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**Inspiratory muscle work in acute hypoxia influences locomotor muscle fatigue and exercise performance of healthy humans**

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Amann M, Pegelow DF, Jacques AJ, Dempsey JA. Inspiratory muscle work in acute hypoxia influences locomotor muscle fatigue and exercise performance of healthy humans. Am J Physiol Regul Integr Comp Physiol 293: R2036–R2045, 2007. First published August 22, 2007; doi:10.1152/ajpregu.00442.2007.—Our aim was to isolate the independent effects of 1) inspiratory muscle work (Wb) and 2) arterial hypoxemia during heavy-intensity exercise in acute hypoxia on locomotor muscle fatigue. Eight cyclists exercised to exhaustion in hypoxia [inspired O2 fraction (FiO2) = 0.15, arterial hemoglobin saturation (SaO2) = 81 ± 1%; 8.6 ± 0.5 min, 273 ± 6 W; Hypoxia-control (Ctrl)] and at the same work rate and duration in normoxia (SaO2 = 95 ± 1%; Normoxia-Ctrl). These trials were repeated, but with a 35–80% reduction in Wb achieved via proportional assist ventilation (PAV). Quadriceps twitch force was assessed via magnetic femoral nerve stimulation before and 2 min after exercise. The isolated effects of Wb in hypoxia on quadriceps fatigue, independent of reductions in SaO2, were revealed by comparing Hypoxia-Ctrl and Hypoxia-PAV at equal levels of SaO2 (P = 0.10). Immediately after hypoxia exercise potentiated twitch force of the quadriceps (Qtw,pot) decreased by 30 ± 3% below preexercise baseline, and this reduction was attenuated by about one-third after PAV exercise (21 ± 4%; P = 0.0007). This effect of Wb on quadriceps fatigue occurred at exercise work rates during which, in normoxia, reducing Wb had no significant effect on fatigue. The isolated effects of reduced SaO2 on quadriceps fatigue, independent of changes in Wb, were revealed by comparing Hypoxia-Ctrl and Normoxia-PAV at equal levels of Wb. Qtw,pot decreased by 15 ± 2% below preexercise baseline after Normoxia-PAV, and this reduction was exacerbated by about one-third after Hypoxia-PAV (−22 ± 3%; P = 0.034). We conclude that both arterial hypoxemia and Wb contribute significantly and independently to increased locomotor muscle fatigue during exercise in acute hypoxia; this occurs at work rates during which, in normoxia, Wb has no effect on peripheral fatigue. Work of breathing; arterial oxygen content; altitude; limb blood flow; expiratory flow limitation

On the basis of studies that mimicked the work of breathing (Wb) obtained during heavy and maximum exercise (1, 2) and unloaded the Wb in maximal exercise (34), it has been estimated that the oxygen cost of breathing or the cardiac output devoted to the respiratory muscles approximates 10–16% of maximal O2 consumption (VO2max) or maximal cardiac output in healthy trained and untrained subjects. More direct microsphere measurements of blood flow distribution during maximal exercise in equines also showed that −15–16% of cardiac output was distributed to the inspiratory and expiratory muscles of the chest wall and abdomen (47). One mechanism protecting blood flow to the respiratory muscles in heavy exercise may be the respiratory muscle metaboreflex, which has been shown to cause sympathetically mediated vasoconstriction of the exercising limb vasculature during heavy exercise in the face of developing inspiratory or expiratory muscle fatigue (32, 56, 57, 59).

We (4–6) and others (48, 53, 62) have shown previously that whole body exercise in acute hypoxia significantly increases the rate of development of locomotor muscle fatigue over that associated with the identical exercise in normoxia. Why is the rate of development of locomotor muscle fatigue increased in hypoxia? First, human studies using isolated muscle exercise in acute hypoxia have shown that a reduced arterial hemoglobin saturation (SaO2), per se, accelerates the rate of accumulation of fatigue metabolites, which in turn exacerbates the development of peripheral muscle fatigue (20, 29–31, 36, 37, 39, 42). These detrimental effects of reduced SaO2 on fatigue metabolite accumulation and the development of peripheral fatigue are supported by studies on isolated animal muscle fibers (21, 27). Second, the Wb has also been shown to be a major contributor to the development of locomotor muscle fatigue and to limit exercise performance. Reducing inspiratory muscle work during high-intensity, constant-workload cycling in normoxia with a proportional assist mechanical ventilator (PAV) significantly attenuated the magnitude of exercise-induced quadriceps fatigue (55) and resulted in a substantial prolongation of cycling time to exhaustion (−14%) (35). Importantly, it has been shown that during exercise at the same absolute work rate ventilation (51, 61) and Wb (17, 18, 64) are significantly increased in hypoxia vs. normoxia. By extension, these latter findings suggest that the significantly higher force output of the inspiratory muscles during heavy-intensity exercise in hypoxia vs. normoxia might further exacerbate exercise-induced peripheral locomotor muscle fatigue and exercise performance independent of any reductions in SaO2.

The purpose of the present study was to distinguish between two main effects of hypoxia on the development of peripheral muscle fatigue, i.e., low SaO2, and high Wb during sustained cycling exercise to exhaustion. We addressed this question by 1) using a proportional assist mechanical ventilator during high-intensity exercise in normoxia and acute hypoxia to create conditions of identical levels of a reduced Wb in the face of significantly different levels of SaO2, and 2) exercising in hypoxia with and without PAV to create conditions of identical levels of reduced SaO2 in the face of significantly different levels of Wb. We hypothesized that both Wb and reduced SaO2 contribute significantly and independently to increased locomotor muscle fatigability during exercise in hypoxia.

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METHODS

Participants

Eight healthy, nonsmoking male athletes volunteered to participate in the study (mean ± SE; age 23.4 ± 1.5 yr, body mass 77.2 ± 2.6 kg, stature 1.81 ± 0.02 m, VO2max 57.8 ± 2.1 ml·kg⁻¹·min⁻¹). All subjects had normal resting pulmonary functions. Written informed consent was obtained from each participant. All procedures were approved by the institution’s human subjects committee.

Protocol

On two preliminary visits to the laboratory, subjects were thoroughly familiarized with the procedures used to assess neuromuscular function. Furthermore, subjects performed two maximal incremental exercise tests (20 W + 25 W/min; Ref. 7) [ambient air or hypoxic gas mixture with an inspired O₂ fraction (FiO₂) of 0.15] on a computer-controlled electromagnetically braked cycle ergometer (Velotron, Elite model, Racer Mate, Seattle, WA) for the determination of peak power output (Wpeak) and VO2max. On later occasions, at the same time of the day separated by at least 48 h, subjects completed five constant-workload trials at 82.1 ± 0.5% of their Wpeak in hypoxia. During the exercise trials, subjects used visual and verbal feedback to maintain a self-selected pedal cadence (95–110 rpm), as inferred from the maximal incremental exercise test, and exercise was terminated when pedal cadence dropped below 60% of the self-selected cadence (task failure). The first trial was performed while breathing a humidified hypoxic gas mixture [FiO₂ = 0.15; Hypoxia-control (Ctrl)] to the limit of tolerance. On a separate visit, subjects repeated the constant-load exercise in hypoxia, at the same intensity (273 ± 6 W) and for the same duration (8.6 ± 0.2 min) as in Hypoxia-Ctrl, but the force output of the inspiratory muscles was reduced with a proportional-assist ventilator (see below; Hypoxia-PAV). Two additional exercise trials were performed in which subjects exercised at the same absolute power output and for the same duration in room air (FiO₂ = 0.21) either while breathing was unimpeded (Normoxia-Ctrl) or while the force output of the inspiratory muscles was reduced (Normoxia-PAV). Finally, to reveal the effects of Wb in hypoxia on exercise performance, all subjects exercised to the limit of exhaustion (Tlim) in hypoxia (FiO₂ = 0.15) while inspiratory muscle work was reduced (Hypoxia-PAV-Tlim). Subjects remained seated throughout all exercise tests to minimize changes in muscle recruitment; the recording period started after the target pedal cadence was reached (<10 s). Neuromuscular functions were assessed before and at 2.5 min after exercise (see below). The order of the trials was randomized. The participants were naive to the purpose of the study and blinded to the respective FiO₂, but could not be blinded with respect to PAV. A FiO₂ of 0.15 was used to simulate acute exposure to moderate altitude and SpO₂ of 80–82% caused substantial quadriceps fatigue.

Exercise Responses

Ventilation and pulmonary gas exchange were measured breath by breath at rest and throughout exercise with an open-circuit system (33). SaO₂ was estimated (SpO₂) with a pulse oximeter (Nellcor N-595, Pleasanton, CA) with adhesive forehead sensors. Alveolar PO₂ (PAO₂) was calculated from the alveolar gas equation:

\[ PAO_2 = \left( P_{\text{aO}_2} - \frac{VO_2}{VA} \right) \times 863 \]

where \( P_{\text{aO}_2} \) is the partial pressure of inspired O₂ and alveolar ventilation (VA) was calculated assuming dead space volume (VD)/tidal volume (VT) = 0.15. Heart rate (HR) was measured from the R-R interval of an electrocardiogram using a three lead arrangement. Ratings of perceived exertion (RPE) for dyspnea and limb discomfort were obtained at rest and every minute during exercise, using Borg’s modified CR10 scale (14). Arterialized (Finalgon, Boehringer Ingelheim, Germany) capillary blood samples were collected from an earlobe at rest and every 3 min during exercise for determination of total whole blood lactate concentration ([La⁻]₀) with an electrochemical analyzer (YSI 1500 Sport). During all constant-workload trials, esophageal pressure (Pes) was measured via a nasopharyngeal balloon (Cooper Surgical, Trumbull, CT) by standard procedures (13). Pes was integrated over the period of inspiratory flow and, the results were multiplied by respiratory frequency (f₀), and labeled the inspiratory muscle pressure-time product (Fig. 1).

Inspiratory Muscle Unloading

A feedback-controlled mechanical ventilator with a PAV mode was used to reduce the work of the inspiratory muscles during exercise (67). Briefly, subjects breathed through a two-way low-resistance nonrebreathing valve (7200 series, Hans Rudolph) that was connected on the inspiratory side to a solenoid switch. During inspiration, the solenoid switch closes and the ventilator delivers positive pressure in proportion to flow and volume. During expiration, the solenoid switch opens and allows unimpeded expiration with no pressure delivery. The amount of assist was set at the maximum level that each subject could tolerate (~3.0 cmH₂O·1⁻¹·s⁻¹ for flow assist, ~3.3 cmH₂O·l⁻¹·min⁻¹ for volume assist). The PAV settings were chosen to cause decreases in inspiratory muscle work similar to or greater in magnitude than those in our previous studies (32, 34, 35), which had shown significant effects of changing respiratory muscle work on limb blood flow and exercise performance in normoxia. Subjects participated in at least two practice sessions to familiarize themselves with the inspiratory unloading.

Expiratory Flow Limitations and Lung Volume Responses

Expiratory flow limitations. Subjects performed three maximal volitional flow-volume maneuvers (MFVL) before and immediately after exercise. Exercise tidal flow-volume (FV) loops were placed within the best of the six maximal loops based on measured inspiratory capacity (IC) maneuvers (rest, 3 min of exercise, and immediately before termination of exercise). Acceptable IC maneuvers during exercise required that peak inspiratory Pes match that obtained at rest.
The amount of expiratory flow limitation was defined as the percentage of the VT that met the boundary of the expiratory portion of the MFVL (41). Measures of potential lung volume changes (see below) and expiratory flow limitation during mechanical unloading were not conducted since IC maneuvers are not feasible during exercise with PAV.

**Lung volumes.** Functional residual capacity (FRC) was measured in a body plethysmograph, and total lung capacity (TLC) was calculated as the sum of FRC and IC. End-expiratory lung volume (EELV) was determined by subtracting the maximal IC as measured during exercise from TLC as measured at rest (8, 43). End-inspiratory lung volume (EIVL) was calculated as the sum of EELV and VT. Inspiratory reserve volume (IRV) during exercise was calculated by subtracting EIVL from TLC, and expiratory reserve volume (ERV) during exercise was determined by subtracting the residual volume from EELV.

**Neuromuscular Function**

*Electromyography.* Quadriceps electromyograms (EMG) were recorded from the right vastus lateralis (VL), vastus medialis (VM), and rectus femoris (RF) by monitoring electrodes with full-surface solid adhesive hydrogel (Kendall H59P, Mansfield, MA), with on-site amplification. Electrodes were placed in a bipolar electrode configuration over the middle of the respective muscle belly. The active electrode was placed over the motor point of the muscle. The recording electrode was moved along the muscle until a good configuration—confirmed by a “maximal” M-wave shape—was achieved. The reference electrode was placed over an electrically neutral site. The position of the EMG electrodes was marked with indelible ink to ensure that they were placed in the same location at subsequent visits. Proper electrode configuration was checked before the beginning of every experiment. To minimize movement artifacts, electrode cables were fastened to the subject’s quadriceps with medical adhesive tape and wrapped in elastic bandage. The VL, VM, and RF electrodes were used to record J, magnetically evoked compound muscle action potentials (M waves), to evaluate changes in membrane excitability, and 2) EMG for VL throughout exercise, to manifest fatigue. The M-wave properties included conduction time, peak amplitude, and area (5, 15, 56).

Raw EMG signals from VL, VM, and RF corresponding to each muscle contraction during the exercise trials and the pre- and postexercise maximal voluntary contraction (MVC) maneuvers were recorded for later analysis. The EMG signals were amplified and filtered by a Butterworth band-pass filter (BMA-830, CWE, Ardmore, PA) with a low-pass cutoff frequency of 10 Hz and a high-pass cutoff frequency of 1 kHz. The slope of the filters was −6 dB/octave. The filtered EMG signals were sampled at 2 kHz by a 16-bit analog-to-digital converter (PCI-MIO-16XE-50, National Instruments, Austin, TX) with custom software (Labview 6.0, National Instruments). A computer algorithm identified the onset of activity where the rectified EMG signals deviated by >2 SD above the baselines for at least 100 ms. Each EMG burst was visually inspected to verify the timing identified by the computer. For data analysis, the integral of each burst [integrated EMG (iEMG)] was calculated with the formula

\[
iEMG[\{m(t)\}] = \int_{0}^{T} \{m(t)\} \, dt
\]

where \(m(t)\) is the raw EMG signal.

A 1,024-point fast Fourier transform was used to compute a power spectrum periodogram. The mean power frequency (MPF) was calculated with the formula

\[
MPF = \frac{\int_{0}^{f} fS_{n}(f) \, df}{\int_{0}^{f} S_{n}(f) \, df}
\]

where \(S_{n}(f)\) is the power density spectrum of the EMG signal. The timing identified by the computer. For data analysis, the rectified EMG signals deviated by digital converter (PCI-MIO-16XE-50, National Instruments, Austin, TX) were analyzed for all Qtw,pot (46, 56).

Reliability measures. Subjects were tested for between-day reliability by repeating the magnetic stimulation protocol at rest on separate visits to the laboratory. For within-day reproducibility subjects were removed from the testing apparatus after baseline measurements of muscle function had been obtained and rested in a chair for 30 min without contracting the quadriceps, after which they were attached to the testing apparatus and measurements of quadriceps muscle function were repeated. There was no systematic bias in the baseline measurements either within or between days. Mean within-day within-subject coefficient of variation across all frequencies was 1.8 ± 0.6% (range: 0.2–7.8%) for Qw, 3.2 ± 0.6% (range: 0.0–8.0%) for MVC, and 1.1 ± 0.3% (range: 0.1–2.4%) for voluntary muscle activation. Mean between-day within-subject coefficient of variation across all frequencies was 4.6 ± 1.0% (range: 1.9–6.5%) for Qw, 6.1 ± 0.9% (range: 2.8–7.4%) for MVC, and 1.4 ± 0.4% (range: 0.5–2.1%) for voluntary muscle activation.

Technical considerations. Technical considerations addressing the limitations of surface EMG and magnetic femoral nerve stimulation have been extensively addressed by us and others and can be found in published reports (4–6, 28, 42, 54).
Statistical Analysis

Repeated-measures ANOVA was used to test for within-group effects over time. If ANOVA yielded a significant result, follow-up pairwise comparisons using the Holm’s sequential Bonferroni procedure were conducted. Results are presented as means ± SE. The α-level was set at 0.05 a priori.

RESULTS

Exercise Intensity

Hypoxia reduced $W_{\text{peak}}$ (395 ± 7 W) by 18% to 333 ± 7 W and $V_{\text{O2max}}$ (4.4 ± 0.1 l/min) by 16% below that achieved in normoxia. During the sustained, constant-workload exercise, absolute exercise intensity (273 ± 6 W) and $V_{O2}$ were not different between normoxia and hypoxia (Table 1). However, relative exercise intensity during the final minute was increased from 69 ± 1% $W_{\text{peak}}$ (81 ± 3% $V_{O2max}$) in normoxia to 82 ± 1% $W_{\text{peak}}$ (99 ± 1% $V_{O2max}$) in hypoxia because of the reduction in $W_{\text{peak}}$ and $V_{O2max}$ in hypoxia. We emphasize that exercise was performed at the same workload and for the identical time that represents time to exhaustion (i.e., task failure) in Hypoxia-Ctrl (8.6 ± 0.2 min), whereas in normoxia (Ctrl and PAV), exercise was terminated by the investigator at isotime (8.6 ± 0.2 min).

Ventilatory Effects of Hypoxia

Ventilatory response. Acute exposure to hypoxia ($F_{O2}$ 0.15) increased inspiratory muscle work by 36 ± 7% above that in normoxia (range: 11–54%; $P < 0.01$) (Figs. 1 and 2) and dropped hemoglobin saturation by 14 ± 1% during the final minute of constant workload exercise. In hypoxia $f_k$ and minute ventilation ($V_e$) rose substantially over the time of exercise, and at end exercise $V_e$ was increased by 53 ± 7% ($P < 0.01$) in hypoxia vs. normoxia. Furthermore, the time ($T_e$) was progressively reduced over time and at end exercise $T_e$ was 36 ± 4% shorter in hypoxia vs. normoxia ($P < 0.01$). $V_{O2}$ was similar in both conditions ($P = 0.50$), and capillary lactate was −78% higher at end exercise in hypoxia vs. normoxia (Table 1).

Table 1. Response to final minute of constant-workload exercise for control and inspiratory muscle unloading in normoxia and hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Hypoxia-Ctrl</th>
<th>Hypoxia-PAV</th>
<th>Normoxia-Ctrl</th>
<th>Normoxia-PAV</th>
<th>Hypoxia-PAV-$T_{\text{lim}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_{O2}$</td>
<td>0.15</td>
<td>0.15</td>
<td>0.21</td>
<td>0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>Exercise time, min</td>
<td>8.6 ± 0.2$^{a}$</td>
<td>8.6 ± 0.2</td>
<td>8.6 ± 0.2</td>
<td>8.6 ± 0.2</td>
<td>10.0 ± 0.3</td>
</tr>
<tr>
<td>Power output, W</td>
<td>273 ± 6</td>
<td>273 ± 6</td>
<td>273 ± 6</td>
<td>273 ± 6</td>
<td>273 ± 6</td>
</tr>
<tr>
<td>Pedal frequency, rev/min</td>
<td>93 ± 4</td>
<td>93 ± 3</td>
<td>93 ± 4</td>
<td>93 ± 5</td>
<td>93 ± 4</td>
</tr>
<tr>
<td>$J_{FV} \times f_k$, cmH2O s$^{-1}$</td>
<td>490 ± 28$^{a,b}$</td>
<td>141 ± 14$^{b}$</td>
<td>369 ± 31$^{a}$</td>
<td>122 ± 12$^{b,c}$</td>
<td>175 ± 15$^{a,d}$</td>
</tr>
<tr>
<td>$SpO_2$, %</td>
<td>81.2 ± 0.9$^b$</td>
<td>82.5 ± 1.2$^b$</td>
<td>94.9 ± 0.5$^a$</td>
<td>95.3 ± 0.5$^{a,b,c}$</td>
<td>80.8 ± 0.7$^b$</td>
</tr>
<tr>
<td>$C_{O2}$, ml O2/dl</td>
<td>17.1 ± 2.0$^a$</td>
<td>17.3 ± 0.2$^b$</td>
<td>20.1 ± 0.1$^a$</td>
<td>20.2 ± 0.1$^{a,c}$</td>
<td>17.1 ± 1.0$^b$</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>183 ± 3$^{d}$</td>
<td>180 ± 2$^b$</td>
<td>169 ± 3$^a$</td>
<td>169 ± 3$^{a,c}$</td>
<td>185 ± 3$^{b,d}$</td>
</tr>
<tr>
<td>RPE (dyspnea)</td>
<td>8.6 ± 0.3$^{b}$</td>
<td>6.3 ± 0.5$^{a,b,c}$</td>
<td>4.4 ± 0.5$^{a,c}$</td>
<td>3.3 ± 0.3$^{a,b,c,d}$</td>
<td>8.4 ± 0.3$^b$</td>
</tr>
<tr>
<td>RPE (limb)</td>
<td>8.7 ± 0.3$^{b}$</td>
<td>6.6 ± 0.4$^{a,b,c}$</td>
<td>4.7 ± 0.4$^{a,c}$</td>
<td>4.1 ± 0.3$^{a,c,d}$</td>
<td>8.9 ± 0.3$^b$</td>
</tr>
<tr>
<td>$T/E_{T_{\text{res}}}$</td>
<td>0.49 ± 0.01$^a$</td>
<td>0.43 ± 0.01$^a$</td>
<td>0.43 ± 0.01$^a$</td>
<td>0.43 ± 0.02$^a$</td>
<td>0.44 ± 0.01$^a$</td>
</tr>
<tr>
<td>$f_k$, breaths/min</td>
<td>59.5 ± 2.7$^a$</td>
<td>49.1 ± 2.3$^b$</td>
<td>40.3 ± 2.8$^c$</td>
<td>36.0 ± 2.0$^{a,b}$</td>
<td>52.6 ± 3.2$^{c,d}$</td>
</tr>
<tr>
<td>$V_t$, L</td>
<td>2.9 ± 0.1$^{a,c}$</td>
<td>3.8 ± 0.1$^b$</td>
<td>2.8 ± 0.1$^c$</td>
<td>3.6 ± 0.1$^b$</td>
<td>3.8 ± 0.2$^a$</td>
</tr>
<tr>
<td>$P_{O2}$, mmHg</td>
<td>88.3 ± 0.1$^{b,c}$</td>
<td>89.0 ± 0.1</td>
<td>123.2 ± 0.1$^{a,c}$</td>
<td>123.4 ± 0.2$^{a,b,c}$</td>
<td>88.3 ± 0.2$^b$</td>
</tr>
<tr>
<td>$V_e$, l/min</td>
<td>172.6 ± 5.6$^{a,c}$</td>
<td>182.7 ± 4.2$^{a,c}$</td>
<td>113.6 ± 6.9$^{a,c}$</td>
<td>129.3 ± 6.8$^{a,c,d}$</td>
<td>194.7 ± 5.3$^{b}$</td>
</tr>
<tr>
<td>$V_{CO2}$, l/min</td>
<td>3.6 ± 0.1$^{a,c}$</td>
<td>3.2 ± 0.1</td>
<td>3.7 ± 0.1$^{a,c}$</td>
<td>3.5 ± 0.1$^{a,c,d}$</td>
<td>3.3 ± 0.1$^b$</td>
</tr>
<tr>
<td>$V_{O2}$, l/min</td>
<td>4.0 ± 0.1$^{b}$</td>
<td>3.7 ± 0.1</td>
<td>3.6 ± 0.1$^{b}$</td>
<td>3.4 ± 0.1$^{b}$</td>
<td>3.8 ± 0.1$^b$</td>
</tr>
<tr>
<td>$V_{CO2}/V_{O2}$</td>
<td>48.5 ± 2.1$^{a,b,c}$</td>
<td>55.2 ± 2.7$^{b,c}$</td>
<td>31.2 ± 1.9$^{a,c}$</td>
<td>37.3 ± 2.2$^{c,b}$</td>
<td>60.2 ± 2.6$^b$</td>
</tr>
<tr>
<td>Capillary [La$^-$], mmol/L</td>
<td>11.7 ± 0.6$^a$</td>
<td>11.0 ± 0.9$^b$</td>
<td>6.9 ± 0.5$^{a,c}$</td>
<td>6.3 ± 0.5$^{a,c}$</td>
<td>11.8 ± 0.8$^a$</td>
</tr>
</tbody>
</table>

Values are means ± SE for $n = 8$ subjects. Ctrl, control; PAV, proportional assist ventilation; $T_{\text{lim}}$, limit of exhaustion; $P_{O2}$, inspired O2 fraction; $f_k$, respiratory frequency; $V_{O2}$, tidal volume; $P_{ACO2}$, alveolar Po2; $V_{E}$, minute ventilation; [La$^-$], whole blood lactate concentration. $^{*}P < 0.01$ vs. Hypoxia-PAV; $^{*}P < 0.01$ vs. Normoxia-Ctrl; $^{*}P < 0.05$ vs. Hypoxia-PAV-$T_{\text{lim}}$; $^{*}P < 0.05$ vs. Hypoxia-PAV; $^{*}P < 0.05$ vs. Normoxia-Ctrl.

Lung volumes. EELV was significantly reduced below resting values ($\sim$3.56 L) at the third minute of exercise in normoxia and hypoxia (3.0 ± 0.22 and 3.16 ± 0.11 L, respectively). With further increases in $V_e$ from the third minute to the end of exercise, EELV in normoxia continued to decrease to 3.27 L ($\sim$0.3 L below resting EELV; $P < 0.001$) in all eight subjects and EILV rose to 84 ± 1% of TLC. In hypoxia EELV progressively increased from the third minute to the termination of exercise and approximated preexercise resting values ($P = 0.34$), with EILV at 88 ± 1% of TLC. The progressive increase in EELV was coincident with the −36% reduction in $T_e$ compared with Normoxia-Ctrl (see above). The average 1.9-L increase in $V_e$ from rest to the final minute of exercise in normoxia was accomplished by encroaching on both the IRV.
In hypoxia, a similar increase in VT was achieved almost exclusively by encroaching on the IRV.

Effects of Inspiratory Muscle Unloading in Normoxia and Hypoxia on Wb, V˙E, and V˙O2

Subjects exercised at the same constant workload (273 ± 6 W) and for the same duration (8.6 ± 0.2 min) under control conditions and while the inspiratory muscles were unloaded by 66 ± 5% (range: 35–80%; P < 0.01) in normoxia (Normoxia-PAV) and by 70 ± 4% (range: 46–80%; P < 0.01) in hypoxia (Hypoxia-PAV) (Fig. 1). PAV significantly increased V˙E by 11 ± 4% in normoxia and by 7 ± 2% in hypoxia without affecting SaO2 in either FiO2 condition (~95% and ~82%, respectively). Inspiratory muscle unloading did not affect V˙O2 in normoxia (P = 0.58) but reduced oxygen consumption by 12 ± 2% (~0.4 l/min) in hypoxia (P < 0.001) vs. control conditions (Table 1). Capillary lactate throughout exercise was not affected by PAV in either FiO2 condition (P > 0.1).

Contractile Functions of Quadriceps Locomotor Muscle

M waves. As a measure of membrane excitability we examined pre- vs. postexercise M-wave characteristics in conjunction with the muscle mechanical properties for VL, VM, and RF. Although there was a similar trend in all trials toward increased M-wave amplitude, increased area, and decreased CT after exercise, none of these changes was significant.

Quadriceps twitch force. HYPOXIA-CTRL VS. NORMOXIA-CTRL. The exercise in hypoxia caused a substantial reduction in Qtw at all stimulation frequencies (16–30%; see Table 2) (high- and
low-frequency fatigue). With the identical exercise in normoxia, \( Q_w \) was significantly reduced from preexercise only at 1 Hz (potentiated and unpotentiated) and 10 Hz (range 9–17%; all \( P < 0.05 \)), indicating low-frequency fatigue, whereas \( Q_w \) associated with 50 and 100 Hz was not significantly different from preexercise baseline, suggesting the absence of high-frequency fatigue (Table 2). Quadriceps fatigue associated with the various stimulation frequencies was significantly greater after Hypoxia-Ctrl than Normoxia-Ctrl (Table 2, Fig. 4). At the low stimulation frequencies hypoxia caused on average a 155% greater reduction in quadriceps force output than the identical exercise in normoxia.

**Hypoxia (CTRL vs. PAV).** Partially unloading the inspiratory muscles during exercise in normoxia did not significantly affect the exercise-induced change in \( Q_w \) at any stimulation frequency (Table 2).

**Hypoxia (CTRL vs. PAV).** Partially unloading the inspiratory muscles during isometric exercise at the same absolute workload (Hypoxia-PAV) attenuated the group mean decrease in \( Q_w \) across the four stimulation frequencies by 44 ± 9%, and this

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**Table 2. Effects of inspiratory muscle unloading during constant-workload exercise in normoxia and hypoxia on fatigue variables**

<table>
<thead>
<tr>
<th></th>
<th>Hypoxia-Ctrl (273 W, 8.6 min)</th>
<th>Hypoxia-PAV (273 W, 8.6 min)</th>
<th>Normoxia-Ctrl (273 W, 8.6 min)</th>
<th>Normoxia-PAV (273 W, 8.6 min)</th>
<th>Hypoxia-PAV-Tlim (273 W, 10.0 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hz potentiated (N)</td>
<td>-29.9 ± 2.8 † ‡ † ‡ ‡</td>
<td>-22.1 ± 2.9 † ‡ ‡ ‡</td>
<td>-16.1 ± 2.7 † ‡ ‡ ‡</td>
<td>-15.2 ± 2.4 † ‡ ‡ ‡</td>
<td>-30.5 ± 3.8 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>1 Hz (N)</td>
<td>-26.1 ± 3.5 † ‡ ‡ ‡</td>
<td>-16.1 ± 3.7 † ‡ ‡ ‡</td>
<td>-9.6 ± 3.5 † ‡ ‡ ‡</td>
<td>-9.3 ± 3.5 † ‡ ‡ ‡</td>
<td>-26.4 ± 4.0 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>10 Hz (N)</td>
<td>-29.0 ± 3.4 † ‡ ‡ ‡</td>
<td>-18.3 ± 3.6 † ‡ ‡ ‡</td>
<td>-9.1 ± 3.5 † ‡ ‡ ‡</td>
<td>-8.2 ± 3.1 † ‡ ‡ ‡</td>
<td>-29.7 ± 4.0 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>50 Hz (N)</td>
<td>-20.5 ± 3.7 † ‡ ‡ ‡</td>
<td>-11.4 ± 3.2 † ‡ ‡ ‡</td>
<td>-1.9 ± 2.6 † ‡ ‡ ‡</td>
<td>-0.7 ± 3.7 † ‡ ‡ ‡</td>
<td>-19.3 ± 3.6 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>100 Hz (N)</td>
<td>-16.3 ± 3.9 † ‡ ‡ ‡</td>
<td>-8.0 ± 3.4 † ‡ ‡ ‡</td>
<td>3.1 ± 2.5 † ‡ ‡ ‡</td>
<td>3.6 ± 2.9 † ‡ ‡ ‡</td>
<td>-15.4 ± 3.4 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>Mean of 4 frequencies (N)</td>
<td>-22.2 ± 3.6 † ‡ ‡ ‡</td>
<td>-12.8 ± 3.4 † ‡ ‡ ‡</td>
<td>-3.3 ± 2.8 † ‡ ‡ ‡</td>
<td>-2.0 ± 3.5 † ‡ ‡ ‡</td>
<td>-21.7 ± 3.7 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>MRFD (N/s)</td>
<td>-23.0 ± 4.4 † ‡ ‡ ‡</td>
<td>-17.0 ± 4.5 † ‡ ‡ ‡</td>
<td>-8.5 ± 4.4 † ‡ ‡ ‡</td>
<td>-8.2 ± 5.0 † ‡ ‡ ‡</td>
<td>-24.8 ± 5.4 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>MRR (N/s)</td>
<td>-26.2 ± 4.5 † ‡ ‡ ‡</td>
<td>-19.1 ± 4.3 † ‡ ‡ ‡</td>
<td>-10.7 ± 4.6 † ‡ ‡ ‡</td>
<td>-9.8 ± 4.7 † ‡ ‡ ‡</td>
<td>-26.8 ± 5.4 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>CT (s)</td>
<td>-3.4 ± 0.6 † ‡ ‡ ‡</td>
<td>-2.5 ± 0.5 † ‡ ‡ ‡</td>
<td>-1.9 ± 0.4 † ‡ ‡ ‡</td>
<td>-2.1 ± 0.6 † ‡ ‡ ‡</td>
<td>-3.6 ± 0.7 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>RT0.5s (s)</td>
<td>10.0 ± 0.4 † ‡ ‡ ‡</td>
<td>6.6 ± 1.1 † ‡ ‡ ‡</td>
<td>2.9 ± 0.9 † ‡ ‡ ‡</td>
<td>3.4 ± 0.9 † ‡ ‡ ‡</td>
<td>9.8 ± 0.9 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>MVC peak force (N)</td>
<td>-11.6 ± 1.7 † ‡ ‡ ‡</td>
<td>-3.6 ± 1.8 † ‡ ‡ ‡</td>
<td>0.8 ± 1.0 † ‡ ‡ ‡</td>
<td>-1.1 ± 1.3 † ‡ ‡ ‡</td>
<td>-9.0 ± 2.2 † ‡ ‡ ‡ ‡</td>
</tr>
<tr>
<td>%Muscle activation</td>
<td>-2.1 ± 2.3 $† ‡ ‡ ‡</td>
<td>-1.3 ± 1.1 $† ‡ ‡ ‡</td>
<td>-0.5 ± 0.9 $† ‡ ‡ ‡</td>
<td>-1.2 ± 1.5 $† ‡ ‡ ‡</td>
<td>-1.4 ± 1.1 $† ‡ ‡ ‡</td>
</tr>
</tbody>
</table>

Values are means ± SE (\( n = 8 \) subjects) for exercise performed for 8.6 ± 0.2 min (10.0 ± 0.3 min in Hypoxia-PAV-Tlim) at 273 ± 6 W. MRFD, maximal rate of force development; MRR, maximal rate of relaxation; CT, contraction time; RT0.5s, one-half relaxation time; MVC, maximal voluntary contraction; iEMG, integrated EMG; MPF, mean power frequency. When adjusted for the reduction in single twitch force, neither MRFD nor MRR was significantly different from preexercise baseline. %Muscle activation is based on superimposed twitch technique. iEMG and MPF are based on myoelectrical activity of vastus lateralis. Majority of values changed significantly compared with baseline 2.5 min after exercise (\( P < 0.01 \)). Preexercise, resting mean values for 1 Hz potentiated, 1 Hz, 10 Hz, 50 Hz, 100 Hz, and mean of 4 frequencies (1-100 Hz) were 185 ± 2, 126 ± 2, 218 ± 2, 255 ± 3, 255 ± 3 N, 213 ± 3 N, respectively. Preexercise, resting mean values for MRFD, MRR, CT, RT0.5s, MVC, and %muscle activation were 1,099 ± 13 N/s, 727 ± 12 N/s, 0.26 ± 0.00 s, 0.13 ± 0.00 s, 560 ± 7 N, and 94.8 ± 0.1%, respectively. *\( P < 0.05 \) from Hypoxia-PAV; †\( P < 0.01 \) from Hypoxia-PAV; ‡\( P < 0.01 \) from Normoxia-Ctrl; §not significantly different from preexercise baseline.
Effect of PAV occurred in all eight subjects (range 38–57%) (Table 2, Fig. 4).

**HYPOXIA-PAV vs. NORMOXIA-PAV.** Since Wb was nearly identical during the PAV trials in both normoxia and hypoxia (see Fig. 1), this comparison emphasizes the independent effects of hypoxemia, per se, on exercise-induced locomotor muscle fatigue without the normally occurring confounding influence of substantial differences in Wb. Hypoxemia per se during exercise exacerbated low-frequency quadriceps fatigue by 52%, 85%, and 180% for 1 Hz potentiated, 1 Hz, and 10 Hz, respectively, and induced significant levels of high-frequency fatigue (Fig. 4).

Within-twitch measurements. MRFD, MRR, and RT0.5 complement the findings reported for Qtw. The pre- to postexercise changes in within-twitch measurements of MRFD, MRR, and RT0.5 were significantly smaller in Hypoxia-PAV vs. Hypoxia-Ctrl and Normoxia-Ctrl vs. Hypoxia-Ctrl. However, the exercise-induced changes were not significantly different between Ctrl and PAV exercise in normoxia (Table 2).

**MVC force and voluntary muscle activation.** The results for MVC peak force output mirror the twitch data. Percent voluntary quadriceps activation was 94.8 ± 0.1% at rest and was not affected by the preceding exercise regardless of the experimental condition.

**Electromyographic Activity During Exercise**

iEMG. iEMG of VL rose significantly from the first to the final minute of exercise in all conditions and in all eight subjects (P < 0.01; see Fig. 5). The rate of rise of iEMG was steeper during the control trial in hypoxia vs. normoxia, and iEMG was significantly greater from minute 5 to end exercise in all subjects (P < 0.01). Unloading the respiratory muscles in either FIO2 condition had no significant effect on the exercise-induced increase in iEMG. Nevertheless, in hypoxia, there was a trend toward an attenuated (15 ± 12%; P = 0.18) exercise-induced increase in iEMG with PAV over the final 3 min (Fig. 5). Five of the eight subjects reduced the increase in iEMG by 12–77%, and three of the eight subjects had a 3–29% greater increase in iEMG with PAV vs. Ctrl in hypoxia.

**Effect of Inspiratory Muscle Unloading in Hypoxia on Exercise Performance (Hypoxia-PAV-Tlim)**

With inspiratory muscle unloading in hypoxia, all eight subjects were able to significantly prolong their exercise time to exhaustion over control conditions (Hypoxia-Ctrl) (1.4 ± 0.2 min, range 0.8–2.8 min, equals 16 ± 3%; P < 0.001). At exhaustion, inspiratory muscle work was 63 ± 4% lower with unloading compared with control (i.e., Hypoxia-PAV-Tlim vs. Hypoxia-Ctrl) (Table 1).

Qtw was further decreased with the extended exercise time (+1.4 ± 0.2 min) during Hypoxia-PAV-Tlim (vs. Hypoxia-Ctrl), so that at exhaustion the magnitude of ΔQtw from before to after exercise across all stimulation frequencies was similar to that for Hypoxia-Ctrl (P = 0.19–0.84) (Table 2).

**DISCUSSION**

This investigation reveals the influences of 1) inspiratory muscle work and associated consequences and 2) arterial hypoxemia during whole body exercise in acute moderate hypoxia on quadriceps fatigue and exercise performance. High-intensity cycling exercise to the limit of exhaustion in acute hypoxia evoked a marked hyperventilatory response, expiratory flow limitation, and a higher EELV than that observed during control exercise in normoxia (“relative hyperinflation”). Accordingly, inspiratory muscle work increased by 36% in hypoxic vs. normoxic exercise. In hypoxia, exercise induced a significantly greater degree of locomotor muscle fatigue compared with the effects of identical exercise in normoxia. By comparing conditions of 1) identical levels of reduced Wb in combination with significantly different levels of SpO2 (Hypoxia-PAV vs. Normoxia-PAV) and 2) identical levels of reduced P0.5 in combination with significantly different levels of Wb (Hypoxia-PAV vs. Hypoxia-Ctrl), we were able to isolate the two main effects of hypoxia on peripheral locomotor muscle fatigue. When the normally occurring inspiratory muscle work during exercise in acute hypoxia was reduced by ~70% via PAV and SpO2 was held constant, end-exercise quadriceps fatigue was attenuated by ~40%, emphasizing the substantial effects of Wb—independent of changes in SpO2—on locomotor muscle fatigue. In normoxia and exercise at the identical work rate and duration, similar reductions in inspiratory muscle work had no effect on the magnitude of changes in Qtw from before to after exercise. This significant effect of Wb in hypoxia on peripheral fatigue was manifested in a substantial improvement in exercise performance when the inspiratory muscle work was reduced. When P0.5 during exercise was acutely reduced to 82% via an FIO2 of 0.15 and Wb was reduced via PAV, end-exercise quadriceps fatigue was increased by >70% compared with that incurred during normoxic exercise with PAV. These latter comparisons at equal Wb showed the substantial effects of SpO2—indepen- dent of changes in Wb—on locomotor muscle fatigue.

**Work of Breathing Is an Important Determinant of Exercise-Induced Peripheral Fatigue and Performance in Hypoxia**

The major finding from this investigation is that inspiratory muscle work has a much greater effect on peripheral locomotor muscle fatigue in hypoxic exercise vs. normoxic exercise. Our findings show that respiratory muscle work incurred in hypoxic
exercise has a relatively greater contribution to peripheral fatigue (and effort perceptions) and therefore to exercise performance than it does in normoxic exercise performed at the identical workload and for the same duration.

Why should an increased $W_b$ in hypoxia have a greater effect on peripheral muscle fatigue? We did not test this directly in the present study, but our previous findings (23, 24, 32, 34, 52, 57, 59) point to respiratory muscle fatigue being a key factor, triggering a metaboreflex from the diaphragm and/or expiratory muscles that in turn increases sympathetic vasoconstriction of the limb, reducing limb blood flow and consequently quadriceps $O_2$ transport. Since hypoxia exacerbates the amount of exercise-induced diaphragm fatigue (10, 65), we would expect stronger metaboreflex effects during exercise in hypoxia and therefore greater compromise of limb blood flow, which has an additional detrimental impact on muscle force production (12, 19, 38). In turn, the greater fatigue incurred by the inspiratory and expiratory muscles in hypoxia has been attributed to three factors: 1) the greater amount of work incurred because of hyperventilation per se; 2) the effect of reduced $O_2$ transport, per se, to the respiratory muscles; and 3) the effects of expiratory flow limitation and relative hyperinflation (see Fig. 3), which places the diaphragm and other inspiratory muscles at a shorter operating length and therefore closer to their dynamic capacity for pressure generation, imposing a higher relative intensity of contraction (41).

Multiple Effects of Hypoxemia on Exercise-Induced Peripheral Muscle Fatigue

We have observed in several studies (4–6, 53–55) that the rate of development of peripheral quadriceps muscle fatigue during heavy-intensity whole body exercise is highly sensitive to $SpO_2$ (98–67%). Mechanisms contributing to this faster rate of fatigue development with reductions in $SpO_2$ are known to be related to a faster rate of accumulation of fatigue metabolites and include an increased type II muscle fiber recruitment (9, 26), metabolic acidosis (3, 16, 25), and inorganic phosphate accumulation (39) (also see introduction).

The elevated respiratory muscle work during exercise in hypoxia has not been evaluated as an additional contributor to locomotor muscle fatigue—either independent of or in combination with changes in $SpO_2$. The present study design enabled us to address two potential determinants of the rate of development of peripheral fatigue in hypoxia. First, by contrasting normoxia vs. hypoxia at equal work rates and durations of exercise at almost identical, very low levels of ventilatory work (Hypoxia-PAV vs. Normoxia-PAV), we isolated the effects of arterial hypoxemia and demonstrated the consequences of a low $SpO_2$ per se—indeed of any influence of $W_b$—on exercise-induced quadriceps fatigue during whole body exercise in hypoxia (see Fig. 4).

Second, by comparing hypoxic exercise vs. hypoxic exercise plus PAV (Hypoxia-Ctrl vs. Hypoxia-PAV) under identical conditions of work rate and duration and at identical levels of $SaO_2$ (see Table 2), we isolated the effects of inspiratory muscle work on quadriceps fatigue independent of any influence of $SaO_2$ (see Fig. 4). These results show that the augmented respiratory muscle work induced by hypoxia, per se, has a substantial effect on peripheral muscle fatigue beyond that attributable to the direct effect of $SaO_2$. This indirect effect of respiratory muscle work amounts to about one-third of the total peripheral fatigue induced by exercise in hypoxia. As outlined above, we believe that the effect of ventilatory muscle work is secondary to the sympathoexcitation induced by respiratory muscle fatigue and its effects on limb vascular conductance, blood flow, and convective $O_2$ transport (22). These estimates are likely conservative, because our experiments only relieved a portion of inspiratory muscle work. However, it has also been shown that expiratory muscles increase their work rate substantially and experience significant fatigue during sustained high-intensity exercise (63); furthermore, like inspiratory muscles, when fatigued they will precipitate increased sympathetic vasoconstrictor outflow to limb muscle vasculature (24).

Conditions Under Which Respiratory Muscle Work Might Be Expected to Affect Exercise-Induced Peripheral Fatigue

In normoxia, it has been shown that a relative exercise intensity of $>85\%$ of $V\dot{O}_{2\text{max}}$ sustained to exhaustion is necessary to elicit diaphragm fatigue (11, 40). Furthermore, a work rate $>80\%$ of $V\dot{O}_{2\text{max}}$ is needed in order for the relief of inspiratory muscle work to significantly increase limb blood flow and limb $O_2$ transport (66). Combined, these findings emphasize the necessity for very high-intensity sustained exercise to exhaustion and the associated ventilatory requirements to cause sufficient diaphragm fatigue to trigger a metaboreflex from the respiratory muscles causing increased vascular resistance and reducing limb blood flow, thereby exaggerating the development of locomotor muscle fatigue (22). The exercise during our normoxic trial in the present study was neither exhaustive nor sufficiently intense to evoke these responses; thus exercise-induced peripheral muscle fatigue was minimal, and relief of much of the inspiratory muscle work via mechanical ventilation was not effective in alleviating peripheral muscle fatigue. In contrast, when hypoxia was superimposed on this same work rate and for the same duration as in normoxia, the $W_b$ was likely sufficiently high to elicit diaphragm fatigue and its associated metaboreflex; accordingly, relief of much of this inspiratory muscle work also provided substantial relief of locomotor muscle fatigue.

How generalizable are our conclusions of a significant contribution of $W_b$ to exercise-induced peripheral muscle fatigue in acute, moderate hypoxemia to conditions of chronic hypoxia or more severe hypoxia? First, the hyperventilatory response to hypoxia at rest and especially during exercise increases quickly over the initial few hours in hypoxia and then further and more gradually over the ensuing 1–2 wk of acclimatization to high altitude (58). Coincidentally, $PaO_2$ increases steadily as does hemoglobin concentration with time in hypoxia, thereby raising arterial $P_O_2$, $SpO_2$, and arterial $O_2$ content ($CaO_2$) over time. On the other hand, the $W_b$ attending the time-dependent hyperventilation increases 1.5-fold during heavy-intensity exercise in the acclimatized sojourner—even at only moderately high altitudes (64). Thus we would predict that the net effect of these acclimatization changes is a greater contribution of the $W_b$—relative to that of the reduced $SpO_2$—to peripheral muscle fatigue and to exercise limitation. Second, with more severe hypoxia (about $<75\%$ $SpO_2$) exercise duration would be reduced even further and both the reduced $CaO_2$ and the $W_b$ would be further intensified at equal exercise duration and work rate. However, an additional factor—namely central
nervous system hypoxia—now also becomes critically important in reducing central motor output to the exercising limbs and causing exercise limitation before substantial levels of peripheral muscle fatigue are incurred (6, 44).

Conclusion

Hypoxia exacerbates the rate of development of peripheral locomotor muscle fatigue elicited via high-intensity exercise and reduces exercise performance in two ways, namely, via reductions in SpO2 and increases in respiratory muscle work. Our present findings with an experimental design that alleviated more than half of the normally incurred inspiratory muscle work during exercise in hypoxia demonstrate significant contributions from both Wb and the reduction in SpO2 to the peripheral locomotor muscle fatigue induced via high-intensity exercise to exhaustion in moderate acute hypoxia. These “indirect” effects of augmented inspiratory muscle work in hypoxia and its consequences on peripheral fatigue also accounted for a significant part of the hypoxia-induced reduction in exercise performance.

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REFERENCES


