Effect of acute severe hypoxia on peripheral fatigue and endurance capacity in healthy humans

Lee M. Romer,1,2 Hans C. Haverkamp,2,3 Markus Amann,2 Andrew T. Lovering,2 David F. Pegelow,2 and Jerome A. Dempsey2

1Centre for Sports Medicine and Human Performance, Brunel University, Middlesex, United Kingdom; 2John Rankin Laboratory of Pulmonary Medicine, Department of Population Health Sciences, University of Wisconsin, Madison, Wisconsin; and 3Vermont Lung Center, College of Medicine, University of Vermont, Burlington, Vermont

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Romer LM, Haverkamp HC, Amann M, Lovering AT, Pegelow DF, Dempsey JA. Effect of acute severe hypoxia on peripheral fatigue and endurance capacity in healthy humans. Am J Physiol Regul Integr Comp Physiol 292: R598–R606, 2007. First published September 7, 2006; doi:10.1152/ajpregu.00269.2006.—We hypothesized that severe hypoxia limits exercise performance via decreased contractility of limb locomotor muscles. Nine male subjects [mean ± SE maximum O₂ uptake (V̇O₂max) = 56.5 ± 2.7 ml·kg⁻¹·min⁻¹] cycled at ≥90% V̇O₂max to exhaustion in normoxia [NORM-EXH; inspired O₂ fraction (FiO₂) = 0.21, arterial O₂ saturation (SpO₂) = 93 ± 1%] and hypoxia (HYPOX-EXH; FiO₂ = 0.13, SpO₂ = 76 ± 1%). The subjects also exercised in normoxia for a time equal to that achieved in hypoxia (NORM-CTRL; SpO₂ = 96 ± 1%). Quadriceps twitch force, in response to supramaximal single (nonpotentiated and potentiated 1 Hz) and paired magnetic stimuli of the femoral nerve (41). Electromyographic evidence suggests that, for the same exercise duration, the magnitude of peripheral fatigue during lower-limb cycle exercise is greater in severe hypoxia than in normoxia (3, 46, 47). In contrast, other reports have not found a cumulative effect of hypoxemia; muscle fatigue; exercise performance

WHOLE BODY EXERCISE PERFORMANCE in aerobic activities is impaired in hypoxia (19). The physiological mechanisms underpinning this impairment are not fully understood, but multiple “peripheral” and “central” mechanisms have been proposed. We have shown recently that preventing the mild arterial O₂ desaturation that occurred in endurance-trained subjects during sustained, heavy-intensity exercise in normoxia (–6% arterial O₂ saturation from baseline) significantly attenuated peripheral fatigue of the quadriceps muscle as assessed via femoral nerve stimulation (41). Electromyographic evidence suggests that, for the same exercise duration, the magnitude of peripheral fatigue during lower-limb cycle exercise is greater in severe hypoxia than in normoxia (3, 46, 47). In contrast, other reports have not found a cumulative effect of exercise and severe hypoxia on peripheral fatigue of the locomotor muscles, despite equal exercise durations (29, 34, 43). These latter findings (29, 34, 43) are compatible with the hypothesis that systemic hypoxemia has inhibitory effects on central motor output to locomotor muscles to ensure that a catastrophic failure of homeostasis does not occur during exercise (8, 24).

We explored further the effects of severe hypoxia on locomotor muscle fatigue that, for the purpose of the present study was defined as a loss of ability to produce force with a muscle that is reversible by rest (9, 37). We were primarily concerned with changes in peripheral muscle fatigue, that is, the loss of force because of processes occurring at or distal to the neuromuscular junction (7, 20). Thus we measured changes in isometric twitch forces in response to direct supramaximal femoral nerve stimulation before and after dynamic lower-limb exercise to exhaustion in normoxia and acute severe hypoxia, and in normoxia for a time equal to that achieved in hypoxia. Our main findings were that decreases in evoked force output of the quadriceps were more pronounced in hypoxia than in normoxia for the same work rate and duration but were not different in hypoxia vs. normoxia at the point of exhaustion. These findings suggest that decreases in endurance capacity in severe hypoxia are due, in part, to fatigue-induced changes within the working muscles.

METHODS

Participants

Nine men volunteered to participate in the study [mean ± SE age 24.9 ± 1.5 yr, range 19–32 yr; body mass 74.4 ± 3.0 kg, range 60.8–85.8 kg; maximal O₂ uptake (V̇O₂max) 56.5 ± 2.7 ml·kg⁻¹·min⁻¹, range 43.7–68.8 ml·kg⁻¹·min⁻¹]. All subjects engaged in competitive endurance sports, including seven cyclists. All subjects had normal resting pulmonary function. Informed consent was obtained in writing from each subject, and the Institutional Review Board of the University of Wisconsin-Madison approved all procedures. The study was performed according to the Declaration of Helsinki.

Protocol

At preliminary visits to the laboratory, subjects were familiarized thoroughly with the procedures used to assess quadriceps muscle function and performed a maximal incremental exercise test (33 watts every 3 min starting from 98 watts) in room air on an electromagnet-
Physically braked cycle ergometer (Elema) for the determination of peak power output ($W_{\text{peak}}$) and related parameters. On separate occasions, subjects performed three constant-load exercise trials at $92 \pm 1\%$ of $W_{\text{peak}}$. During the first constant-load exercise trial, the subjects exercised to exhaustion while breathing either room air [inspired $O_2$ fraction ($F_{\text{IO}_{2}}$) = 0.21; inspired $O_2$ partial pressure ($P_{\text{IO}_{2}}$) = 142.9 $\pm$ 0.3 mmHg], which represented the normoxic (NORM-EXH) condition, or while breathing a humidified hypoxic gas mixture ($F_{\text{IO}_{2}}$ = 0.13; $P_{\text{IO}_{2}}$ = 91.7 $\pm$ 0.9 mmHg), which represented the hypoxic (HYPOX-EXH) condition. The order of these first two trials was randomized and balanced. During the third constant-load exercise trial, the subjects breathed room air ($F_{\text{IO}_{2}}$ = 0.21; $P_{\text{IO}_{2}}$ = 143.5 $\pm$ 0.3 mmHg) but exercised for the same time as in HYPOX-EXH; this represented the normoxic control (NORM-CTRL) condition. The participants could not be blinded to the treatments, but they were unaware of the experimental hypotheses and naive to the purpose of the study. Contractile function and membrane excitability of the quadriceps muscle in response to supramaximal magnetic stimulation of the femoral nerve were assessed before and up to 70 min after each of the exercise trials (see Neuromuscular function). Each exercise session was separated by at least 48 h and was completed at the same time of day. Subjects refrained from caffeine for 12 h and stressful exercise for 48 h before each exercise test. Ambient temperature and relative humidity were not different between conditions.

Exercise Responses

Ventilation and pulmonary gas exchange were measured using apparatus and techniques that have been described previously (23). Arterial $O_2$ saturation ($S_{\text{PaO}_{2}}$) was estimated using a pulse oximeter (model N-595; Nellcor, Pleasanton, CA) with adhesive forehead sensors (Max-Fast; Nellcor). Based on a combination of published (41) and unpublished (A. T. Lovering, unpublished observations) data, we found that there was excellent agreement between directly measured arterial $O_2$ saturation and $S_{\text{PaO}_{2}}$ across the range of values observed in the present study [mean coefficient of variation (CV) = 1.1\%; intraclass correlation coefficient $r = 0.986$; $y = 1.06x - 6.0$, where $y = % S_{\text{SaO}_{2}}$ and $x = % S_{\text{PaO}_{2}}$, SE of the estimate = 1.4\%]. Heart rate was measured from the R-R interval of an electrocardiogram using a three-lead arrangement. Ratings of perceived exertion (dyspnea and limb discomfort) were obtained every min using Borg’s (12) modified CR10 scale. Written instructions for using the ratings scale were given to subjects before data collection (12). The scale was located in full view of the subject throughout testing, and subjects pointed in alternating order to the perceptual ratings that best reflected their sensations of dyspnea and limb discomfort. Capillary blood samples were collected from an ear lobe for determination of total whole blood lactate concentration ([La]$_{\text{b}}$) using an electrochemical analyzer (YSI 1500 Sport). We have previously shown a close correspondence between measures of lactate concentration in arterial blood vs. those in capillary blood when obtained simultaneously (23). $\text{Paco}_2$ and $\text{PCO}_2$ were measured at 50, 60, 70, 80, 85, 90, 95, and 100\% of maximal power output for one of the stimulators at the start of every experiment. A near plateau in baseline $Q_{\text{ss}}$ and $M$-wave amplitudes with increasing stimulus intensities was observed in every subject, indicating maximal depolarization of the femoral nerve. Twitch force at 100\% of maximal power output measured at the beginning of the progressive increase in power output was not different from that obtained at the end, indicating that the incremental protocol did not elicit twitch potentiation.

Assessment of fatigue. Subjects rested for at least 10 min, after which stimulus power was set at 100\% of maximum, and paired stimuli were given at interstimulus intervals of 10, 20, and 100 ms, corresponding to stimulus frequencies of 100, 50, and 10 Hz, respectively. Paired stimuli were separated by 30 s and were repeated four times each. Next, eight single stimuli were given, each separated by 30 s. The potentiated quadriceps twitch ($Q_{t,\text{pot}}$) and $M$-wave amplitudes were located, and this position was marked with indelible ink. To determine whether nerve stimulation was supramaximal, three single twitches were obtained every s at 50, 60, 70, 80, 85, 90, 95, and 100\% of maximal power output for one of the stimulators at the start of every experiment. A near plateau in baseline $Q_{\text{ss}}$ and $M$-wave amplitudes with increasing stimulus intensities was observed in every subject, indicating maximal depolarization of the femoral nerve. Twitch force at 100\% of maximal power output measured at the beginning of the progressive increase in power output was not different from that obtained at the end, indicating that the incremental protocol did not elicit twitch potentiation.

Neuromuscular Function

The apparatus and techniques for assessing membrane excitability and contractile function have been described in detail previously (41); therefore, we provide only a brief description.

Electromyography. Quadriceps electromyograms (EMG) were recorded from three pairs of skin-surface electrodes (model H59P; Kendall, Mansfield, MA) positioned over the right vastus lateralis, rectus femoris, and vastus medialis. Membrane excitability was inferred from the peak-to-peak amplitude of the quadriceps compound muscle action potentials (M-waves), which were captured on paper using a multichannel chart recorder. There was no effect of the recording site on the relative changes in M-wave amplitudes; therefore, data for all three muscles were pooled.

Magnetic stimulation. Subjects lay supine on a table with the right knee joint angle set at 1.57 rads (90\%) of flexion and the arms folded across the chest. A noncompliant strap was attached around the subject’s right leg just superior to the malleoli of the ankle joint. The strap was connected to a calibrated load cell (model SM 1000, Interface, Scottsdale, AZ). Two magnetic stimulators (Magstim 200; Jali Medical, Newton, MA), connected to a transformer (TwinCap Module; Jali Medical) and a double 40-mm coil, were used to stimulate the femoral nerve (3, 33, 39, 41, 42). We used single and paired stimuli to discriminate between low- and high-frequency fatigue (38, 51). For the paired stimuli, the two stimulators were synchronized by a separate module (BiStim Module; Jali Medical).

The area of stimulation associated with the largest quadriceps twitch ($Q_{t,\text{ss}}$) and $M$-wave amplitudes was located, and this position was marked with indelible ink. To determine whether nerve stimulation was supramaximal, three single twitches were obtained every s at 50, 60, 70, 80, 85, 90, 95, and 100\% of maximal power output for one of the stimulators at the start of every experiment. A near plateau in baseline $Q_{\text{ss}}$ and $M$-wave amplitudes with increasing stimulus intensities was observed in every subject, indicating maximal depolarization of the femoral nerve. Twitch force at 100\% of maximal power output measured at the beginning of the progressive increase in power output was not different from that obtained at the end, indicating that the incremental protocol did not elicit twitch potentiation.

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The entire assessment procedure took 15 min to complete and was...
performed before exercise (~30 min) and at 2.5, 35, and 70 min after exercise while the subjects breathed room air.

**Statistical Analyses**

Repeated-measures ANOVA was used to test for within-group effects across time. Following significant main effects, planned pairwise comparisons were made using the Bonferroni method. Pearson product moment correlation coefficients (r) were used to examine for relationships between selected physiological variables. Results are expressed as means ± SE. Statistical significance was set at P < 0.05. Statistical analyses were performed using the 11.5 release version of SPSS for Windows (SPSS, Chicago, IL).

**RESULTS**

**Arterial O₂ Saturation**

In NORM-EXH (PIO₂ = 142.9 ± 0.3 mmHg), SpO₂ fell from 99 ± 1% at resting baseline to 93 ± 1% (88–95%) by the final minute of exercise (P < 0.01; see Table 1). In HYPOX-EXH (PIO₂ = 91.7 ± 0.9 mmHg), SpO₂ was reduced even further to 76 ± 1% (71–82%; P < 0.01 vs. NORM-EXH and NORM-CTRL).

**Neuromuscular Function**

In NORM-EXH and NORM-CTRL, M-wave amplitudes after exercise were not different from baseline values. In HYPOX-EXH, however, M-wave amplitudes (10, 50, and 100 Hz) immediately postexercise (<10 min) were elevated above baseline levels (108% of preexercise), and these increases were greater than the changes in NORM-CTRL (see Fig. 1 in online data supplement). Within- and between-group differences were not observed at 35 and 70 min postexercise.

The percent decrease in Qw,pot was larger in HYPOX-EXH vs. NORM-CTRL in the immediate postexercise period (~34 vs. ~24%, respectively; P < 0.01; Fig. 1). At 35 and 70 min postexercise, however, the percent changes in Qw,pot were not different between HYPOX-EXH and NORM-CTRL (see Table 1 in online data supplement). The postexercise decrease in Qw,pot in NORM-EXH was not different from the decrease in HYPOX-EXH, either in the immediate postexercise period (~39 vs. ~34%, P > 0.05; Fig. 1) or up to 70 min postexercise (see Table 2 in online data supplement).

In HYPOX-EXH, postexercise twitch force averaged across all of the stimulus frequencies was less than baseline values (~16 ± 6%, P < 0.05; Fig. 2); in the immediate postexercise period, significance was achieved only for 1 Hz (P < 0.01), although at 35 and 70 min postexercise differences were detected for 1, 10, and 50 Hz. In NORM-CTRL, postexercise twitch force (10–100 Hz) increased slightly above preexercise values (9 ± 4% across frequencies; P > 0.05). That the largest increases in force occurred at the highest frequencies of stimulation, which were performed first during the postexercise period, suggests that postactivation potentiation was present during this period. The magnitude of fatigue was greater in HYPOX-EXH vs. NORM-CTRL across all of the stimulus frequencies (~15 vs. +9%; P < 0.01), and this effect persisted up to 35 min postexercise (~14 vs. ~5%; P < 0.05; see Table 1 in online data supplement).

**Within-twitch Responses**

Immediately postexercise, there was a slowing of the maximal rate of force development, and of the maximal relaxation.
rate in response to 1 Hz (nonpotentiated and potentiated) and 100 Hz stimuli, that was more pronounced in HYPOX-EXH vs. NORM-CTRL and in NORM-EXH vs. HYPOX-EXH (see Table 3 in online data supplement). When the decreases in twitch force amplitude were taken into account, however, only maximal relaxation rate (1 Hz nonpotentiated) and one-half relaxation time (1 Hz nonpotentiated) were different between HYPOX-EXH and NORM-CTRL, whereas no differences were found between NORM-EXH and HYPOX-EXH. There were no between-condition differences in either the contraction or relaxation measurements at 35 or 70 min postexercise.

Voluntary Activation

The effect of hypoxia on actual and predicted MVC force is shown in Fig. 3. Preexercise, subjects were unable to fully activate their quadriceps during the MVC maneuvers (90–91% of full activation). Postexercise reductions in MVC and voluntary activation tended to be larger in HYPOX-EXH vs. NORM-CTRL (−24 vs. −11% for MVC and −10 vs. −5% for activation, respectively), although these comparisons did not reach statistical significance (P = 0.066 and 0.11, respectively). Despite a shorter duration of exercise in HYPOX-EXH, the decreases in MVC and activation were attenuated in NORM-CTRL (−5 and −11%, respectively; P < 0.05 for activation). The decreases in activation and MVC were attenuated in NORM-CTRL (−5 and −11%, respectively; P < 0.05 for activation).

Exercise Responses

The effects of FiO2 on the physiological and perceptual responses to the final minute of exercise are summarized in Table 1. Although subjects exercised at the same power output (298 ± 12 watts) under both conditions, time-to-exhaustion was 70 ± 3% (range 55–86%) less in HYPOX-EXH vs. NORM-EXH (4.2 ± 0.5 vs. 13.4 ± 0.8 min, respectively; P < 0.01). In NORM-EXH, minute ventilation (V̇E) rose by 36% from minute 3 to exhaustion, entirely through an increase in fR as VT peaked early and then fell slightly throughout the remainder of exercise. In HYPOX-EXH, V̇E at end exercise was lower in all subjects compared with in NORM-EXH and in NORM-CTRL, although only the HYPOX-EXH vs. NORM-EXH comparison achieved statistical significance.

Diaphragm force output (JPdi × fR), total inspiratory muscle force output (JPes × fR), and abdominal muscle force output (JPga × fR) were increased throughout HYPOX-EXH relative to control values (Fig. 4, A–C). However, JPdi × fR was the
only measure of respiratory force output in HYPOX-EXH to be significantly elevated above NORM-EXH at end exercise (P < 0.05). Correlations between the percent changes in respiratory muscle force output and the pre- to postexercise percent changes in Qtw force (mean for all frequencies) at exercise isotime were statistically nonsignificant (r = 0.15–0.22; P > 0.05).

[La−]B was higher throughout exercise and recovery in HYPOX-EXH vs. NORM-CTRL (Fig. 5). The rate of rise of [La−]B was also higher in HYPOX-EXH vs. NORM-CTRL (2.63 ± 0.42 vs. 0.66 ± 0.10 mM/min, respectively; P < 0.01). End-exercise values, however, were not different between HYPOX-EXH and NORM-EXH (10.1 ± 0.6 vs. 10.7 ± 0.9 mM, respectively; P > 0.05).

Perceptions of limb discomfort and dyspnea were rated higher throughout most of exercise in HYPOX-EXH vs. NORM-CTRL (Fig. 6, A and B). The rates of rise of the ratings of perceived exertion were also higher in HYPOX-EXH vs. NORM-CTRL (2.19 ± 0.45 vs. 0.95 ± 0.29 for limb discomfort, P < 0.01; 1.79 ± 0.28 vs. 0.87 ± 0.18 for dyspnea, P < 0.05). Dyspnea at end exercise was lower in HYPOX-EXH vs. NORM-EXH (8.4 ± 0.3 vs. 9.6 ± 0.3, respectively; P < 0.05); however, limb discomfort at end exercise was not different between HYPOX-EXH and NORM-EXH (9.8 ± 0.3 vs. 9.8 ± 0.1, respectively). There was a significant correlation between the percent change in peripheral quadriceps muscle fatigue (mean for all frequencies) for HYPOX-EXH vs. NORM-CTRL and the percent change in the rate of rise of limb discomfort for HYPOX-EXH vs. NORM-CTRL (r = 0.66; P < 0.01). That is, the larger the relative increase in peripheral fatigue in HYPOX-EXH vs. NORM-CTRL, the larger the rate of rise of limb discomfort.

DISCUSSION

Main Findings

We determined the effect of acute, severe hypoxia on peripheral fatigue and endurance capacity in healthy, physically trained humans. Heavy-intensity cycling exercise to exhaustion in hypoxia resulted in reductions in force produced at low and high frequencies of supramaximal magnetic stimulation of the femoral nerve that were in excess of those found in normoxia for the same power output and exercise duration. Thus the rate of development of exercise-induced peripheral fatigue was likely increased in severe hypoxia. The absolute values and the rates of rise of blood lactate concentration and ratings of perceived exertion were also exacerbated by hypoxia compared with values in normoxic exercise at the same work rate and duration. Exercise time to exhaustion was 70% less in hypoxia than in normoxia. However, the levels of peripheral fatigue and
blood lactate at exhaustion did not differ in hypoxia vs. normoxia. Furthermore, ratings of limb discomfort at exhaustion were similar and maximal in hypoxia vs. normoxia. Collectively, these findings are consistent with existing evidence that whole body exercise in hypoxia reduces the contractility of locomotor muscles (3, 41). Furthermore, they support the hypothesis that decreases in endurance capacity in severe hypoxia may be due, in part, to fatigue-induced changes within the working muscles.

Technical Considerations

The interpretation of our findings that severe hypoxia exacerbated exercise-induced peripheral fatigue and that the level of fatigue at exhaustion was similar between normoxia and hypoxia is critically dependent on being able to detect relatively small systematic within- and between-day changes in our measures of neuromuscular function. We have previously reported typical errors (CV) of ≤7% for our measurements of evoked force (3, 41, 42). We think there is little doubt that we achieved similar levels of precision in the present study because eight of the nine subjects were the same as those studied previously (41, 42). We have also shown previously that we can reproduce, both technologically and biologically, the effects of heavy-intensity exercise on limb muscle fatigue when exercise trials are repeated on different days (42). Furthermore, we have shown that the evoked Qsw is a sensitive measure of peripheral fatigue in that the magnitude of the reduction in Qsw force is less in shorter-duration exercise than in longer-duration exercise conducted at the same work rate (41, 42). Therefore, we are confident that the fatigue differences observed in the present study (i.e., HYPOX-EXH vs. NORM-CTRL) were not merely a function of the insensitivity of our measures and that similarities in fatigue (i.e., HYPOX-EXH vs. NORM-EXH) were not through an inability to detect change.

A potential problem with using twitch measurements in the assessment of peripheral fatigue is that factors that serve to increase force (i.e., postactivation potentiation) compete with factors that decrease force production (i.e., fatigue; see Ref. 40). Such an influence was not expected to affect our fatigue comparisons between HYPOX-EXH and NORM-CTRL because the exercise durations and work rates were identical for both conditions. Differences in the exercise durations between NORM-EXH and HYPOX-EXH, however, may have affected our fatigue comparisons. To circumvent this problem, we focused on the pre- to postexercise changes in the 1-Hz potentiated twitch (33). Using this approach, we found that the postexercise decrease in potentiated twitch force was not significantly different in NORM-EXH (−39%) vs. HYPOX-EXH (−34%). The slightly larger, albeit nonsignificant, postexercise decrease in potentiated twitch force after the longer trial (NORM-EXH) may have been because of differences in muscle temperature (13), the compliance of noncontractile elements such as tendons (32), the motor output to the muscle during peripheral nerve stimulation because of activity-dependent hyperpolarization (50), or a combination of these factors.

Effect of Severe Hypoxia on Peripheral Fatigue (HYPOX-EXH vs. NORM-CTRL)

We defined muscle fatigue as a decrease in the capacity for developing force that is reversible by rest (9, 37). Using this definition, it is clear that exercise to exhaustion in hypoxia (HYPOX-EXH) resulted in significant limb muscle fatigue and that the severity of this fatigue was greater than for the same intensity and duration of exercise in normoxia (NORM-CTRL). Thus reductions in the force response to the second twitch at stimulus frequencies ranging from 10 to 100 Hz and to the nonpotentiated and potentiated single 1-Hz twitch were greater in HYPOX-EXH vs. NORM-CTRL. Furthermore, exercise in HYPOX-EXH elicited reductions in the contraction and relaxation rates of single (nonpotentiated and potentiated) and paired (100 Hz) twitches that were significantly greater than those observed after NORM-CTRL, although these differences were less marked when the corresponding decreases in peak twitch force were taken into account.

Changes in action potential transmission did not account for the differences in fatigue between HYPOX-EXH and NORM-CTRL because M-wave amplitudes for three muscles of the quadriceps did not differ over time in NORM-CTRL and, compared with baseline values, actually increased immediately postexercise in HYPOX-EXH. An additive effect of hypoxia and exercise on M-wave potentiation has been reported previously (21, 44) and may be because of a greater recruitment of fast-twitch (type II) motor units (47), which are known to exhibit greater potentiation than type I fibers during fatiguing exercise (22).

The increased deficit in force-generating capacity at low frequencies of stimulation in HYPOX-EXH is consistent with impaired release of Ca2+ by the sarcoplasmic reticulum (16, 17, 52) via a more rapid accumulation of energy metabolites such as hydrogen ions (1) and inorganic phosphate (25), and altered redox balance (36). The larger loss of force at the higher frequencies of stimulation in HYPOX-EXH vs. NORM-CTRL suggests disruption of action potential propagation along the T-tubule, potentially by increased extracellular K+ concentration (27). The Na+/K+ pump is recruited more during exercise, and this effect is magnified during exercise in
hypoxia (35). However, an accumulation of metabolites, which would be expected to be elevated during exercise in hypoxia, can inhibit pump activity (31).

In addition to the direct effect of hypoxia on muscle contractile function, there may have been an indirect effect via the elevated ventilatory work that accompanied the exercise in hypoxia. Increasing the work of breathing during heavy exercise by >50% via inspiratory resistive loads resulted in a decrease in vascular conductance and blood flow in the working limb muscles (23) and a small but significant increase in the fatigability of these muscles (42). In HYPOX-EXH, the increases in respiratory muscle force outputs were considerably less than in our previous inspiratory loading studies (23, 42). Furthermore, the difference in the severity of quadriceps fatigability between HYPOX-EXH and NORM-CTRL was considerably greater than in our previous study (42). Accordingly, we do not believe that an increase in ventilatory work contributed in a major way to the observed increase in locomotor muscle fatigue in HYPOX-EXH.

**Hypoxia, Fatigue, and Endurance Capacity (HYPOX-EXH vs. NORM-EXH)**

Exercise time to exhaustion was reduced by 70% in HYPOX-EXH vs. NORM-EXH. Although it is already well known that exercise performance is reduced in hypoxia (19), the physiological mechanisms underpinning such an impairment are not fully understood. That the threefold differences in exercise time to exhaustion were accompanied by similar levels of peripheral fatigue, blood lactate, and perceptions of limb discomfort (but not dyspnea) at end exercise suggests strongly that the marked deleterious effect of severe hypoxemia on endurance capacity was because of fatigue-induced changes within the exercising muscle. This contention is in line with the sensory feedback hypothesis (10, 18), which states that negative afferent feedback from peripheral receptors originating within a fatigued muscle triggers a decline in net discharge rate of motorneurons. In hypoxia, an exaggerated decrease in discharge rate with fatigue may occur via inhibitory influences of group III/IV afferents (4, 5, 14, 15). Although such effects on motor unit discharge may be mediated synaptically (10, 18), more recent evidence suggests that firing of group III/IV afferents acts upstream of the motor cortex to impair voluntary descending drive (48).

Although the reduced fusion frequencies associated with prolonged relaxation times may partially compensate for a decline in discharge rate (i.e., muscle wisdom), there is evidence that force remains reduced at low stimulus frequencies when fatigue is induced by voluntary activation of the quadriceps (11). A further consideration is that type II motor units exhibit a larger reduction in force for a given stimulus frequency compared with type I motor units (49), which is important in the context of exercise in hypoxia where the recruitment of type II motor units is increased (5, 15). A decrease in discharge rate to motorneurons during fatigue necessitates an increased recruitment of motor units to maintain a target work rate (18). The associated increase in central command would be perceived, via corollary discharge to the primary somatosensory cortex, as an increased sense of effort (28). Thus both a decline in discharge rate to motorneurons and an increase in the sense of effort with the recruitment of more motor units would be expected to curtail endurance capacity.

In the present study, we believe that a critical level of peripheral fatigue was reached much sooner in HYPOX-EXH than in NORM-EXH because the rate of peripheral fatigue development was increased in HYPOX-EXH. However, this does not mean that the only reason for stopping exercise is contractile failure, rather that the critical level of peripheral fatigue and/or the rate of its development served as a marker of failing muscle function that could also serve, via negative feedback and increased sense of effort, to inhibit central motor output. That exercise significantly reduced voluntary activation of the quadriceps (as assessed via twitch interpolation) in NORM-EXH, and that this was exacerbated in HYPOX-EXH, indirectly implicates a contribution from decreased central drive to motorneurons on exercise limitation in hypoxia. However, a problem with this interpretation is that it is impossible to know whether the change in isometric force with the superimposed twitch, as conducted in the resting subject during recovery, truly represents central inhibition of the volitional force produced during the preceding rhythmic exercise task.

To date, there is no direct evidence of an effect of arterial hypoxemia on central motor output to locomotor muscles during exercise. We have recently shown, however, that even moderate hypoxia elicits a decrease in central motor output (estimated via quadriceps EMG) during a time trial performance test in which power output is voluntarily adjustable (2). Although this effect of hypoxia on exercise performance time may well be explained by intensified sensory feedback from fatigued, acidic muscles, there is also the possibility that cerebral hypoxia may be an important contributing factor. Such an effect may be especially important in severe hypoxia, at the end of which syncopal symptoms were obvious. In the only study to partly address this issue, inhibiting neural feedback from contracting limb muscles using epidural anesthesia did not significantly affect exercise performance in hypoxia (30). In this previous study (30), however, arterial O₂ saturation was considerably lower than in the present study (≤53% vs. 76%, respectively), and it is possible, therefore, that cerebral hypoxia may dominate as the severity of hypoxia increases (26).

**Conclusion**

Severe arterial hypoxemia (SpO₂ 76%) had a detrimental effect on the force output of the limb locomotor muscles in response to sustained heavy-intensity exercise. Although time to exhaustion was reduced by more than two-thirds in severe hypoxia, the levels of peripheral quadriceps muscle fatigue, blood lactate, and limb discomfort at end exercise were similar compared with in normoxia. This suggests that the exercise limitation in severe hypoxia was due, in part, to fatigue-induced changes within the muscle and that peripheral fatigue is an important regulated variable.

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