Effect of expiratory muscle fatigue on exercise tolerance and locomotor muscle fatigue in healthy humans

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Taylor BJ, Romer LM. Effect of expiratory muscle fatigue on exercise tolerance and locomotor muscle fatigue in healthy humans. J Appl Physiol 104; 1442–1451, 2008. First published March 6, 2008; doi:10.1152/japplphysiol.00428.2007.—High-intensity exercise (≥90% of maximal O2 uptake) sustained to the limit of tolerance elicits diaphragm fatigue in healthy humans, as demonstrated by a significant reduction relative to prior baseline values in magnetically evoked gastric twitch pressure. That achieved in EMF-EX but without prior induction of EMF (ISO-EX) would be expected to increase central respiratory drive to maintain expiratory muscle force production, as has been shown to occur when the inspiratory muscles are loaded before (21) or during exercise (33). In addition, expiratory muscle fatigue (EMF) would be expected to increase central respiratory drive to maintain expiratory muscle force production (8), as has been shown to occur when the inspiratory muscles are fatigued (39). Such an increase in central drive would likely be perceived as an increased sense of effort (12), which might impair exercise tolerance.

Recent evidence suggests that prior loading of the expiratory muscles can also impair subsequent exercise tolerance (45), although the precise mechanisms for such an effect are unclear. Fatiguing contractions of the expiratory muscles carried out to task failure have been shown to elicit a time-dependent increase in sympathetic vasoconstrictor outflow in resting limb musculature (6). In resting and exercising canines, a bolus injection of lactic acid into the deep circumflex iliac artery elicits a reduction in both hindlimb blood flow and vascular conductance (32). A reduction in blood flow to the working limb muscles would be expected to limit exercise tolerance via an increased severity of limb muscle fatigue and heightened perceptions of limb discomfort, as has been shown to occur when the inspiratory muscles are loaded before (21) or during exercise (33). In addition, expiratory muscle fatigue (EMF) would be expected to increase central respiratory drive to maintain expiratory muscle force production (8), as has been shown to occur when the inspiratory muscles are fatigued (39). Such an increase in central drive would likely be perceived as an increased sense of effort (12), which might impair exercise tolerance.

Based on the aforementioned considerations, we investigated the effect of prior EMF on subsequent exercise tolerance. To quantify the magnitude of EMF induced by expiratory resistive loading or exercise, we measured the reduction in magnetically evoked twitch Pga (Pgatw) relative to prior baseline values. In addition, we assessed the severity of exercise-induced limb locomotor muscle fatigue by measuring the reduction in the quadriceps twitch force (Qtw) response to direct femoral nerve stimulation from pre- to postexercise and the increase in the integrated electromyographic response of the quadriceps during the exercise. We hypothesized that prior EMF would impair subsequent exercise tolerance through an exacerbation of exercise-induced limb muscle fatigue and heightened perceptions of dyspnea and leg discomfort.

METHODS

Subjects

Eight healthy, nonsmoking male subjects participated in the study (means ± SD: age = 28 ± 5 years, stature = 183 ± 9 cm, body mass = 82.9 ± 8.6 kg). The subjects were physically active and had normal forced vital capacity (105 ± 3% of predicted), forced expiratory volume in 1 s (116 ± 3%), and maximal voluntary ventilation (108 ± 7%). The study was approved by the local Research Ethics Committee, and each subject provided written informed consent.

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Experimental Procedures

The experimental procedures were conducted during four laboratory sessions that were each separated by at least 48 h. For each subject, exercise trials were performed at a similar time of day to minimize diurnal biological variation. The subjects abstained from caffeine for 12 h and exercise for 48 h before each session. During the first session, the subjects were familiarized with the magnetic stimulation procedures and the volitional maneuvers. Pulmonary function was assessed using an on-line spirometer (Oxycon Pro; Jaeger, Höchberg, Germany) according to standard procedures (26). Subjects performed a maximal incremental exercise test (35 W every 3 min starting at 95 W) on an electromagnetically braked cycle ergometer (Excalibur; Lode, Groningen, The Netherlands). Peak power output (Wpeak) was calculated as the sum of the final completed work rate plus the fraction of the partially completed work rate performed before exhaustion. VO2max was the highest mean value recorded over 30 s. During the next two sessions, the subjects performed constant-load exercise at 90% of Wpeak either with (EMF-EX) or without (CON-EX) prior induction of EMF (Fig. 1). Exercise time to the limit of tolerance (Tlim) was recorded for each trial. To induce EMF, subjects breathed against an expiratory flow resistor until task failure. The order of the two trials was randomized and counterbalanced such that four subjects performed CON-EX first and four subjects performed EMF-EX first. During the fourth session, subjects exercised for a time equal to that achieved in EMF-EX but without prior induction of EMF (ISO-EX) (Fig. 1). Abdominal and quadriceps muscle contractilities were assessed before and up to 30 min after each of the exercise trials by measuring the Pgatw and Qtw response to muscle contractilities were assessed immediately after expiratory resistive loading during EMF-EX (Fig. 1). The participants could not be blinded to the EMF, but they were unaware of the experimental hypotheses and naïve to the purpose of the study.

Respiratory Pressure Measurements

Pga and esophageal pressure (Pes) were measured by using two balloon-tipped catheters (Ackrad Labs, Cooper Surgical, Berlin, Germany) that were placed as described previously (42). Each catheter was connected to a differential pressure transducer (Validyne DP45, Northridge, CA; range of ±229 cmH2O), calibrated across the physiological range with an electromanometer (model M14; Mercury, Glasgow, Scotland). The esophageal balloon was filled with 2 ml of air. The gastric balloon was filled with 2 ml of air to ensure that it did not collapse under high expiratory pressure (23, 30).

Magnetic Stimulation

Abdominal muscles. The subjects sat facing an inclined bench with their hips flexed and chest supported. Magnetic stimuli were delivered to the thoracic nerve roots supplying the abdominal muscles via a circular 90-mm coil powered by a magnetic stimulator (Magstim 200; Magstim, Whitland, Wales). The coil was positioned over the vertebral column between the 8th (T8) and 11th (T11) thoracic vertebrae. The optimal coil position was defined as the vertebral level that when stimulated evoked the highest Pga, and was marked with indelible ink to ensure the coil position was identical for subsequent stimulations. The stimulations were performed at end-expiratory Pes against a semi-occluded airway. End-expiratory Pes and Pga results were not different across time for any of the trials (see Table 2), indicating that all stimulations were delivered at the same lung volume and at the same abdominal muscle length.

Quadriceps muscles. The subjects lay semi-recumbent on a strength-testing chair (Techno Gym, Cesena, Italy) with the right knee at 1.57 rads (90°) of flexion and arms folded across the chest. A noncompliant strap was fastened just superior to the malleoli of the right ankle joint. The strap was attached via a swivel link to a calibrated load cell (model ABA Ergo Meter, Globus Italia, Codogne, Italy), which was fixed to the chair and adjusted to a height that was in the direct line of applied force for each subject. Magnetic stimuli were delivered to the femoral nerve via a double 70-mm coil powered by another magnetic stimulator (Magstim 200). The area of stimulation that evoked the greatest quadriceps Qtw was located and marked with indelible ink.

Electromyography

Electromyograms (EMG) were recorded from the rectus abdominis (RA), vastus lateralis (VL), and rectus femoris (RF) as described previously (2, 42). The electrodes were positioned according to the optimal M-wave response to magnetic stimulation. The position of the EMG electrodes was marked with indelible ink to ensure that they were placed in the same location at subsequent visits.

Supramaximal Stimulation

To determine whether nerve stimulation of the abdominal and quadriceps muscles was supramaximal, three single twitches were delivered to each muscle group at 50, 60, 70, 80, 85, 90, 95, and 100% of the stimulator’s maximum power output. The incremental protocol was applied after 10 min of rest and 20 min before the preexercise assessment of neuromuscular function during session 2. There was a plateau in RA M-wave amplitude [i.e., no significant increase in amplitude with increasing stimulation intensity (paired t-tests with Bonferroni adjustment)] but no plateau in Pga, indicating that only the RA was stimulated supramaximally (Fig. 2). The technical considerations associated with submaximal nerve stimulation have been discussed previously (14, 42, 44). There was a plateau in Qtw and VL.
Stimulator’s power output for P_{gatw} (subjects. *P < 0.05, values significantly different from those at 100% of the stimulator’s power output for P_{gatw} (A) and rectus abdominis (B); †P < 0.05, values significantly different from those at 100% of the stimulator’s power output for Q_{tw} (A) and rectus femoris and vastus lateralis (B).

Fig. 2. A: gastric twitch pressure (P_{gatw}) and quadriceps twitch force (Q_{tw}) in response to 1-Hz magnetic stimulation of the thoracic nerves and the femoral nerve, respectively. B: M-wave amplitudes in response to 1-Hz magnetic stimulation of the thoracic nerves (rectus abdominis) and the femoral nerve (rectus femoris and vastus lateralis). The incremental protocol was applied after 10 min of rest and completed 20 min before the preexercise assessment of neuromuscular function at visit 1. Values are group means ± SD for 8 subjects. *P < 0.05, values significantly different from those at 100% of the stimulator’s power output for P_{gatw} (A) and rectus abdominis (B); †P < 0.05, values significantly different from those at 100% of the stimulator’s power output for Q_{tw} (A) and rectus femoris and vastus lateralis (B).

Neuromuscular Function

Abdominal and quadriceps muscle functions were assessed before (~20 min) and after (4 and 30 min) each of the exercise trials. In addition, abdominal muscle function was assessed immediately after (1 min) expiratory resistive loading during EMF-EX (Fig. 1). The stimulations were administered at 100% of the stimulator’s power output and were each separated by 30 s. Four 1-Hz stimulations were delivered to the nerve roots supplying the abdominal muscles such that four nonpotentiated twitches were obtained. The potentiated twitch is a more sensitive measure of muscle fatigue than the nonpotentiated twitch, particularly when the degree of fatigue is small (13, 15). Furthermore, the potentiated twitch is a more valid measure for comparing differences in fatigue when the levels of postactivation potentiation are unequal (31), as we expected to occur in the present study because of different exercise durations. Accordingly, P_{gatw} was measured ~5 s after a maximal expulsive maneuver against a semioccluded airway. The maneuver was initiated from total lung capacity and maintained for ~5 s. This procedure was repeated six times such that six potentiated P_{gatw} results were obtained. The degree of potentiation was slightly smaller after the first and, to a lesser extent, after the second voluntary effort; therefore, we discarded the first two measurements.

Four 1-Hz stimulations were also delivered to the right femoral nerve. The stimulations were delivered at 100% of the stimulator’s power output and were separated by 30 s. In accordance with our abdominal muscle assessment procedures, we measured peak Q_{tw} elicited by a 1-Hz stimulation ~5 s after a maximal voluntary isometric contraction of the right quadriceps that was maintained for ~5 s. This procedure was repeated six times such that six potentiated Q_{tw} measurements were obtained; again, the first two measurements were discarded. Although the potentiated twitches were reduced more than the nonpotentiated twitches after each trial (CON-EX, EMF-EX, ISO-EX), the percent changes between each of the trials were not different. Thus only changes in potentiated P_{gatw} and potentiated Q_{tw} are reported. The order of abdominal and quadriceps muscle assessment was randomized and balanced between subjects but remained constant within subjects for each of the trials.

The amplitudes (baseline to peak) of the abdominal muscle pressure response and the quadriceps muscle force response were analyzed for each stimulation. In addition, the maximal rate of pressure and force development, maximal relaxation rate, contraction time, and one-half relaxation time were assessed for the abdominal and quadriceps muscles (42). Membrane excitability was determined by measuring the magnetically evoked peak-to-peak amplitude (mV), duration (ms), and area (mV/ms) of the RA, VL, and RF M waves (42). To quantify the progression of limb muscle fatigue throughout the constant-load exercise tests, EMG was recorded from VL and the integral of the EMG burst (iEMG) during each contraction was calculated as described previously (2).

Reproducibility

To determine the within-day, between-occasion reproducibility of neuromuscular measurements, abdominal and quadriceps muscle functions were assessed before and after 20 min of rest (Fig. 1), during which time the subjects were removed from the testing apparatus and sat quietly in a chair. There were no systematic differences in either evoked pressure or evoked force measurements before vs. after the 20-min rest period. In addition, reproducibility coefficients were all <11% for coefficients of variation and >0.61 for intraclass correlation coefficients (Table 1).

Expiratory Resistive Loading

EMG was induced with a protocol that we have previously shown to elicit significant abdominal muscle fatigue yet minimizes fatigue of the diaphragm and inspiratory rib cage muscles (43). Subjects exhaled against a flow-resistive load provided by a variable aperture (MicroRMA: Micro Medical, Kent, UK); inspiration was unimpeded. Subjects maintained a respiratory frequency (fR) of 15 breaths/min and an expiratory duty cycle [expiratory time (TE)/total breath time (TTOT)] of 0.7 while targeting 40% of maximal expiratory P_{gat}. The target expiratory pressure was displayed on a computer screen, and the subjects maintained fR and TE/TTOT by following a computer-generated audio signal. Subjects were instructed to maintain a constant P_{gat} at the target level throughout each expiration. End-tidal PaCO_{2} (P_{ETCO_{2}}) was measured using the on-line gas-analysis system (Oxycon Pro). The inspired fraction of CO_{2} was manually adjusted to prevent P_{ETCO_{2}} from dropping below eupneic values. Task failure was defined as an inability to generate the target pressure for three consecutive expiratory efforts despite verbal encouragement.

Exercise Responses

Subjects cycled for 2 min at 40% of W_{peak} before work rate was increased to 90% of W_{peak}. Each subject pedaled at a self-selected cadence and maintained this cadence during all subsequent trials. Subjects pedaled until they were unable to maintain pedal cadence.
turbine in combination were 0.074 cmH2O resistance and dead space provided by the ultrasonic flow meter and \( P_{gatw} \). Ventilatory and pulmonary gas exchange indexes were also monitored using a phase-shift flow meter (Birmingham Flowmetrics, Birmingham, UK). Ventilatory and pulmonary gas exchange indexes were also measured using inspiratory capacity maneuvers (11).

End-expiratory and end-inspiratory lung volumes were measured using inspiratory capacity maneuvers (11).

The pressure, force, flow, \( S_aO_2 \), and EMG signals were passed through an amplifier (model 1902; Cambridge Electronic Design, Cambridge, UK), digitized at sampling rates of 150 Hz and 3 kHz (EMG only) with an analog-to-digital converter (micro 1401 mKII; Cambridge Electronic Design), and acquired on a personal computer running commercially available software (Spike 2 version 5.12; Cambridge Electronic Design).

### Statistical Analyses

Repeated-measures ANOVA was used to compare absolute pressure and force measurements across time (preexercise, 4 min postexercise, and 30 min postexercise) and percent changes in these measurements between trials (EMF-EX, CON-EX, ISO-EX). When significant main effects were shown, planned pair-wise comparisons were made with the Bonferroni method. Repeated-measures ANOVA with Bonferroni adjustment was also used to compare the absolute physiological responses at equivalent time points between the three trials. Pearson’s product-moment correlation coefficients (r) were computed to assess the relationship between the percent changes in selected physiological variables at the end of exercise (EMF-EX vs. ISO-EX) and the percent changes in TLIM (CON-EX vs. EMF-EX). The acceptable type I error was set at \( P < 0.05 \). Results are expressed as means ± SD. Statistical analyses were performed using SPSS version 13 for Windows (SPSS, Chicago, IL).

### RESULTS

#### Preliminary Exercise

During maximal incremental exercise, \( W_{peak} \) was 325 ± 27 W and \( V\dot{O}_{2max} \) was 4.36 ± 0.56 l/min (53.5 ± 5.2 ml·kg⁻¹·min⁻¹).

#### Expiratory Resistive Loading and EMF

Task failure during expiratory resistive loading occurred at 24 ± 5 min. There was a 27 ± 5% reduction in \( P_{gatw} \) pre- vs. post-expiratory loading (34.9 ± 6.3 vs. 24.9 ± 5.7 cmH2O; \( P = 0.009 \)). Similarly, \( P_g \) in response to maximal voluntary expulsive maneuvers decreased by 21 ± 8% pre- vs. post-expiratory loading (193 ± 27 vs. 154 ± 30 cmH2O; \( P < 0.001 \)).

#### EMF and Exercise Tolerance

Individual subject changes in exercise tolerance (\( T_{LIM} \)) in response to prior EMF are shown in Fig. 3. \( T_{LIM} \) was reduced by 33 ± 10% in EMF-EX vs. CON-EX (6.85 ± 2.88 vs. 9.90 ± 2.94 min; \( P < 0.001 \)). All of the individual subject data points above 60 rpm. The subjects received no information on either exercise time or heart rate, and verbal encouragement was not provided to prevent bias due to potential intertrial inconsistency. Inspiratory and expiratory air flows were measured breath-by-breath using an ultrasonic phase-shift flow meter (Birmingham Flowmetrics, Birmingham, UK). Ventilatory and pulmonary gas exchange indexes were also measured with the on-line gas-analysis system (Oxycon Pro) with a calibrated turbine for volume measurement and paramagnetic (\( O_2 \)) and infrared absorption (\( CO_2 \)) gas sensors for gas analysis. The resistance and dead space provided by the ultrasonic flow meter and turbine in combination were 0.074 cmH2O and 27 vs. 154 min.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abdominals</th>
<th>Quadriceps</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{gatw}, \ cmH_2O )</td>
<td>34.5±7.1</td>
<td>13.2±06</td>
</tr>
<tr>
<td>CT, ms</td>
<td>325±122</td>
<td>345±325</td>
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<tr>
<td>MRPD/P(_{gatw}, \ s)</td>
<td>8.9±2.3</td>
<td>11.2±11.1</td>
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<tr>
<td>RT(_{0.5}, \ ms)</td>
<td>107±45</td>
<td>116±26</td>
</tr>
<tr>
<td>MRR/P(_{gatw}, \ s)</td>
<td>–8.1±2.3</td>
<td>–8.8±2.5</td>
</tr>
<tr>
<td>RA M-wave amplitude, mV</td>
<td>1.3±0.6</td>
<td>1.2±1.1</td>
</tr>
<tr>
<td>RA M-wave duration, ms</td>
<td>24.1±5.9</td>
<td>22.3±6.8</td>
</tr>
<tr>
<td>RA M-wave area, mV/ms</td>
<td>0.010±0.008</td>
<td>0.009±0.001</td>
</tr>
<tr>
<td>( P_{Emax}, \ cmH_2O )</td>
<td>191±34</td>
<td>186±28</td>
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</table>

Values are group means ± SD for 8 subjects. \( Trial~1 \) and \( trial~2 \) represent measurements taken before and after 30 min of quiet rest, respectively. CV, coefficient of variation; ICC, intraclass correlation coefficient; \( P_{gatw} \), gastric twitch pressure; CT, contraction time; MRPD, maximal rate of pressure development; RT\(_{0.5} \), relaxation time from peak twitch to one-half peak twitch; MRR, maximal relaxation rate; RA, rectus abdominis; \( P_{Emax} \), expiratory gastric pressure during maximal expulsive maneuver; \( Q_{aw} \), quadriceps twitch force; MRFD, maximal rate of force development; VL, vastus lateralis; RF, rectus femoris; MVC, maximal voluntary contraction force.

### Table 1. Within-day reproducibility of neuromuscular function measurements

[Image](http://jap.physiology.org/)

**Fig. 3.** An identity plot showing individual subject \( T_{LIM} \) for control exercise (CON-EX) and after induction of EMF (EMF-EX). The dotted line represents the regression line of CON-EX vs. EMF-EX.
are below the line of identity, indicating that EMF induced a reduction in exercise tolerance in all subjects. The regression line of CON-EX vs. EMF-EX is parallel to the line of identity, indicating that the effect of prior EMF on subsequent exercise tolerance was similar across all of the exercise times.

Exercise-Induced Muscle Fatigue

Magnetic stimulation. Evoked M-wave amplitude, duration, and area for RA, VL, and RF did not differ before vs. after exercise in CON-EX, EMF-EX, or ISO-EX (Table 2). Immediately after exercise in CON-EX, EMF-EX, and ISO-EX, Pgaw and Qtw were reduced below preexercise baseline values, despite some recovery and remained below baseline at 30 min postexercise (Fig. 4). The percent decreases in Pgaw and Qtw immediately after exercise did not differ for CON-EX vs. EMF-EX. However, the decreases in Pgaw and Qtw were greater after EMF-EX vs. ISO-EX (−28 ± 9% vs. −12 ± 5% for Pgaw, P = 0.001; −28 ± 7 vs. −14 ± 6% for Qtw, P = 0.015). The severity of abdominal muscle fatigue was not different after expiratory resistive loading vs. after CON-EX (−27 ± 5 vs. −26 ± 6% for Pgaw, P > 0.05).

Maximal rates of pressure/force development and relaxation were reduced below baseline after each of the exercise trials. When the decreases in Pgaw and Qtw were taken into account, however, neither maximal rate of pressure/force development nor maximal relaxation rate was altered (Table 2). Furthermore, there were no pre- vs. postexercise differences in contraction time or one-half relaxation time (Table 2). The pressure and force responses to maximal volitional efforts were reduced below baseline immediately after CON-EX and EMF-EX, but these responses were blunted after ISO-EX (Table 2).

iEMG. From the first minute to the last minute, iEMG of VL increased significantly in CON-EX, EMF-EX, and ISO-EX (Fig. 5). The percent increase in iEMG was significantly higher at end exercise in EMF-EX than in ISO-EX (119 ± 9% vs. 110 ± 6%; P = 0.021).

Exercise Responses

Heart rate, oxygen saturation, and blood lactate concentration. In CON-EX, cardiac frequency at end exercise was 98 ± 5% of maximum and was not different between EMF-EX, CON-EX, and ISO-EX. No change was found in SpO2 during CON-EX, EMF-EX, or ISO-EX. Blood lactate concentration was not different at end exercise during EMF-EX vs. CON-EX but was significantly higher at end exercise in EMF-EX vs. ISO-EX (Table 3).

Pulmonary gas exchange and breathing pattern. In CON-EX, O2 consumption rose steadily throughout exercise, reaching 98 ± 6% of VO2max. At end exercise, O2 consumption was not different between EMF-EX, CON-EX, and ISO-EX. In CON-EX, minute ventilation (Ve) rose throughout exercise, reaching 97 ± 5% of maximum. In EMF-EX, Ve at end exercise was significantly greater than that in CON-EX and ISO-EX. This increase in Ve was due primarily to an increase in fR because tidal volume did not differ between trials. The increase in fR was due to a decrease in both Ti and inspiratory time. The increased ventilatory response to exercise after induction of EMF was reflected by a lower PETCO2 at end exercise in EMF-EX than in CON-EX and ISO-EX. Neither

Table 2. Neuromuscular function measurements before and immediately (4 min) after exercise

<table>
<thead>
<tr>
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<th>CON-EX</th>
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<th>EMF-EX</th>
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<td>End-expiratory Pes, cmH2O</td>
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<td>−2.1 ± 2.1</td>
<td>−2.7 ± 1.1</td>
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<tr>
<td>End-expiratory Pga, cmH2O</td>
<td>10.8 ± 3.1</td>
<td>10.4 ± 3.7</td>
<td>11.3 ± 2.8</td>
<td>10.9 ± 4.8</td>
<td>11.7 ± 4.2</td>
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<td>CT, ms</td>
<td>325 ± 65</td>
<td>317 ± 68</td>
<td>362 ± 82</td>
<td>351 ± 74</td>
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<td>MRFD/Pgaw, s</td>
<td>10.6 ± 1.9</td>
<td>11.8 ± 3.7</td>
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<td>RToF, ms</td>
<td>109 ± 40</td>
<td>108 ± 48</td>
<td>116 ± 42</td>
<td>114 ± 59</td>
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<td>MRR/Pgaw, s</td>
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<td>RA M-wave amplitude, mV</td>
<td>1.1 ± 0.6</td>
<td>1.1 ± 0.8</td>
<td>1.1 ± 0.6</td>
<td>1.0 ± 0.6</td>
<td>1.3 ± 0.6</td>
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<tr>
<td>RA M-wave duration, ms</td>
<td>24.2 ± 7.4</td>
<td>23.8 ± 7.6</td>
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<td>RA M-wave area, mV/ms</td>
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<td>0.009 ± 0.009</td>
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<td>PEmax, cmH2O</td>
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<td>151 ± 31</td>
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<td><strong>Quadriceps</strong></td>
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<td>CT, ms</td>
<td>381 ± 88</td>
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<td>MRFD/Qtw, s</td>
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<td>RToF, ms</td>
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<td>110 ± 42</td>
<td>109 ± 31</td>
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<td>MRR/Qtw, s</td>
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<td>1.4 ± 0.8</td>
<td>1.4 ± 0.6</td>
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<td>VL M-wave duration, ms</td>
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<td>40.7 ± 8.2</td>
<td>37.9 ± 6.8</td>
<td>40.1 ± 9.3</td>
<td>41.3 ± 4.5</td>
<td>40.7 ± 8.8</td>
</tr>
<tr>
<td>VL M-wave area, mV/ms</td>
<td>0.010 ± 0.008</td>
<td>0.012 ± 0.011</td>
<td>0.011 ± 0.005</td>
<td>0.015 ± 0.010</td>
<td>0.012 ± 0.011</td>
<td>0.011 ± 0.006</td>
</tr>
<tr>
<td>RF M-wave amplitude, mV</td>
<td>1.1 ± 10</td>
<td>1.4 ± 11</td>
<td>1.2 ± 9</td>
<td>1.4 ± 11</td>
<td>1.1 ± 6</td>
<td>1.0 ± 1.4</td>
</tr>
<tr>
<td>RF M-wave duration, ms</td>
<td>41.9 ± 7.9</td>
<td>43.8 ± 5.7</td>
<td>40.2 ± 8.8</td>
<td>40.8 ± 8.2</td>
<td>42.8 ± 7.1</td>
<td>43.9 ± 8.5</td>
</tr>
<tr>
<td>RF M-wave area, mV/ms</td>
<td>0.011 ± 0.010</td>
<td>0.010 ± 0.006</td>
<td>0.012 ± 0.009</td>
<td>0.014 ± 0.008</td>
<td>0.009 ± 0.002</td>
<td>0.010 ± 0.008</td>
</tr>
<tr>
<td>MVC, N</td>
<td>537 ± 169</td>
<td>453 ± 150</td>
<td>554 ± 170</td>
<td>433 ± 110</td>
<td>553 ± 161</td>
<td>522 ± 181</td>
</tr>
</tbody>
</table>

Values are group means ± SD. CON-EX, without prior induction of expiratory muscle fatigue (EMF); EMF-EX, with prior induction of EMF; ISO-EX, with exercise for a time equal to that achieved in EMF-EX but without prior induction of EMF; Pes, esophageal pressure; Pga, gastric pressure. *P < 0.05 and †P < 0.01, significantly different from preexercise values.
The major findings were that acute induction of EMF resulted in 1) a decrease in exercise time (TLIM), 2) an exacerbation of exercise-induced abdominal and quadriceps muscle fatigue at exercise isotime, 3) elevated perceptions of dyspnea and leg discomfort, and 4) relative tachypnea during high-intensity exercise.

**DISCUSSION**

**Main Findings**

The major findings were that acute induction of EMF resulted in 1) a decrease in exercise time (TLIM), 2) an exacerbation of exercise-induced abdominal and quadriceps muscle fatigue at exercise isotime, 3) elevated perceptions of dyspnea and leg discomfort, and 4) relative tachypnea during high-intensity exercise.

End-expiratory lung volume nor end-inspiratory lung volume was different at end exercise in CON-EX vs. that shown in EMF-EX and ISO-EX (Fig. 6 and Table 3).

**Respiratory pressures.** The cumulative force output of the abdominal muscles (Pga/dt) and the diaphragm (Pdi/dt) was significantly greater in EMF-EX than in ISO-EX (4,721 ± 956 vs. 3,984 ± 1,216 cmH2O/s, P = 0.001, and 3,348 ± 825 vs. 3,067 ± 953 cmH2O/s, P = 0.013, respectively). In addition, peak expiratory Pga was significantly elevated in EMF-EX vs. ISO-EX at end exercise (Table 3). This was likely a result of the shortened TE and increased expiratory flow associated with the tachypnic breathing pattern after EMF.

**Perceptual ratings.** Perceptions of leg discomfort and dyspnea were rated higher at 1 and 3 min and at end-exercise during EMF-EX vs. ISO-EX but were not different at end exercise between EMF-EX and CON-EX (Fig. 7).

**Correlations Between Variables**

The correlations between the percent changes in selected variables for EMF-EX vs. ISO-EX at end exercise are shown in Fig. 8. The changes in leg fatigue and leg discomfort correlated significantly with the changes in TLIM (r = 0.67, P = 0.025 and r = 0.72, P = 0.001, respectively). In addition, the change in dyspnea tended to correlate with the change in TLIM (r = 0.66, P = 0.085). Neither the increase in the cumulative abdominal force output nor the cumulative diaphragm force output correlated significantly with the change in TLIM (r = 0.47, P = 0.133 and r = 0.41, P = 0.218).

### Table 3. Exercise responses for the final minute of exercise

<table>
<thead>
<tr>
<th></th>
<th>CON-EX</th>
<th>EMF-EX</th>
<th>ISO-EX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate, W</td>
<td>298 ± 37</td>
<td>298 ± 32</td>
<td>298 ± 32</td>
</tr>
<tr>
<td>TLIM, min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fV, beats/min</td>
<td>9.9 ± 2.88</td>
<td>6.2 ± 2.94</td>
<td>6.2 ± 2.94</td>
</tr>
<tr>
<td>VO2, l/min</td>
<td>4.0 ± 3.38</td>
<td>1.23 ± 1.54</td>
<td>1.24 ± 1.28</td>
</tr>
<tr>
<td>VO2, l/min</td>
<td>4.17 ± 1.21</td>
<td>4.08 ± 1.35</td>
<td>4.08 ± 1.24</td>
</tr>
<tr>
<td>VE, liters</td>
<td>3.27 ± 0.48</td>
<td>3.31 ± 0.54</td>
<td>3.23 ± 0.62</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>45 ± 9</td>
<td>49 ± 8.9</td>
<td>40 ± 11</td>
</tr>
<tr>
<td>VT, liters</td>
<td>6.5 ± 0.72</td>
<td>7.2 ± 0.61</td>
<td>7.2 ± 0.72</td>
</tr>
<tr>
<td>VT, l/min</td>
<td>26.6 ± 9.1</td>
<td>35.9 ± 9.1</td>
<td>32.0 ± 4.8</td>
</tr>
<tr>
<td>Ve/VCO2, Torr</td>
<td>34.9 ± 4.0</td>
<td>33.6 ± 4.2</td>
<td>38.3 ± 6.2</td>
</tr>
<tr>
<td>Peak expiratory Pga, cmH2O</td>
<td>33.5 ± 13.0</td>
<td>35.9 ± 14.1</td>
<td>26.6 ± 12.2</td>
</tr>
</tbody>
</table>

Values are group means ± SD for 8 subjects. TLIM, exercise time to the limit of tolerance; fV, cardiac frequency; SVo2, arterial oxygen saturation; [La-]a, blood lactate concentration; VE, minute ventilation; VT, tidal volume; fV, respiratory frequency; Ti, inspiratory time; Te, expiratory time; Ti/Ttot, fractional inspiratory time; Ti/Te, inspiratory vs. expiratory time; VE/VCO2, end-expiratory lung volume; EILV, end-inspiratory lung volume; FVC, forced vital capacity; VO2, oxygen uptake; VCO2, carbon dioxide output; PetCO2, end-tidal PCO2. **P < 0.05 values significantly different from CON-EX; †P < 0.05, values significantly different from EMF-EX.
Technical Considerations

Performance measure. One concern about using $T_{\text{lim}}$ as a measure of exercise tolerance is the relatively large variability of this measure (28). Day-to-day differences in subject motivation, effort perceptions, learning effects, and biological variability can lead to variations in this performance measure. We randomized and balanced the order of CON-EX and EMF-EX trials to avoid any potential learning effect, and the subjects performed exercise at similar times of day to minimize diurnal biological variation. Although we acknowledge that time trials are more reproducible than fixed work-rate tests (28), a time-trial test was not feasible in the present study because of the need to measure physiological variables during exercise at identical times and work rates. Nevertheless, the expected changes in time-trial performance are of a much smaller magnitude than the expected changes in $T_{\text{lim}}$. In the present study, we found a significant 33% reduction in $T_{\text{lim}}$ and the likely range of the true effect of EMF on the average subject (95% confidence interval) included changes (−22% to −37%) more than twice the variation previously reported for an exercise trial of similar duration (−15%) (22). Furthermore, we observed a reduction in $T_{\text{lim}}$ in every subject. We are therefore confident that the change in $T_{\text{lim}}$ represents a true effect of EMF on exercise performance.

Subject expectation. A potential problem with assessing the effects of prior EMF on subsequent exercise tolerance is that subject expectations may have contributed an unknown amount to the observed changes. That is, if the subjects believed that the inspiratory loading protocol would induce EMF, then it is perhaps not surprising that exercise tolerance was reduced. Although the subjects could not be blinded to EMF, we ensured that they remained unaware of the experimental hypotheses and naive to the purpose of the study. Subjects received no information on exercise time or physiological cues such as heart rate, and no verbal encouragement was given to the subjects at any point during the exercise trials. Thus, although we cannot rule out an effect of subject expectation on exercise tolerance, we propose that any such effect was likely minimal.

EMF: expiratory resistive loading vs. whole-body exercise. One concern is that the demands placed on the expiratory muscles during expiratory resistive loading may not be representative of the normally occurring demands placed on these muscles during exercise. Any such discrepancy may lead to a subsequent overestimation or underestimation of the effect of the normally occurring level of EMF on exercise tolerance. The degree of EMF induced by expiratory loading and whole-body exercise (CON-EX), however, was remarkably similar (−27 vs. −26%, respectively). We therefore conclude that the reduction in expiratory muscle function induced by expiratory loading was representative of the magnitude of EMF induced by the breathing requirements of high-intensity exercise.

Inspiratory muscle fatigue. We and others have shown that expiratory resistive loading can elicit inspiratory muscle fatigue and EMF (40, 43). This is important because prior fatiguing contractions of the inspiratory muscles have been shown to impair subsequent exercise tolerance (17). To circumvent this potential problem, we used an expiratory loading protocol that elicits a level of abdominal muscle fatigue similar to that found after whole body exercise yet minimizes the severity of diaphragm and rib cage muscle fatigue (43). Thus, although we cannot rule out an effect of inspiratory muscle fatigue on exercise tolerance, we are confident that any inspiratory muscle fatigue induced would have had only a minor effect on subsequent exercise tolerance.
Effect of EMF on breathing pattern. With prior induction of EMF, there were marked increases in V˙E and fR compared with that with ISO-EX, whereas tidal volume was unchanged. Thus it appears that EMF, like inspiratory muscle fatigue (16, 17, 36), elicits a pattern of rapid but not shallow breathing. This increase in ventilation resulted in a significant increase in the cumulative force output of the abdominal muscles and the diaphragm, which in turn may have contributed to the observed reduction in exercise tolerance. However, neither the increase in abdominal force output nor diaphragm force output correlated significantly with the change in TLIM. Accordingly, we are confident that the increases in abdominal and diaphragm force production were not primary determinants of the decrease in exercise tolerance.

Comparisons With Previous Studies

Several studies have investigated the effect of prior inspiratory muscle work (17, 36), expiratory muscle work (45), or global respiratory muscle work (7, 19, 37) on subsequent exercise tolerance, with studies reporting either an impairment (17, 19, 45) or no change (7, 36, 37). We propose two main reasons that could account for the divergent findings between studies. First, most of the studies did not assess respiratory muscle fatigue (7, 19, 37) or quantified fatigue using indirect, effort-dependent measures (17, 45). It is therefore possible that some studies either failed to induce significant respiratory muscle fatigue before subsequent exercise or overestimated the normally occurring level of fatigue after whole body exercise. In the present study, the direct evidence that the abdominal muscles were fatigued after expiratory loading. Furthermore, expiratory loading and cycle exercise elicited a similar degree of abdominal muscle fatigue (27 vs. 26% reduction in Pga ew). Second, the discrepant findings may have been because of differences in exercise protocol. Recent evidence has shown that partially unloading the inspiratory muscles during maximal incremental exercise does not elicit an increase in exercise time (34), likely because other limiting factors reach predominance before any effects of respiratory muscle fatigue are manifest. It is perhaps not surprising, therefore, that acute...
inspiratory muscle loading also does not affect exercise time during maximal incremental exercise (36).

Why Did EMF Limit Exercise Tolerance?

Locomotor muscle fatigue. The severity of quadriceps muscle fatigue was greater after cycle exercise of the same intensity and duration with prior induction of EMF than without. Furthermore, the exacerbation of quadriceps muscle fatigue accounted for a significant amount of the variation in TLIM, suggesting that the reduction in exercise tolerance was mediated largely by the increased rate of leg muscle fatigue. The exacerbation of exercise-induced quadriceps muscle fatigue was likely a consequence of two mechanisms. First, prior fatigue of the abdominal muscles may have caused a sympathetically mediated vasoconstriction in exercising limb muscles, similar to that described previously for fatiguing inspiratory muscle work (35). Fatiguing abdominal work in the otherwise resting human was shown to elicit a reflex increase in limb muscle sympathetic nerve activity that was likely triggered by an accumulation of metabolites in the fatiguing abdominal muscles (6). In the resting and exercising canine, infusion of lactic acid into the deep circumflex iliac artery resulted in a reduction in hindlimb blood flow, an effect that was prevented via pharmacological sympathetic blockade (32). A reduction in blood flow to working limb muscles would be expected to limit exercise tolerance via an increased severity of leg muscle fatigue, as has been shown to occur when the inspiratory muscles are loaded before (21) or during exercise (33).

Second, an increase in abdominal pressure during active expiration mechanically impedes venous return from the locomotor limb muscles, thereby reducing the steady-state hyperemic response to dynamic exercise (1, 24, 25, 38). For example, Stark-Leyva et al. (38) applied an expiratory load during submaximal cycle exercise that resulted in an additional 7–18 cmH2O increase in Pga and a consequent decrease in cardiac output in healthy humans. Such elevations in expiratory pressure production are thought to decrease venous return from the legs and, in turn, decrease blood flow through the inferior vena cava via a “starling resistor” mechanism (41). In the present study, peak expiratory Pga was 9.3 cmH2O greater in EMF-EX than in ISO-EX, and this increase was of a magnitude similar to that induced by Stark-Leyva et al. (38). It is therefore possible that the increase in abdominal pressure production after induction of EMF resulted in a reduction in cardiac output that contributed to the exacerbation of quadriceps muscle fatigue and the consequent reduction in exercise tolerance.

Perceived exertion. Perceptions of dyspnea and leg discomfort were rated higher at every time point during EMF-EX vs. during ISO-EX. In turn, the changes in exercise tolerance correlated closely with both perceptions, although only leg discomfort correlated significantly. It is therefore possible that our subjects terminated exercise prematurely after induction of EMF due, in part, to heightened perceptions of dyspnea and leg discomfort during exercise. The increases in dyspnea and leg discomfort with prior EMF were likely related to the exacerbation of both exercise-induced abdominal and quadriceps muscle fatigue, respectively. With the onset and development of muscle fatigue, there is an increased central drive to maintain force production in the muscle (8) that is subsequently perceived via corollary discharge to the primary somatosensory cortex as an increased sense of effort (12), which may provide a critical signal to the central nervous system to curtail exercise. Because prior EMF exacerbated both abdominal and quadriceps muscle fatigue, there was likely an increased central drive to the muscles during EMF-EX with a subsequent increase in effort perception and premature curtailment of exercise. This notion is supported by the finding that both VE and abdominal muscle pressure production were greater at end-exercise in EMF-EX than in ISO-EX. That is, the enhanced ventilatory response to exercise with EMF likely represents an increase in central motor drive. In addition, iEMG from the VL during each pedal stroke was significantly greater at end exercise in EMF-EX than in ISO-EX, indicating a concurrent increase in central motor drive to the fatiguing quadriceps muscles.

Conclusions

Prior EMF limited subsequent exercise tolerance, primarily via an increased severity of limb locomotor muscle fatigue and a heightened perception of leg discomfort. We postulate that the increased severity of limb muscle fatigue arose from impairment in limb muscle blood flow. This impairment may have been caused by a sympathetically mediated vasoconstrictor influence exerted by an exacerbation of abdominal muscle fatigue, combined with a reduction in cardiac output facilitated by an augmented expiratory Pga.

REFERENCES