Locomotor muscle fatigue increases cardiorespiratory responses and reduces performance during intense cycling exercise independently from metabolic stress

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Marcora SM, Bosio A, de Morree HM. Locomotor muscle fatigue increases cardiorespiratory responses and reduces performance during intense cycling exercise independently from metabolic stress. Am J Physiol Regul Integr Comp Physiol 294: R874–R883, 2008. First published January 9, 2008; doi:10.1152/ajpregu.00678.2007.—Locomotor muscle fatigue, defined as an exercise-induced reduction in maximal voluntary force, occurs during prolonged exercise, but its effects on cardiorespiratory responses and exercise performance are unknown. In this investigation, a significant reduction in locomotor muscle force (−18%, P < 0.05) was isolated from the metabolic stress usually associated with fatiguing exercise using a 100-drop-jumps protocol consisting of one jump every 20 s from a 40-cm-high platform. The effect of this treatment on time to exhaustion during high-intensity constant-power cycling was measured in study 1 (n = 10). In study 2 (n = 14), test duration (871 ± 280 s) was matched between fatigue and control condition (rest). In study 1, locomotor muscle fatigue caused a significant curtailment in time to exhaustion (636 ± 278 s) compared with control (750 ± 281 s) (P = 0.003) and increased cardiac output. Breathing frequency was significantly increased in the fatigue condition in both studies despite similar oxygen consumption and blood lactate accumulation. In study 2, high-intensity cycling did not induce further fatigue to eccentrically-fatigued locomotor muscles. In both studies, there was a significant increase in heart rate in the fatigue condition, and perceived exertion was significantly increased in study 2 compared with control. These results suggest that locomotor muscle fatigue has a significant influence on cardiorespiratory responses and exercise performance during high-intensity cycling independently from metabolic stress. These effects seem to be mediated by the increased central motor command and perception of effort required to exercise with weaker locomotor muscles.

perception of effort; central motor command; cardiorespiratory regulation; motivation; endurance

SIGNIFICANT LOCOMOTOR MUSCLE fatigue, defined as an exercise-induced reduction in maximal voluntary force produced with the locomotor muscles (17), occurs during sustained exercise (1, 3, 5, 29, 33, 36) and is commonly thought to directly limit exercise performance (13, 38). Accordingly, most studies on the determinants of exercise performance have focused on various mechanisms contributing to central and/or peripheral fatigue during prolonged exercise such as metabolic and ionic changes within the locomotor muscles, insufficient oxygen delivery, and hyperthermia (28). However, in spite of its importance, the fundamental assumption that reduced locomotor muscle force has a negative effect on exercise performance has never been tested experimentally and remains one of the important unknowns in exercise physiology (12). Another related and still unanswered research question is whether the increased central motor command required to exercise at the same workload with fatigued locomotor muscles has a significant influence on the cardiorespiratory responses to sustained exercise (11, 32, 44, 45).

The main challenge in testing these hypotheses experimentally is to isolate the reduction in locomotor muscle force (and consequent increase in central motor command) from other physiological effects of fatiguing exercise, which may independently affect cardiorespiratory responses and performance during prolonged exercise. Of particular concern is the metabolic stress usually associated with muscle fatigue during high-intensity exercise (37). Indeed, accumulation of various metabolites, such as lactic acid, is known to stimulate group IV and some group III muscle afferents that generate reflexes (the metaboreflex), which can significantly affect the cardiorespiratory responses to sustained exercise independently from increased central motor command (27, 42). Furthermore, in conditions ranging from hypoxemia to moderate hypoxia, stimulation of these small sensory neurons by fatigue-related metabolites might limit exercise performance by generating a painful sensation of leg discomfort and/or a not yet identified inhibitory supraspinal reflex that forces the subject to reduce exercise intensity or terminate exercise well before locomotor muscle fatigue becomes a limiting factor (1, 2). Indeed, the proponents of this conscious and/or subconscious inhibitory feedback mechanism believe that its function is to protect the locomotor muscles from excessive peripheral fatigue (1, 2).

The primary aim of the present investigation was to control for these confounding effects of metabolic stress and test the hypotheses that a reduction in locomotor muscle force per se causes 1) a significant increase in central motor command with consequent alterations in the cardiorespiratory responses to high-intensity constant-power cycling, despite unaltered metabolic requirements and 2) a reduction in time to exhaustion, a sensitive measure of exercise performance (4). To test these hypotheses, we used an unusual fatiguing exercise protocol as experimental treatment to induce a significant and prolonged reduction in locomotor muscle force without accumulation of muscle metabolites (30, 41). Indeed, the excitation-contraction coupling failure induced by this eccentric exercise protocol is caused by structural alterations rather than metabolic stress (30, 34).

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Another aim of our investigation was to determine whether the hypothesized negative effect of reduced locomotor muscle force on exercise performance is direct or mediated by the consequent increase in central motor command, which is consciously perceived as increased effort (22, 31). According to Brehm’s motivational intensity theory (9, 48), people engage in a task until the effort required reaches the maximum level of effort they are willing to invest for succeeding in that task, the so-called potential motivation. After this critical level of effort is reached, or when success in the task is perceived as impossible, the subjects exert very little or no voluntary effort, i.e., disengage from the task. This theory has been validated by several psychophysiological studies using a variety of mental tasks and experimental manipulations (48), but it applies to any motivated behavior including exercise (9). Indeed, exhaustion may be a form of task disengagement, rather than physiological failure, as it normally occurs when ratings of perceived exertion (RPE) are very high (33) regardless of exercise intensity, environmental conditions, and physiological state of the subject (31). Because perceived exertion increases over time during constant-power cycling, subjects’ potential motivation (and subsequent task disengagement) would be reached earlier than normal if perception of effort is increased when cycling at high intensity with fatigued locomotor muscles. Such psychobiological mechanism might cause exhaustion well before maximal voluntary locomotor muscle force/power falls below the level required by the exercise task as postulated by the traditional physiological model of fatigue and performance (13, 28, 38). Because perceived exertion is largely independent of afferent neural feedback from locomotor muscles (43), this psychobiological model of exercise performance based on Brehm’s motivational intensity theory may also provide a valid alternative to the inhibitory feedback model recently proposed by Amann and Dempsey (1, 2).

METHODS

Subjects

This investigation consisted of two separate studies. For the first study, we recruited 10 healthy male subjects undergoing regular aerobic exercise for recreational or competitive purposes (age, 23 ± 4 yr; height, 176 ± 7 cm; body mass, 79 ± 14 kg; peak power output, 346 ± 56 W; VO2peak, 51 ± 8 ml·kg⁻¹·min⁻¹). For the second study, we recruited a similar population of 14 subjects (age, 26 ± 5 yr; height, 179 ± 5 cm; body mass, 79 ± 9 kg; peak power output, 334 ± 56 W; VO2peak, 51 ± 7 ml·kg⁻¹·min⁻¹). Only one subject participated in both studies. The experimental protocols were approved by the Ethics Committee of the School of Sport, Health and Exercise Sciences and conformed to the standards set by the Declaration of Helsinki.

Experimental Protocols

All volunteers visited the laboratory on three different occasions. During the first visit, the study and its aims were explained, and a medical and training questionnaire was administered. Eligible subjects signed an informed consent form and anthropometric measures were taken. An incremental exercise test (2 min at 50 W + 50 W increments every 2 min) was then performed until exhaustion (operationally defined as a pedaling frequency of < 60 rpm for more than 5 s, despite strong verbal encouragement) on an electromagnetically-braked cycle ergometer (Excalibur Sport; Lode, Groningen, The Netherlands) to measure peak oxygen uptake (VO2peak) and peak power output, which was calculated according to the equation of Kuipers et al. (23). The cycle ergometer was set in hyperbolic mode, which allows the power output to be set independently of pedal frequency over the range of 30 to 120 rpm. Before the incremental exercise test, the position on the cycle ergometer was adjusted for each subject and settings were recorded so that they could be reproduced at each subsequent visit. Subjects were also given standard instructions for overall RPE using the 6 to 20 scale developed by Borg (8). During the incremental exercise test, the low and high anchor points were established using standard procedures (31).

In study 1, after a minimum of 24 h, subjects reported for the second time to the laboratory where delayed-onset muscle soreness (DOMS) was assessed using a seven-point Likert scale (26). Creatine kinase concentration (UI/l) was measured with a colorimetric assay (Reflotron; Boehringer Mannheim, Germany) in a 30-μl sample of whole fresh blood taken from the right earlobe. After a 5-min warm-up on the cycle ergometer at 10% of peak power output, bilateral maximal voluntary contraction (MVC) of the knee extensors, an index of locomotor muscle force, was assessed in isometric condition with subjects seated in a rigid, straight-backed chair with a 90° knee and ankle angle. After three submaximal warm-up and familiarization trials (25%, 50%, 75% of maximal effort), subjects were asked three times to push maximally for 5 s against pads placed just proximal to their ankle joints and inextensibly attached to a load cell (model 615; Tedea Hunteleigh, Vishay, CA) connected to a computerized A/D converter for data recording and analysis (Bridge Amp, Powerlab/16SP, Power Lab Chart V 4.2.3; ADI Instruments, Bella Vista, Australia). Between all six trials 1-min rest was observed. During the maximal trials, strong verbal encouragement was given. Peak force (N) produced during each of the three maximal trials was recorded, and the best score was noted for statistical analysis. After this baseline isometric test, subjects were randomly assigned to either the fatigue or control condition with a 1-to-1 allocation ratio. The fatigue condition consisted of the eccentric exercise protocol developed by Skurvydas et al. (41). Subjects dropped 100 times from a 40-cm high platform down to 90° knee angle before jumping upward as high as possible. Between each drop jump there was a 20-s rest period to allow for recovery, through oxidative phosphorylation, of the ATP and phosphocreatine expended during each drop jump. Indeed, in a pilot study (Marcora SM, Bosio A, de Morree HM, un unpublished results), we measured no increase in capillary blood lactate concentration after this fatiguing exercise protocol, which requires only moderate cardiovascular strain, an average of 58% of maximum heart rate (HR) for 33 min. Furthermore, it does not induce any respiratory muscle fatigue, another factor, that might affect breathing pattern and exercise performance (25). The control condition consisted of resting comfortably for 33 min. Two minutes after completing the assigned treatment, locomotor muscle force was assessed again with three maximal trials only (prechycling isometric test). After this second isometric test, a 30-min rest period was prescribed to allow for further cardiorespiratory and metabolic recovery after the 100 drop jumps, while at the same time controlling for the confounding effects of DOMS, which usually peaks 48 h after eccentric exercise because of increased sensitivity of small muscle afferent neurons to mechanical stimuli (46). After this rest period, subjects began the high-intensity constant-power cycling test to exhaustion with the ergometer set in hyperbolic mode. This cycling test consisted of 3 min of rest sitting on the cycle ergometer, 3 min of warm-up at 10% of peak power output, and a rectangular workload corresponding to 80% of peak power output, which corresponded to 90 ± 7% of VO2peak measured during the preliminary incremental exercise test. Pedal frequency was freely chosen between 60–100 rpm and was recorded every minute. Time to exhaustion was measured from the start of the rectangular workload until the pedal frequency was < 60 rpm for more than 5 s, despite strong verbal encouragement that was provided by a research assistant blinded to the assigned treatment. Physiological and perceptual responses were measured throughout the cycling test. After a period of 10–14 days to washout the detrimental
effects of muscle damage induced by the 100-drop-jumps protocol, subjects reported for the third time to the laboratory. During this visit, the same procedures as during the second visit were followed except for the experimental treatment, which was the opposite of the second visit (randomized counterbalanced AB/BA cross-over design).

In study 2, the same procedures as in study 1 were used apart from the following. First of all, treatment order was not randomized. During the second visit, all subjects performed the 100-drop-jumps protocol before the high-intensity constant-power cycling test to exhaustion at 80% of peak-power output, which, in these subjects, corresponded to 86 ± 5% of \( V_{O2\text{peak}} \) measured during the preliminary incremental exercise test. During the third visit, all subjects rested comfortably for 33 min. On this occasion, the cycling test was stopped at the same time that exhaustion occurred during the second visit. None of the subjects reached exhaustion before the prescribed time during this second cycling test. Furthermore, 2 min after the end of the cycling test, locomotor muscle force was assessed for a third time. In this postcycling isometric test, subjects were asked to perform only the three maximal trials.

All subjects were instructed to avoid smoking, intense exercise, alcohol, tea, and beverages containing caffeine in the 24 h preceding each visit. During the same time, they were asked to drink 40 ml of water per kilogram of body mass and to maintain their usual diet. They were also instructed to have a light meal at least 3 h before reporting to the laboratory. All visits were scheduled at the same time of the day, and environmental conditions in the laboratory were kept between 18 and 22 °C for temperature and 45–60% for humidity.

### Physiological and Perceptual Responses to Exercise

In both studies, tidal volume (liters), breathing frequency (minutes), ventilation (l/min), \( V_{O2} \) (l/min), and carbon dioxide production (\( V_{CO2}; \) l/min) were measured breath-by-breath using computerized metabolic gas analysis systems (study 1: 600Ergo Test, ZAN Messgeräte, Oberthulba, Germany; study 2: MetaLyzer 3B, Cortex Biophysik, Leipzig, Germany) connected to an oro-(mouth) mask (7600 series; Hans Rudolph, Kansas City, MO). These automated devices were calibrated before each test using certified gases of known concentration (11.5% \( O_2 \) and 5.1% \( CO_2 \)) and a 3.01 calibration syringe (series 5530; Hans Rudolph). All respiratory gas exchange data were averaged over 1-min periods before statistical analysis.

During rest and 1 min after the end of the high-intensity constant-power cycling test, a 5-μl sample of whole fresh blood was taken from the right earlobe and analyzed for lactate concentration (mmol/l) using a portable analyzer (Lactate Pro LT-1710; Arkray, Shiga, Japan). Lactate accumulation was calculated by subtracting the resting value from the value obtained after cycling. During the final 15 s of each minute of exercise, subjects were asked to rate their perceived exertion using a 6–20 RPE scale, which was displayed throughout the cycling test.

In study 1, a bioimpedance device (Physioflow PF05L1; Manatec, Petit-Ebersviller, France) was used to measure HR, stroke volume (SV), and cardiac output (CO). Two sets of two electrodes (Ambu Blue Sensor VL; Ambu, Ballerup, Denmark), one transmitting and the other one receiving a low amperage alternating electrical current, were applied on the supraclavicular fossa at the left base of the neck and along the xiphoid. Another set of two electrodes was used to monitor a single ECG lead in the V1/V6 position. All electrode placement areas were shaved, if necessary, cleaned with an alcohol pad, and dried with a paper towel. Wires connected to the electrodes were fixed on the body using tape to reduce movement artifacts. SV (ml) is estimated by this computerized device from changes in transthoracic impedance during cardiac ejection according to the method described in detail by Charloux et al. (10). CO (l/min) was calculated as CO = (HR × SVi × BSA)/1,000, where BSA is body surface area (m²) calculated according to the Haycock formula [BSA = 0.02465 × height (cm)²⁰⁷⁶⁴] and SVi (ml/m²−1) = SV/BSA. HR (min−1) is based on the R-R interval determined from the first derivative of the ECG. These data were averaged over 1-min periods before statistical analysis. Accuracy of CO estimation has been validated against direct Fick methods (10). Furthermore, in a group of 20 healthy men with characteristics similar to the subjects included in this investigation, reproducibility during intense cycling was high (coefficient of variation 3.4%) (21). Before each test, the Physioflow was autocalibrated using a procedure based on 1) 30 consecutive heartbeats recorded while the participant was resting in a seated position on the cycle ergometer, 2) anthropometric data, and 3) resting systolic and diastolic blood pressure values (mmHg) (10). These values were the averages of two separate blood pressure recordings taken before and after the Physioflow autocalibration using an automated blood pressure monitor (Tango; SunTech Medical, Morrisville, NC). The Tango device was interfaced to the Physioflow by an analog cable for the ECG trigger. The size of the cuff, which was placed on the left arm of the subject, was based on individual arm girth. Blood pressure was also monitored at the end of warm-up and every 2 min during the time-to-exhaustion test. Mean arterial pressure (MAP) (mmHg) was calculated as MAP = \( [(2 × \text{diastolic pressure}) + \text{systolic pressure}] / 3 \). Total peripheral resistance (TPR) (mmHg·l·min⁻¹·min⁻¹) was calculated as TPR = MAP/CO.

In study 2, HR was measured every 5 s using a telemetric monitor (Polar S610i; Polar Electro, Kempele, Finland). These data were averaged over 1-min periods before statistical analysis. Rectal temperature was measured continuously during the cycling test with a disposable temperature probe (Henleys Medical Supplies, Herts, UK) inserted 10 cm beyond the anal sphincter and connected to a monitor (model 4000A; YSI, Dayton, OH). Temperature data were recorded every minute.

### Statistical Analysis

Unless otherwise noted, all data are presented as means ± SD. The effects of condition (fatigue vs. control) and time on locomotor muscle force (study 1: baseline and precycling; study 2: baseline, precycling, and postcycling) and on all physiological/perceptual parameters at isotime [study 1: end of warm-up (0 min) + first 5 min of exercise; study 2: end of warm-up + 33, 66, and 100% of total time] were tested using fully repeated-measures multivariate ANOVAs (MANOVAs). For all MANOVAs, if a significant condition × time interaction was revealed, the main effect of condition was not considered, and tests of simple main effects of condition were conducted as follow-up using the Holm-Bonferroni method (20). In addition to the standard follow-up procedures, in study 2 precycling vs. postcycling changes in locomotor muscle force were analyzed using a paired \( t \)-test within each condition (fatigue and control). A two-way fully repeated-measures MANOVA was conducted to compare the locomotor muscle fatigue induced by the 100-drop-jumps protocol (baseline vs. precycling locomotor muscle force in the fatigue condition) with the locomotor muscle fatigue induced by the high-intensity constant-power cycling test (precycling vs. postcycling locomotor muscle force in the control condition). For this purpose, only the interaction was considered.

With the exception of time to exhaustion, which was analyzed using the Hills-Harmitage approach (39), when comparing two means, paired \( t \)-tests or Wilcoxon signed-ranks tests were used as appropriate. Significance was set at 0.05 (two-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences Version 11.

### Results

#### Study 1

Effect of experimental treatment on locomotor muscle force. There were no significant baseline differences in DOMS (median/interquartile range) (fatigue 0.00/1.00, control 0.50/1.25)
and creatine kinase concentration (fatigue 183 ± 204 UI/l, control 151 ± 59 UI/l) between conditions. Furthermore, follow-up tests of the significant condition × time interaction ($P = 0.003$) for knee extensor MVC revealed no significant baseline difference in this parameter (fatigue 703 ± 114 N, control 694 ± 122 N). Taken together, these three markers of exercise-induced muscle damage suggest that the 10–14 days washout period prescribed in both studies was appropriate. As expected, follow-up tests revealed that precycling locomotor muscle force was lower in the fatigue condition (599 ± 127 N) compared with control (697 ± 111 N) ($P = 0.001$). None of the subjects reported muscle pain before the cycling test in the fatigue condition, but some reported symptoms of leg weakness.

**Effect of experimental treatment on time to exhaustion.** Average self-selected pedal frequency during the high-intensity constant-power cycling test to exhaustion was not significantly different between the fatigue (77 ± 7 rpm) and control (76 ± 7 rpm) condition. As shown in the condition-by-condition scatter-plot (Fig. 1), all but one subject had a reduction in exercise performance in the fatigue condition compared with control. On average, time to exhaustion was 636 ± 278 s after the 100 drop jumps and 750 ± 281 s in the control condition ($P = 0.003$). There was no significant order effect between the first and the second time-to-exhaustion test regardless of condition.

**Effects of experimental treatment on physiological and perceptual responses to exercise.** All physiological and perceptual parameters showed the expected response to high-intensity constant-power cycling to exhaustion (time $P < 0.05$). No significant effects of experimental treatment on $\dot{V}O_2$ were found during the first 5 min of exercise (isotime) or at exhaustion (Fig. 2A). Similarly, lactate accumulation was not significantly different between the fatigue (8.9 ± 2.4 mmol/l) and control condition (10.0 ± 2.4 mmol/l). Even when normalized for the different duration of two cycling tests, the increase in capillary blood lactate concentration was not significantly different between the fatigue (1.0 ± 0.5 mmol·l$^{-1}$·min$^{-1}$) and control (0.9 ± 0.4 mmol·l$^{-1}$·min$^{-1}$) conditions. Despite similar metabolic requirements, ventilation at isotime was significantly higher after the 100 drop jumps compared with control (condition, $P = 0.016$) (Fig. 2C). However, no significant difference was found at exhaustion. The hyperpnea observed during the first 5 min of exercise in the fatigue condition was due to higher breathing frequency (condition, $P = 0.019$) (Fig. 2D) as tidal volume was not affected by experimental treatment (Fig. 2E). No significant differences between conditions were found at exhaustion in both breathing frequency and tidal volume. During the first 5 min of exercise there was a small but statistically significant increase in $\dot{V}CO_2$ (condition, $P = 0.026$) (Fig. 2B). No significant difference between conditions was found at exhaustion. Transthoracic impedance analysis revealed that during the first 5 min of exercise CO was significantly increased in the fatigue condition compared with control (condition, $P = 0.047$) (Fig. 3D). This was a hyperdynamic circulatory response as HR (condition, $P < 0.001$) (Fig. 3B) rather than SV (Fig. 3C) was significantly affected by experimental treatment. However, the eccentric exercise protocol did not significantly affect CO, HR, and SV at exhaustion. The effect of experimental treatment on MAP during the first 5 min of exercise did not reach statistical significance (condition, $P = 0.097$) (Fig. 3E). The last MAP reading was taken (median/interquartile range) 29/82 s before exhaustion in the fatigue condition and 26/76 s before exhaustion in the control condition ($P = 0.646$). No significant difference in MAP was found between conditions at these times. Similarly, the 100-drop-jumps protocol did not have a significant effect on TPR either at isotime or at exhaustion (Fig. 3F). The small increase in RPE at isotime observed in the fatigue condition compared with control was not statistically significant (Fig. 3A). Perception of effort at exhaustion was unaffected by experimental treatment.

**Study 2**

**Effects of experimental treatment and high-intensity cycling on locomotor muscle force.** As in study 1, follow-up tests of the significant condition × time interaction ($P < 0.001$) for knee extensor MVC (Fig. 4) revealed no significant differences except a significant simple main effect in the precycling isotonic test with locomotor muscle force significantly lower in the fatigue condition ($P = 0.001$). None of the subjects reported muscle pain before the cycling test in the fatigue condition but some reported symptoms of leg weakness.

In both the fatigue and control condition, subjects cycled for an average of 871 ± 280 s, and average self-selected pedal frequency was not different between conditions (fatigue 80 ± 8 rpm, control 81 ± 6 rpm). The longer duration of the cycling test in study 2 is due to the slightly lower exercise intensity (86 ± 5% of $\dot{V}O_2$peak) compared with study 1 (90 ± 7% of $\dot{V}O_2$peak). At the end of this exercise, knee extensor MVC was not significantly different between the fatigue and control condition. The two additional follow-up tests conducted between pre- and postcycling in both conditions revealed no

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**Fig. 1.** Effect of experimental treatment on time to exhaustion during high-intensity constant-power cycling ($n = 10$). Scatterplot of time to exhaustion in the fatigue condition (33 min rest) compared with the control condition (33 min rest). The points below the identity line represent a decreased performance in the fatigue condition compared with the control condition in individual participants.
significant change in locomotor muscle force in the fatigue condition. However, in the control condition there was a significant decline in knee extensor MVC ($P < 0.001$). The additional two-way fully repeated-measures MANOVA comparing this muscle fatigue (precycling vs. postcycling in the control condition) with the muscle fatigue induced by the 100-drop-jumps protocol (baseline vs. precycling in the fatigue condition) revealed no significant interaction (Fig. 4).

**Fig. 2.** Effects of experimental treatment on metabolic and respiratory responses during high-intensity constant-power cycling ($n = 10$). Fatigue condition consisted of 100 drop jumps over 33 min. Control condition consisted of 33 min rest. #Significant main effect of time ($P < 0.05$). *Significant main effect of condition ($P < 0.05$). Data are presented as means ± SD. VCO$_2$, carbon dioxide production.

**Fig. 3.** Effects of experimental treatment on perception of effort and cardiovascular responses during high-intensity constant-power cycling ($n = 10$). Fatigue condition consisted of 100 drop jumps over 33 min. Control condition consisted of 33 min rest. #Significant main effect of time ($P < 0.05$). *Significant main effect of condition ($P < 0.05$). Data are presented as means ± SD. RPE, ratings of perceived exertion. MAP, mean arterial pressure. TPR, total peripheral resistance.
Effects of experimental treatment on physiological and perceptual responses to exercise. All physiological and perceptual parameters showed the expected response to high-intensity constant-power cycling (time $P < 0.05$). Although there was a significant interaction ($P < 0.036$), tests of simple main effects revealed no significant differences in $\dot{V}O_2$ between fatigue and control condition at any time point (Fig. 5A). Similarly, lactate accumulation was not significantly different between the fatigue (12.7 ± 2.1 mmol/l) and control condition (12.3 ± 2.4 mmol/l). As expected, there was a significant effect of experimental treatment on breathing pattern (interaction, $P = 0.021$) (Fig. 5D). Tests of simple main effects of condition revealed a significant difference in breathing frequency at 100% of total time ($P < 0.001$). Despite this tachypnea, ventilation was only marginally different between the fatigue condition and control (condition, $P = 0.065$) (Fig. 5C). This occurred because there was a concurrent marginal reduction in tidal volume (condition, $P = 0.064$) (Fig. 5E). The small effect of experimental treatment on ventilation did not result in a significant difference in $\dot{V}CO_2$ between the fatigue and control condition (Fig. 5B). However, there was a significant effect of experimental treatment on rectal temperature, which was 0.5 °C higher in the fatigue condition compared with control throughout the cycling test (condition, $P < 0.001$) (Fig. 5F). As in study 1, the HR response to exercise was affected by experimental treatment (interaction, $P = 0.008$). Tests of simple main effects revealed that HR was significantly higher in the fatigue condition compared with control at each time point (0%, 33%, and 66% $P < 0.001$; 100% $P = 0.002$) (Fig. 6B). In this study the effect of experimental treatment on perception of effort was statistically significant with higher RPE in the fatigue condition compared with control (condition, $P = 0.043$) (Fig. 6A).

DISCUSSION

Effects of Experimental Treatment and Intense Cycling Exercise on Locomotor Muscle Force

The 100-drop-jumps protocol induced, on average, a significant 18% reduction in knee extensor MVC. This locomotor muscle force was significantly lower in the fatigue condition compared with control (condition, $P < 0.05$). This suggests that the experimental treatment had a significant effect on locomotor muscle force, which may be due to the high-intensity constant-power cycling protocol used. Further studies are needed to investigate the mechanism underlying this effect and its implications for exercise performance.
muscle fatigue is similar to that reported in previous studies using the same eccentric exercise protocol (30, 40), and it is physiologically relevant. In fact, a similar reduction in knee extensor MVC has been measured after high-intensity constant-power cycling tests to exhaustion (1, 3, 5, 36), and, from a functional point of view, it is irrelevant whether excitation-contraction coupling failure is induced by structural alterations or by metabolic stress (15).

Interestingly, in study 2 the locomotor muscle fatigue induced by the 100 drop jumps (difference between baseline and preycycling in the fatigue condition, Fig. 4) was not significantly different from the locomotor muscle fatigue induced by 14.5 min of intense cycling in the control condition (difference between precycling and postcycling, Fig. 4). The same exercise intensity and duration, however, did not induce a further reduction in locomotor muscle force in the fatigue condition (difference between precycling and postcycling in Fig. 4). These findings are extremely interesting if we consider that metabolic fatigue at whole muscle or muscle group level is primarily due to mechanical dysfunction in a relatively small population of fast-fatigue-sensitive fibers, which occurs early during intense cycling (37), and that these muscle fibers are also the most sensitive to the fatiguing effects of eccentric exercise (34, 35). We therefore speculate that 1) the same population of fast-fatigue-sensitive fibers was fatigued during both the 100-drop-jumps protocol and high-intensity constant-power cycling in the control condition, and 2) no further loss of knee extensor MVC occurred in the fatigue condition because the fast-fatigue-sensitive fibers were already fatigued by the 100-drop-jumps protocol, and metabolic stress did not affect the remaining fast- and slow-fatigue-resistant fibers (37).

**Effect of Locomotor Muscle Fatigue on Markers of Central Motor Command**

To cycle at high-intensity and the same constant power with locomotor muscles weakened by the 100 drop jumps, central motor command must have been increased. This effect of experimental treatment was checked by measuring HR and RPE, two markers of central motor command commonly used in physiological studies (16, 32, 43). In agreement with our hypothesis, we found significant increases in HR in both studies and a significant increase in RPE in study 2. The nonsignificant increase in RPE in study 1 is likely due to lower statistical power [because of smaller sample size and higher variability of RPE scores below 17 (14)] rather than to a lack of effect. Indeed, the difference in perception of effort at isotime between the fatigue and control condition in study 1 (Fig. 3A) is similar to the one measured in study 2 (Fig. 6A). The small increases in HR and RPE measured in our investigation should be expected if a dose-response relationship exists between muscle weakness, central motor command, HR, and RPE. Indeed, our eccentric exercise protocol induced an 18% reduction in force, which was limited to the locomotor muscles. In curarization studies, experimental treatment affects all skeletal muscles, not just the locomotor muscles, and force was reduced by 50% or more to obtain larger changes in central motor command, HR, and RPE (6, 16).

**Effects of Locomotor Muscle Fatigue on Metabolic Stress and Cardiorespiratory Responses to Exercise**

As expected from the results of a previous muscle biopsy study (30) and our pilot, the 100-drop-jumps protocol did not affect the metabolic stress associated with high-intensity constant-power cycling. Indeed, in both studies VO₂ and lactate accumulation did not differ between the fatigue and control condition. Furthermore, eccentric exercise does not increase the sensitivity of group III and IV muscle afferents to metabolic stimuli (46). Therefore, we can assume that the influence of the metaboreflex on the cardiorespiratory responses to exercise (27, 42) was similar between the fatigue and control condition. The influence of the mechanoreflex was also controlled as power output and cadence were the same in both conditions, and eccentric exercise does not alter the sensitivity of muscle spindles and Golgi tendon organs (18, 19). Nevertheless, in study 1 we measured a significant increase in CO (which was mainly due to the increase in HR) and a trend for increased MAP in the fatigue condition with no significant changes in TPR compared with control. This hyperdynamic circulatory response in excess of metabolic requirements is similar to the one reported in studies using low doses of curare.
to weaken skeletal muscles (6, 16). The smaller magnitude of the cardiovascular effects of our experimental treatment is likely to reflect the smaller change in central motor command induced by the 100-drop-jumps protocol compared with partial neuromuscular blockade. In study 1 we also noticed a remarkable effect of experimental treatment on breathing frequency, particularly near exhaustion (Fig. 7). This tachypneic response has been described in previous studies (44) and it is typical of high-intensity constant-power cycling (45).

To study this phenomenon in more detail, in study 2 we compared ventilatory responses at the same time points and measured core body temperature, another potential mechanism for the tachypnea observed during high-intensity constant-power cycling (11). As expected, the phenomenon observed in study 1 was replicated in study 2 where a higher breathing frequency was found in the fatigue condition compared with control, particularly at the end of the cycling test (Fig. 5D). Despite the 30-min rest period between the end of the experimental treatment and the beginning of the cycling test, the heat accumulated during the 100-drop-jumps protocol was not fully dissipated. For this reason, in the fatigue condition subjects started cycling with a rectal temperature 0.5°C higher than in the control condition. The rate of heat storage was not affected by experimental treatment, and, therefore, this difference in rectal temperature was maintained throughout the cycling test. Nevertheless, this effect of experimental treatment is not large enough to explain the different breathing pattern observed during exercise between the fatigue and control condition. Indeed, a difference in core body temperature of more than 1.0°C is necessary to significantly affect respiratory responses to exercise (27). There is also evidence that the sensitivity of group III and IV muscle afferents to thermal stimuli is not altered by eccentric exercise (46). Therefore, it is unlikely that the small difference in core and, most likely, muscle temperature induced by the 100-drop-jumps protocol mediated its striking effect on the tachypneic response to high-intensity constant-power cycling (Fig. 7).

Overall, the results of our study provide experimental support to previous suggestions that the increased central motor command required to exercise at a constant workload with fatigued locomotor muscles plays an important role in the complex regulation of the cardiorespiratory responses to sustained exercise (11, 32, 44, 45).

Effect of Locomotor Muscle Fatigue on Exercise Performance

In study 1 we demonstrated for the first time that reduced locomotor muscle force curtails time to exhaustion during high-intensity constant-power cycling. At first glance, this result seems to support the traditional physiological model of fatigue and exercise performance (13, 28), which assumes that subjects stop exercise when their fatigued neuromuscular system fails to produce the force/power required by the task despite maximal voluntary effort (38). In other words, it is assumed that locomotor muscle fatigue directly causes task failure. However, study 2 shows that subjects in the fatigue condition stopped cycling despite no further decline in locomotor muscle force. Furthermore, locomotor muscle force was always well above the requirement of high-intensity cycling, which is about 20% of MVC (24). Even when tested dynamically and immediately after stopping exercise, the maximal power output produced with fatigued locomotor muscles is almost four times what is required during intense cycling (37). Therefore, failure to produce the force/power required by the exercise task despite maximal voluntary effort does not seem to limit performance as commonly assumed.

Our results also provide experimental evidence against the inhibitory feedback mechanism recently proposed by Amann and Dempsey (1, 2). According to this new physiological model of exercise performance, peripheral fatigue is a variable carefully regulated by the central nervous system (CNS) on the basis of sensory information from locomotor muscle nociceptors stimulated by fatigue-related metabolites. However, as previously discussed, we used the 100-drop-jumps protocol to reduce locomotor muscle force without affecting afferent neural feedback related to metabolic stress. Therefore, the CNS should have been “fooled” to believe that the development of peripheral locomotor muscle fatigue during intense cycling was the same in the fatigue and control condition and should have forced our subjects to stop exercise at exactly the same point in time. The finding that reduced locomotor muscle force per se caused premature exhaustion suggests that the conscious (leg discomfort) and/or subconscious (inhibitory supraspinal reflex) inhibitory effects of afferent neural feedback from metabolically stressed locomotor muscles do not play a determinant role in regulating exercise performance in normoxia as hypothesized by Amann and Dempsey on the basis of correlative data (1, 2).

The results of the present investigation, however, fit with the predictions of Brehm’s motivational intensity theory briefly described in the Introduction (9, 48). This theory postulates that people engage in a task until the effort required reaches the maximum level of effort they are willing to invest for succeeding in that task. In both conditions, this level of effort corresponded to ~ 19 on the 6–20 Borg RPE scale (Fig. 3A). However, because of increased central motor command to the weaker locomotor muscles and related tachypneic response (22, 31), overall perceived exertion was significantly increased in the fatigue condition compared with control (Fig. 6A). As RPE increases over time during constant power cycling, fatigued subjects reached their potential motivation on average 2
min earlier than in the control condition (Fig. 3A). At this time point, task disengagement, rather than task failure, occurred. In other words, we propose that exhaustion occurred because subjects were unwilling to invest further effort in keeping their cadence >60 rpm rather than because they were physiologically unable to do so. According to this novel psychobiological model, any physiological or psychological factor affecting perception of effort and/or potential motivation (e.g., Ref. 47) would affect exercise performance. Therefore, Brehm’s motivational intensity theory may provide a unifying theoretical framework to explain the known effects of various interventions and conditions on exercise performance (31).

**Perspectives and Significance**

By dissociating locomotor muscle fatigue from the metabolic stress that usually accompanies it, we demonstrated for the first time that reduced locomotor muscle force per se has significant effects on cardiorespiratory responses and time to exhaustion during intense cycling exercise. These experimental findings are in contrast with the recent proposal that exercise performance in normoxia is regulated by the CNS on the basis of afferent neural feedback related to metabolic stress in the locomotor muscles to prevent peripheral fatigue from trespassing a task-specific critical threshold (1, 2). However, our results confirm previous suggestions that increased central motor command to fatigued locomotor muscles has an important influence on cardiorespiratory regulation during prolonged constant-workload exercise (11, 32, 44, 45). In accordance with the largely ignored recommendation that the study of fatigue should address both perception of effort and the decline in force that occurs during sustained exercise (7), we propose that further studies are necessary to investigate the sensory psychobiology of perceived exertion and its important role in the regulation of exercise performance (22).

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