controlled unconsciously in relation to peripheral conditions. In that model, we experimentally manipulated the pacing pattern in a way that likely created different conditions in the skeletal muscles, and

found that despite increases in motor recruitment, PO decreased. Conversely, in the present study, the experimental model was designed to have reasonably consistent conditions within the skeletal muscles at the point where the hypoxic stimulus was presented. The rapidity with which PO decreased, and its temporal relationship to decreases in S_aO_2 , suggests that S_aO_2 is at least one important signaling mechanism that can regulate PO very quickly. These findings suggest that this may be a viable experimental model for teasing out central from peripheral regulators of fatigue and PO. In the end, the present results are consistent with the concept that the central nervous system is engaging in a rich and dynamic two-way conversation with the exercisers body, as recently suggested in the concepts of teleoanticipation (Ulmer 1996), interoception (Craig 2002) and of a central governor (Lambert et al. 2004; Noakes and St Clair Gibson 2004; St Clair Gibson et al. 2006).

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Conflict of interest statement None of the authors has relevant conflicts of interest to declare.

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