Central alterations of neuromuscular function and feedback from group III-IV muscle afferents following exhaustive high-intensity one-leg dynamic exercise

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Pageaux B, Angius L, Hopker JG, Lepers R, Marcora SM. Central alterations of neuromuscular function and feedback from group III-IV muscle afferents following exhaustive high-intensity one-leg dynamic exercise. Am J Physiol Regul Integr Comp Physiol 308: R1008–R1020, 2015. First published April 8, 2015; doi:10.1152/ajpregu.00280.2014.—The aims of this investigation were to describe the central alterations of neuromuscular function induced by exhaustive high-intensity one-leg dynamic exercise (OLDE, study 1) and to indirectly quantify feedback from group III-IV muscle afferents via muscle occlusion (MO, study 2) in healthy adult male humans. We hypothesized that these central alterations and their recovery are associated with changes in afferent feedback. Both studies consisted of two time-to-exhaustion tests at 85% peak power output. In study 1, voluntary activation level (VAL), M-wave, cervicomедullary motor evoked potential (CMEP), motor evoked potential (MEP), and MEP cortical silent period (CSP) of the knee extensor muscles were measured. In study 2, mean arterial pressure (MAP) and leg muscle pain were measured during MO. Measurements were performed preexercise, at exhaustion, and after 3 min recovery. Compared with preexercise values, VAL was lower at exhaustion (−13 ± 13%, P < 0.05) and after 3 min of recovery (−6 ± 6%, P = 0.05). CMEParea/Marea was lower at exhaustion (−38 ± 13%, P < 0.01) and recovered after 3 min. MPEParea/Marea was higher at exhaustion (+25 ± 27%, P < 0.01) and after 3 min of recovery (+17 ± 20%, P < 0.01). CSP was higher (+19 ± 9%, P < 0.01) only at exhaustion and recovered after 3 min. Markers of afferent feedback (MAP and leg muscle pain during MO) were significantly higher only at exhaustion. These findings suggest that the alterations in spinal excitability and CSP induced by high-intensity OLDE are associated with an increase in afferent feedback at exhaustion, whereas central fatigue does not fully recover even when significant afferent feedback is no longer present.

muscle fatigue; corticospinal excitability; cervicomедullary stimulation; endurance performance; central fatigue

ONE-LEG DYNAMIC EXERCISE (OLDE) is characterized by rhythmic voluntary isotonic contractions of the knee extensor muscles interspaced by passive knee flexions (8). Contrary to whole body dynamic exercise (e.g., cycling), because of the reduced muscle mass involved, OLDE is not limited by cardiorespiratory function (54). Therefore, OLDE has been used with patients suffering from cardiorespiratory limitations (53, 55), for studying mechanisms regulating circulatory responses to dynamic exercise (6, 27), and as a training method to improve muscle oxidative capacity (1). Furthermore, high-intensity OLDE has recently been used to investigate the role of the central nervous system in muscle fatigue and exercise performance (7, 54, 56). Thus, the use of OLDE is of particular interest for researchers, clinicians, and athletes.

Contrary to one-leg isometric exercise (e.g., 30, 32, 52) and one-leg isokinetic eccentric and concentric exercise (e.g., Ref. 9), neuromuscular alterations induced by OLDE have been scarcely investigated. OLDE has been shown to induce a progressive decrease in maximal voluntary contraction (MVC) force/torque up to ~50% of preexercise values (24). This muscle fatigue is associated with both peripheral fatigue (i.e., fatigue produced by changes at or distal to the neuromuscular function; see Ref. 25) and central fatigue (i.e., decrease in voluntary activation level during maximal voluntary muscle contractions; see Ref. 25) (54, 56). However, it has to be noted that measures of peripheral fatigue and central fatigue were taken within 2.5 min after cessation of exercise (54, 56). Therefore, because muscle fatigue recovery is known to plateau within 1–2 min postexercise (23), the true extent of muscle fatigue at exhaustion following OLDE remains unknown. Furthermore, it is well known that fatiguing exercise induces not only a decrease in voluntary activation level but also alterations in cortical and spinal excitability (for review, see Ref. 25). To the best of our knowledge, no study has investigated how high-intensity OLDE affects cortical and spinal excitability. In the present investigation, we assessed the extent of central alterations of neuromuscular function (i.e., decrease in voluntary activation level and changes in corticospinal excitability) and their recovery following exhaustive high-intensity OLDE.

Group III-IV muscle afferents are free nerve endings activated by contraction-induced mechanical and chemical stimuli (39, 57). It has been proposed that this afferent feedback from fatigued locomotor muscles might be one of several contributors of central fatigue by spinal (for review, see Ref. 25) and supraspinal reflexes (for review, see Refs. 2 and 25), but could also alter corticospinal excitability (for review, see Ref. 25). However, in these studies, feedback from group III-IV muscle afferents was never quantified. Indeed, to date there is no noninvasive methodology to directly quantify feedback from group III-IV muscle afferents in humans.

Conveniently, feedback from group III-IV muscle afferents is known to increase mean arterial pressure (MAP; see Refs. 15 and 40). This response is called metaboreflex and is independent of central motor command (40, 45). Furthermore, in the absence of central motor command, which is known to alter pain perception (19), rating of muscle pain reflects feedback from group III-IV muscle afferents (50). Therefore, when...
measurements are performed in the absence of central motor command (i.e., during muscle occlusion), MAP and leg muscle pain could be considered markers to indirectly quantify feedback from group III-IV muscle afferents.

The aims of this investigation were to describe the dynamics of central alterations of neuromuscular function induced by exhaustive high-intensity OLDE (study 1), and to indirectly quantify feedback from group III-IV muscle afferents via muscle occlusion (study 2). We hypothesized that central alterations of neuromuscular function induced by exhaustive high-intensity OLDE and their recovery are associated with changes in afferent feedback. Because central fatigue and peripheral fatigue induced by exercise might be underestimated if significant recovery occurs between cessation of exercise and start of neuromuscular testing (12), we used an OLDE model developed in our laboratory to perform both high-intensity OLDE and neuromuscular testing on the same dynamometer.

METHODS

Subjects and Ethical Approval

Ten subjects [mean ± SD; 8 males, age: 27 ± 4 yr, height: 182 ± 3 cm, weight: 82 ± 12 kg, body mass index (BMI): 25 ± 3 kg/m²; 2 females, age: 26 ± 2 yr, height: 171 ± 9 cm, weight: 66 ± 2 kg, BMI: 23 ± 2 kg/m²] volunteered to participate in study 1, and eight male subjects (age: 25 ± 3 yr, height: 180 ± 6 cm, weight: 78 ± 15 kg, BMI: 24 ± 4 kg/m²) volunteered to participate in study 2. Five males participated in both studies. All subjects were regularly involved in aerobic exercise at least two times a week in the previous 6 mo. This level of aerobic training corresponds to the performance level 2 in the classification of subject groups in sport science research (17). None of the subjects had any known mental or somatic disorder. Each subject gave written informed consent before the study. Experimental protocol and procedures were approved by the local Ethics Committee of the School of Sport and Exercise Sciences, University of Kent. The study conformed to the standards set by the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (2008). All subjects were given written instructions describing all procedures related to the study but were naive of its aims and hypotheses. At the end of the last session, subjects were debriefed and asked not to discuss the aims of the study with other participants.

Experimental Protocol

Each of the two studies described below included two experimental sessions (one with testing shortly after exhaustion and one with testing 3 min after exhaustion) to avoid the confounding effects of testing shortly after exhaustion on subsequent recovery of neuromuscular parameters (study 1) and markers of feedback from group III-IV muscle afferents (study 2). Furthermore, since MAP and leg muscle pain can be considered as markers of feedback from group III-IV muscle afferents only in the absence of central motor command (40, 50), neuromuscular testing (study 1) and muscle occlusion (study 2) were performed in two separate studies.

Study 1. The main aim of this study was to assess central fatigue and changes in corticospinal parameters shortly after exhaustion (OLDE_exh) and after 3 min of recovery (OLDE_rec) following exhaustive high-intensity OLDE [intensity fixed at 85% peak power output and average rating of perceived exhaustion (RPE) >14; see Ref. 20]. Subjects visited the laboratory on four different occasions. During the first visit, subjects were familiarized with all experimental procedures, including OLDE (see One-Leg Dynamic Exercise for more details) and neuromuscular testing (see Neuro-

muscular Tests for more details). As suggested by Andersen et al. (8), torque and electromyogram (EMG) feedback were used during the first visit to ensure a quick and reliable familiarization to the OLDE model used in the present investigation. During the second visit, a preliminary OLDE incremental test was performed to determine peak power output (see One-Leg Dynamic Exercise for more details). After 30 min of recovery, subjects were familiarized with neuromuscular testing and performed a time-to-exhaustion test at 85% of peak power output. During the third and fourth visits, subjects performed a time-to-exhaustion test at 85% of peak power output, with neuromuscular testing being performed either shortly after exhaustion or after 3 min of passive recovery (no leg movement with knee angle fixed at 90°) in a randomized and counterbalanced order.

Study 2. The main aim of study 2 was to indirectly assess feedback from group III-IV muscle afferents via measurement of MAP and leg muscle pain during muscle occlusion shortly after exhaustion and after 3 min of recovery following exhaustive high-intensity OLDE. Muscle oxygenation was also recorded via near-infrared spectroscopy during exercise and subsequent recovery. Experimental procedures are similar to those in study 1 with muscle occlusion (see Markers of Feedback from Group III-IV Muscle Afferents for more details) performed instead of neuromuscular testing. An overview of visits 3 and 4 can be seen in Fig. 1.

Each visit was interspaced by a minimum of 48 h recovery. All participants were given instructions to sleep for at least 7 h, refrain from the consumption of alcohol, and not to undertake vigorous physical activity the day before each visit (compliance checked before each visit). Participants were also instructed not to consume caffeine and nicotine at least 3 h before testing and were asked to declare if they were ill and/or were taking any medication.

One-Leg Dynamic Exercise

Model development. The OLDE model we used for the present study was developed to reproduce the exercise model of Andersen et al. (8) on a dynamometer to remove the time delay involved in transferring the participant from the exercising ergometer to the dynamometer used to measure neuromuscular function. This new OLDE model allows isolating the knee extensor muscles during a dynamic exercise involving an active isometric knee extension and a passive knee flexion. We carefully controlled the power output produced by the subject according to the formula:

\[ P = T \times \omega \]

\( P \) corresponds to the power expressed in watts (W), \( T \) denotes the torque in newton meter (N-m), and \( \omega \) denotes the angular speed in radians per second.

OLDE was performed on a Cybex NORM dynamometer (CMSi; Computer Sports Medicine, Stoughton, MA) with customized software specially designed by the company for our experiment. The axis of the dynamometer was aligned with the knee axis, and the lever arm was attached to the shank with a strap. Two-shoulder harnesses and a belt across the abdomen limited extraneous movement of the upper body. As used in previous studies using the original exercise model of Andersen et al. (8), a range of motion from 10° to 90° (0° = kneel fully extended) was chosen (7, 56). The software was configured for a passive flexion (CPM mode) speed of 300°/s automatically cushioned by the dynamometer for safety purposes (speed of the arm movement decreasing when close to the range of motion to protect the subject). Because of this cushion, the passive knee flexion speed was \( \approx 180°/s \). After pilot testing in our laboratory, a cadence of 50 contractions per minute (cpm) was chosen, thus allowing an active knee extension of \( \approx 106°/s \). Therefore, during the incremental test performed on the dynamometer, each isometric increment of 1 N-m corresponded to an increment of \( \approx 1.85 \) W. Subjects maintained a cadence of 50 cpm at all visits via the use of a metronome.

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During the second visit, a preliminary OLDE incremental test was performed to measure peak power output (study 1: 72.6 ± 37.4 W, study 2: 65.3 ± 28.1 W). For males, the incremental test started with the isotonic resistance set at 4 N·m (7.4 W) for 1 min and increased each minute by 3 N·m (4.5 W) until exhaustion. For females, the isotonic resistance was set up at 4 N·m (7.4 W) for 1 min and increased each minute by 2 N·m (3.7 W) until exhaustion. Exhaustion was defined as a decrease in cadence below 40 cpm for a duration ≥10 s despite strong verbal encouragement.

Time-to-exhaustion test. After 3 min warm-up at 20% of peak power output, subjects performed a time-to-exhaustion test at 85% of peak power output (study 1: 61.7 ± 31.6 W, study 2: 55.5 ± 23.9 W). Exhaustion was defined as a decrease in cadence below 40 cpm for a duration ≥10 s. RPE referred to the exercising leg (leg RPE) and leg muscle pain were recorded during the last 15 s of the warm-up (baseline) and at exhaustion using the 6–20 Borg scale (10) and Cook scale (49), respectively.

Neuromuscular Tests

In study 1, each session began with a warm-up of 10 brief (4-s) submaximal voluntary isometric contractions at 50% of the estimated MVC torque, followed by a 1-min rest before neuromuscular testing. A 4-s MVC with superimposed doublet was performed followed by a resting potentiated doublet (4 s post-MVC). After the MVC, subjects performed four brief (3-s) submaximal contractions at 50% MVC with superimposed transcranial magnetic stimulation and one submaximal contraction at 50% MVC with superimposed femoral nerve stimulation. Six subjects tolerated electrical cervicomedullary stimulation, and so also performed four brief (3-s) submaximal contractions at 50% MVC with superimposed cervicomedullary stimulation, interspaced between the transcranial magnetic stimulations and femoral nerve stimulation. The target contraction of 50% MVC corresponds to the MVC previously performed (i.e., MVC preexercise and MVC postexercise). Each contraction was interspaced by 3 s. Once transcranial magnetic stimulation and cervicomedullary stimulation were performed, three single resting femoral nerve stimulations (interspaced by 3 s) were performed. An overview of stimulation timing can be found in Fig. 1. Visual force feedback and strong verbal encouragement were provided during MVCs.

Femoral nerve stimulation. A high-voltage constant-current stimulator (maximal voltage 400 V, model DS7 modified; Digitimer, Hertfordshire, UK) was used to perform transcutaneous electrically evoked contractions of the knee extensor muscles. The femoral nerve was stimulated using a surface electrode (Swaromed, Ref. no. 1066; Nessler Medizintechnik, Innsbruck, Austria) positioned over the nerve, high in the femoral triangle. The anode was a rectangular electrode (10 × 5 cm; Phoenix Healthcare Products, Nottingham, UK) located in the gluteal fold opposite the cathode. The optimal intensity of stimulation required to evoke a maximal compound muscle action potential (Mmax) was determined at rest and during brief (3-s) submaximal isometric contractions of the knee extensor muscles (~50% MVC). The optimal intensity of stimulation was set to 130% of that required to elicit Mmax during the submaximal isometric contraction (current higher during submaximal contractions compared with rest). Stimulation intensity was determined before each session and kept constant throughout the protocol (mean current, 364 ± 57 mA). The stimulus duration was 200 μs, and the interval of the stimuli in the doublet was 10 ms (100 Hz frequency).

Transcranial magnetic stimulation. A magnetic stimulator (Magstim 200; Magstim, Whittance, UK) was used to deliver transcranial magnetic stimulation. A concave double-cone coil (110 mm diameter) was held over the vertex (postero-anterior intracranial current
flow) to elicit motor evoked potentials (MEP) in the right knee extensor muscles. The optimal coil position (marked on the scalp with permanent marker) was determined to elicit a large MEP in the exercising vastus lateralis and a small MEP in the biceps femoris (<10% of the raw quadriceps MEP amplitude). The stimulator output intensity (mean: 56 ± 9% of maximum stimulator output) was set to produce the largest possible MEP in the vastus lateralis while causing a small MEP in the biceps femoris during brief (3-s) submaximal isometric contractions of the knee extensor muscles at 50% MVC (61). MEP were elicited at 50% MVC, since this intensity of submaximal isometric contraction is known to provide the most stable and informative cortical silent period (CSP; see Ref. 59). Because CSP is known to be influenced by instructions provided to the subjects, subjects were instructed “to contract as fast as possible after the stimulation” (25, 43). This instruction is known to provide the most reliable CSP (43). The stimulator output was determined before the experiment on each day and was kept constant throughout the protocol. All MEP parameters at exhaustion were obtained within ~50 s.

Corticospinal stimulation. The corticospinal tract was stimulated via a high-voltage constant-voltage stimulator (maximal voltage 1,000 V, model D185; Digitimer). Surface EMG electrodes (Ambu Neuroline 720; Ambu, Ballerup, Denmark) were positioned 1–2 cm posterior and superior to the tip of the mastoid process (cathode on the left side). The stimulus intensity required to evoke a maximal cervicomedullary motor evoked potential (CMEP) was determined during brief (3-s) submaximal isometric contractions at 50% MVC before the experiment on each day; 50% MVC was chosen to elicit CMEP at the same submaximal isometric contraction intensity used to elicit MEP. All CMEP parameters at exhaustion were obtained within ~81 s. The stimulator output (mean current: 375 ± 54 V) was determined before the experiment on each day and was kept constant throughout the protocol.

Mechanical recordings. Mechanical parameters were recorded using the same dynamometer used to perform the time-to-exhaustion tests. Neuromuscular tests were performed with the right leg at a knee joint angle of 90° of flexion (0° = knee fully extended) and a hip angle of 90°. The following parameters were analyzed from the twitch response (average of 3 single stimulations interspaced by 3 s): peak twitch (Tw), time to peak twitch (contraction time, C), and average rate of force development (RFD = Tw/C). The peak torque of the doublet (potentiated doublet, 4 s after the MVC) was also analyzed. MVC torque was considered as the peak torque attained during the MVC. Voluntary activation level (VAL) during the MVC was estimated according to the following formula:

\[
\text{VAL} = 100 \times \left(1 - \frac{\text{superimposed doublet amplitude}}{\text{potentiated doublet amplitude}}\right)
\]

All voluntary activation level measures at exhaustion were obtained within ~15 s. Mechanical signals were digitized online at a sampling frequency of 1 kHz using a computer and stored for analysis with commercially available software (AcqKnowledge 4.2 for MP Systems; Biopac Systems).

Electromyographic recordings. EMG of the vastus lateralis and biceps femoris was recorded with pairs of silver chloride circular electrodes (recording diameter of 10 mm) surface electrodes (Swaromed, Ref. 1066; Nessler Medizintechnik) with an interelectrode (center-to-center) distance of 20 mm. Recording sites (belly of the vastus lateralis muscle proximal to the knee axis and belly of the biceps femoris) were then carefully adjusted by eliciting the greatest M-wave amplitude for each muscle at a given intensity via femoral nerve stimulation at the beginning of each testing session. Low resistance between the two electrodes (≤5 kΩ) was obtained by shaving the skin, and dirt was removed from the skin using alcohol swabs. The reference electrode was attached to the patella of the right knee. Myoelectrical signals were amplified with a bandwidth frequency ranging from 10 to 500 Hz (gain = 500), digitized online at a sampling frequency of 2 kHz using a computer, and stored for analysis with commercially available software (AcqKnowledge 4.2 for MP Systems; Biopac Systems). The root mean square (RMS), a measure of EMG amplitude, was automatically calculated with the software.

Peak-to-peak amplitude and EMG RMS (including positive and negative phase of the EMG signal) of the resting M-waves were calculated and averaged for the three stimulations. For MEP, CMEP, and M-waves obtained during brief submaximal contractions at 50% MVC, the area (including positive and negative phase of the EMG signal) was calculated and averaged for the four stimulations (MEP and CMEP). CSP duration of the MEP was determined by the same experimenter from the point of stimulation to the return of continuous EMG signal (29). EMG amplitude during MVC of the knee extensor muscles was quantified as the RMS for a 0.5-s interval at peak torque (250-ms interval either side of the peak torque). Maximal RMS EMG values were then normalized by the resting M-wave RMS EMG to obtain the RMS&MVC-to-RMS%M ratio. RMS EMG during OLDE was calculated for the last 30 s of the 1st min (baseline) and the last 30 s before exhaustion.

Physiological Measurements

Cardiovascular parameters. In study 2, heart rate and arterial blood pressure were recorded via an automatic blood pressure device (Tango+, SunTech Medical, Morrisville, NC). Cardiovascular parameters were recorded during the 3-min rest (baseline), preexercise muscle occlusion, and postexercise muscle occlusion (see Markers of Feedback from Group III-IV Muscle Afferents for more details). Cardiovascular parameters were averaged from the values recorded at the end of each minute (last 15 s) of the 3-min rest, preexercise muscle occlusion, and postexercise muscle occlusion. Cardiovascular parameters were also recorded at exhaustion. MAP was calculated as:

\[
\text{MAP} = \frac{\text{diastolic pressure} + 1 / 3 \times (\text{systolic pressure} - \text{diastolic pressure})}{2}
\]

Muscle oxygenation. In study 2, muscle oxygenation was assessed via near-infrared spectroscopy using an OxyMon Mk III device (Artinis, Zetten, The Netherlands) emitting continuous wavelengths of 780- and 850-nm light on the exercising vastus lateralis (~15 cm proximal and 5 cm lateral to the midline of the superior border of the patella) with transmitters-receptor probes interspaced by 4.0 cm. Probe position was marked on the skin with indelible ink to ensure reliability of repositioning between sessions. Muscle near-infrared spectroscopy data were collected with a sampling frequency of 10 Hz. Data were averaged for the 5 s before each time point measurement (preexercise, at exhaustion, after 3 min of passive recovery, and each 10% of the exercise). Relative concentration changes (Δμmol) were measured from resting baseline (see Fig. 1) for oxyhemoglobin (ΔO2Hb), deoxyhemoglobin (ΔHHb), total hemoglobin (ΔHb = O2Hb + HHb), and hemoglobin difference (ΔHb diff = O2Hb - HHb). ΔHb was calculated to give an index of change in regional blood volume (64).

Blood lactate concentration. In study 2, blood lactate concentration was measured at rest before preexercise muscle occlusion, at exhaustion, and after 2 min of recovery. We did not collect blood samples after 3 min of recovery so as to not influence the measurement of MAP and leg muscle pain during muscle occlusion; 10-μl samples of capillary blood were taken from the thumb of the right hand of the subjects and immediately analyzed for lactate concentration (Biosen; EFK Diagnostics, London, UK).

Markers of Feedback from Group III-IV Muscle Afferents

In study 2, muscle occlusion was used at exhaustion or after 3 min of recovery to trap in the knee extensor muscles the metabolites known to stimulate group III-IV muscle afferents. At present, there is no noninvasive method allowing direct assessment of feedback from
group III-IV muscle afferents in humans. However, in the absence of central motor command, feedback from these muscle afferents is known to induce an increase in MAP during muscle occlusion (38) and also to be the sensory signal processed by the brain to generate muscle pain (50). Therefore, when measured during muscle occlusion at rest (in the absence of central motor command), MAP and leg muscle pain can be used as indirect markers of feedback from group III-IV muscle afferents in humans. Usually, cardiovascular responses to postexercise muscle occlusion are compared with resting values with no muscle occlusion. However, because muscle occlusion per se is known to induce degradation of adenosine triphosphate, increase in bradykinin and reactive oxygen species in the muscle milieu, and consequently activate group III-IV muscle afferents (14, 16), we compared MAP and leg muscle pain values recorded during postexercise muscle occlusion with values recorded during preexercise muscle occlusion.

Mean arterial pressure. Subjects sat on the same ergometer where the time-to-exhaustion test was performed. After 3 min at rest, a pneumatic cuff previously placed as high as possible on the exercising thigh was rapidly inflated (<2 s) to 300 mmHg by an automatic inflator device (Hokanson E20 Rapid Cuff Inflator and AG101 Air Source, Bellevue, WA). The preexercise occlusion was maintained for 3 min to identify whether the muscle occlusion (in the absence of exercise-induced metabolites) could elicit an increase in arterial blood pressure. Subjects then performed the OLDE warm-up and the time-to-exhaustion test. Immediately at exhaustion, or after 3 min of passive recovery, the pneumatic cuff was then inflated to 300 mmHg for 3 min.

Leg muscle pain. Leg muscle pain was recorded during preexercise and postexercise muscle occlusions using the Cook scale (49). Values were collected at the end of each minute of the occlusion and then averaged. Subjects were also asked to report any muscle pain before starting each session.

Statistical Analysis

All data are presented as means ± SD unless stated. Assumptions of statistical tests such as normal distribution and sphericity of data were checked as appropriate. Greenhouse-Geisser correction to the degrees of freedom was applied when violations to sphericity were present. Paired t-tests were used to compare time to exhaustion between sessions in each study, and MAP at rest and during preexercise muscle occlusion. Fully repeated-measures $2 \times 2$ ANOVAS were used to test the effects of session (OLDEexh vs. OLDE3min) and time (baseline and exhaustion) on leg RPE, leg muscle pain, cardiovascular parameters, and EMG RMS. Fully repeated-measures $2 \times 11$ ANOVAS were used to test the effects of session (OLDEexh vs. OLDE3min) and time on muscle oxygenation during exhaustive OLDE. One-way repeated-measures ANOVAs were used to test the effects of time (pre, exhaustion, and 3 min recovery) on muscle oxygenation, blood lactate concentration, cardiovascular parameters during muscle occlusion, and neuromuscular function parameters. Significant effects of time were followed up with Holm-Bonferroni tests as appropriate. Because no cardiovascular and neuromuscular function parameter differed between sessions at preexercise, preexercise values of each session were averaged. Assumption of normality for leg muscle pain during muscle occlusion after 3 min recovery was violated. Therefore, a Friedman ANOVA was performed. A significant effect of time was followed up by Wilcoxon signed-rank tests with Holm-Bonferroni correction. When interactions are not significant, only main effects are reported. When interactions are significant, relevant simple main effects are reported. Significance was set at 0.05 (2-tailed) for all analyses, which were conducted using the Statistical Package for the Social Sciences, version 20 for Mac OS X (SPSS, Chicago, IL). Cohen’s effects sizes ($d$) were calculated with G*Power software (version 3.1.6; Universität, Düsseldorf, Germany) and reported for follow-up tests on cardiovascular parameters and leg muscle pain during muscle occlusion and neuromuscular function parameters.

RESULTS

OLDEexh and OLDE3min refer to the session with either muscle occlusion or neuromuscular tests performed, respectively, shortly after exhaustion and after 3 min of recovery. Time to exhaustion was similar between sessions in study 1 (OLDEexh: 9.0 ± 2.9 min, OLDE3min: 10.3 ± 4.3 min, $P = 0.164$) and study 2 (OLDEexh: 10.7 ± 5.4 min, OLDE3min: 11.1 ± 5.4 min, $P = 0.555$).

Physiological and Perceptual Responses to Exhaustive High-Intensity OLDE

Cardiovascular and perceptual responses. Main effects of time for cardiovascular and perceptual responses to exhaustive OLDE are presented Table 1. Except systolic arterial pressure, which presented a significant interaction effect ($P = 0.002$), all parameters did not present any main effect of session (all $P > 0.05$) or interaction (all $P > 0.05$) and significantly increased at exhaustion compared with baseline (all $P < 0.01$). Follow-up tests on the interaction effect ($P = 0.007$) for the systolic arterial pressure revealed that exhaustion values were significantly higher than baseline in both sessions ($P < 0.001$). However, baseline values ($P = 0.817$) and exhaustion values ($P = 0.066$) did not significantly differ between sessions. Blood lactate concentration did not recover after 2 min ($P = 0.174$).

Muscle oxygenation. Main effects of time for muscle oxygenation during exhaustive high-intensity OLDE are presented in Fig. 2. All parameters did not present any main effect of session (all $P > 0.05$) or interaction (all $P > 0.05$). $\Delta O_2Hb$ (Fig. 2A) was lower than baseline ($P < 0.001$) only from 10 to 50% of the time to exhaustion. $\Delta HHb$ (Fig. 2B) progressively increased until 20% of the time to exhaustion had been completed, and then plateaued ($P < 0.001$). $\Delta Hb$ diff (Fig. 2C) decreased and then plateaued after 10% of the time to exhaustion ($P < 0.001$). Despite that $\Delta Hb$ (Fig. 2D) increased over time ($P = 0.001$), follow-up tests failed to reveal any significant difference between different times compared with baseline and exhaustion values.

Muscle oxygenation parameters at baseline, exhaustion, and after 3 min recovery are presented in Fig. 3. At exhaustion, $\Delta O_2Hb$ (Fig. 3A) was lower than baseline ($P = 0.013$). After 3 min recovery, $\Delta O_2Hb$ diff (Fig. 3B) was lower than baseline ($P < 0.001$).

Table 1. Cardiovascular and perceptual responses to exhaustive high-intensity one-leg dynamic exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Exhaustion</th>
</tr>
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<tbody>
<tr>
<td>Leg RPE</td>
<td>7.6 ± 0.9</td>
<td>19.7 ± 0.4***</td>
</tr>
<tr>
<td>Leg muscle pain</td>
<td>0.3 ± 0.5</td>
<td>6.8 ± 2.8***</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>1.13 ± 0.27</td>
<td>5.27 ± 1.69***</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>64.3 ± 10.9</td>
<td>129 ± 10.8***</td>
</tr>
<tr>
<td>Systolic arterial pressure, mmHg</td>
<td>113.7 ± 8.6</td>
<td>185.5 ± 26.8***</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mmHg</td>
<td>71.9 ± 7.5</td>
<td>94.9 ± 17.0**</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>85.8 ± 6.5</td>
<td>125.1 ± 17.4***</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD for the main effect of time. Baseline values were measured at rest before preexercise muscle occlusion. Leg rating of perceived exertion (RPE) and leg muscle pain baseline values were measured during the last 15 s of the warm-up. ***$P < 0.001$ and **$P < 0.01$, significant difference from baseline.
3 min of recovery, ΔO₂Hb was higher than baseline (P = 0.006) and differed from exhaustion (P = 0.002). At exhaustion, ΔHHb (Fig. 3B) was higher than baseline (P = 0.014). After 3 min of recovery, ΔHHb was lower than exhaustion (P = 0.006) but did not differ from baseline (P = 0.101). At exhaustion, ΔHb (Fig. 3C) did not differ from baseline (P = 0.208) but was higher after 3 min of recovery compared with baseline (P = 0.036). At exhaustion, muscle ΔHb diff (Fig. 3D) was lower than baseline (P = 0.006), but after 3 min recovery muscle ΔHb diff was higher than baseline (P = 0.006) and higher than exhaustion (P = 0.002).

Changes in Neuromuscular Function Following Exhaustive High-Intensity OLDE

There were no significant differences in preexercise neuromuscular function parameters between sessions (all P > 0.090). Therefore, preexercise values of each session were averaged. Changes in neuromuscular parameters induced by exhaustive OLDE are presented in Table 2. MVC torque decreased significantly at exhaustion (−41 ± 17%, P < 0.001, dₛ = 2.897). MVC torque partially recovered after 3 min of recovery (P = 0.005, dₛ = 1.401), but it was still significantly lower than preexercise values (−25 ± 15%, P = 0.002, dₛ = 2.073).

Peripheral fatigue. Doublet amplitude decreased significantly at exhaustion (−40 ± 15%, P < 0.001, dₛ = 2.735) and remained lower than preexercise values after 3 min of recovery (−28 ± 9%, P < 0.001, dₛ = 5.128). However, doublet amplitude partially recovered after 3 min (P = 0.023, dₛ = 0.722). Tw and TWRFD decreased at exhaustion and remained lower than preexercise values after 3 min recovery (all P < 0.001). Tw and TWRFD did not recover after 3 min (P = 0.740, dₛ = 0.122 and P = 0.814, dₛ = 0.086). Mamplitude at rest did not change over time (P = 0.373). Mamplitude at 50% MVC was significantly higher than preexercise only at exhaustion (+7 ± 6%, P = 0.036, dₛ = 1.198). Marea at 50% MVC was significantly higher than preexercise at exhaustion (+20 ± 12%, P = 0.006, dₛ = 1.727) and tended to be higher than preexercise after 3 min recovery (+12 ± 12%, P = 0.060, dₛ = 0.958).

Central fatigue. Voluntary activation level (Fig. 4A) decreased significantly at exhaustion (−13 ± 13%, P = 0.039, dₛ = 1.160) and remained lower than preexercise values after 3 min of recovery (−6 ± 6%, P = 0.036, dₛ = 1.087). However, voluntary activation level partially recovered after 3 min (P = 0.050, dₛ = 0.835). RMS<sub>MVC</sub>/RMS<sub>M</sub> of the vastus lateralis did not change over time (P = 0.272).

Cortical and spinal excitability. MEP<sub>area</sub>/M<sub>area</sub> ratio (Fig. 4B) increased at exhaustion (+25 ± 27%, P < 0.001, dₛ = 1.005) and remained higher than preexercise values after 3 min of recovery (+17 ± 20%, P < 0.001, dₛ = 0.902). However, MEP<sub>area</sub>/M<sub>area</sub> ratio partially recovered after 3 min (P = 0.003, dₛ = 0.249). CMEP<sub>area</sub>/M<sub>area</sub> ratio (Fig. 4C) was significantly lower than preexercise only at exhaustion (−38 ± 13%, P < 0.001, dₛ = 4.245). CMEP<sub>area</sub>/M<sub>area</sub> ratio fully recovered after 3 min (P = 0.032, dₛ = 1.450). CMEP<sub>area</sub>/MEP<sub>area</sub> (Fig. 4D) decreased at exhaustion (−48 ± 17%, P = 0.003, dₛ = 2.891) and remained lower than preexercise values after 3 min of recovery (−17 ± 14%, P = 0.033, dₛ = 1.192). CMEP<sub>area</sub>/MEP<sub>area</sub> ratio partially recovered after 3 min (P = 0.010, dₛ = 0.249).
Changes in Markers of Feedback from Group III-IV Muscle Afferents Following Exhaustive High-Intensity OLDE

Cardiovascular parameters. MAP during muscle occlusion preexercise was significantly higher compared with preexercise MAP with no muscle occlusion (90.0 ± 7.9 vs. 85.9 ± 5.9)

1.975). Finally, CSP (Fig. 4E) was significantly higher than preexercise only at exhaustion (+19 ± 9%, P = 0.003, d = 1.946) and not after 3 min of recovery (+5 ± 13%, P = 0.345, d = 0.358). A typical recording of MEP and CMEP for one subject is shown in Fig. 5. This figure illustrates the alterations in corticospinal parameters previously described.

| Table 2. Changes in neuromuscular function following exhaustive high-intensity one-leg dynamic exercise |
|-------------------------------------------------|-----------------|-----------------|
| | Pre | Exhaustion | +3 min |
| MVC, N-m | 236 ± 46 | 141 ± 50*** | 180 ± 62**xx |
| **Periphera fatigue** | | | |
| Doublet, N-m | 91 ± 14 | 55 ± 21*** | 66 ± 13***££ |
| TWREFD, N-m·ms⁻¹ | 41 ± 8 | 25 ± 12*** | 26 ± 10*** |
| Mamp (VL) at rest, mV | 0.50 ± 0.07 | 0.32 ± 0.12*** | 0.33 ± 0.09*** |
| Mamp (VL) at 50% MVC, mV | 15.0 ± 0.5 | 15.5 ± 1.1 | 15.2 ± 0.8 |
| Marea (VL) at 50% MVC, mV/s | 13.9 ± 0.8 | 14.8 ± 0.6* | 14.2 ± 1.2 |
| **Central fatigue** | | | |
| RMS_MVC/RMS_EMG (VL) EMG, % | 36.3 ± 11.4 | 43.0 ± 19.7 | 40.9 ± 19.2 |
| VAL, % | 93.2 ± 6.7 | 81.4 ± 15.2* | 88.2 ± 9.7**££ |
| **Cortical and spinal excitability** | | | |
| MPEmax, mV/s | 0.058 ± 0.010 | 0.085 ± 0.015*** | 0.074 ± 0.013***££ |
| MEPmax/Marea, % | 63.3 ± 13.9 | 76.7 ± 11.8*** | 72.8 ± 16.6***££ |
| CSP, ms | 105.6 ± 13.2 | 126.3 ± 20.0** | 110.5 ± 19.7 |
| CMEPmax, mV/s | 0.033 ± 0.011 | 0.026 ± 0.015 | 0.034 ± 0.010 |
| CMEPmax/Marea, % | 35.9 ± 13.7 | 23.2 ± 12.7*** | 32.4 ± 10.9£ |
| CMEPmax/MPEmax, % | 57.3 ± 16.1 | 31.4 ± 16.3** | 47.2 ± 11.8**££ |

Values are presented as means ± SD; n = 8 subjects for motor evoked potential (MEP) parameters, n = 6 for CMEPmax/MEPmax. Neuromuscular tests were performed pre- and postexercise, either shortly after exhaustion or after 3 min of recovery (+3 min). CSP, cortical silent period; M, maximal M-wave; MVC, maximal voluntary contraction; RMS, root mean square; VAL, voluntary activation level; VL, vastus lateralis; RFD, rate of force development; Tw, peak twitch; EMG, electromyogram. *P < 0.05, **P < 0.01, and ***P < 0.001, significant difference from pre. £P < 0.05 and ££P < 0.01, significant difference from exhaustion.
confirming that muscle occlusion per se can stimulate group III and IV muscle afferents. Therefore, to assess changes in afferent feedback induced by exhaustive high-intensity OLDE exercise and recovery, cardiovascular parameters during postexercise muscle occlusion were compared with cardiovascular parameters during preexercise muscle occlusion. There were no significant differences between sessions in cardiovascular parameters during the preexercise muscle occlusion. Therefore, preexercise values of each session were averaged. Cardiovascular parameters during muscle occlusion preexercise and postexercise are presented in Fig. 6. Heart rate (Fig. 6A) was higher during muscle occlusion at exhaustion \((P = 0.009, d_z = 1.294)\) and remained higher than preexercise values after 3 min of recovery \((P = 0.006, d_z = 1.264)\). Systolic arterial pressure (Fig. 6B) was higher during muscle occlusion at exhaustion \((P = 0.006, d_z = 1.388)\) and remained higher than preexercise values after 3 min of recovery \((P = 0.014, d_z = 0.940)\). After 3 min of recovery, systolic arterial pressure during muscle occlusion was lower compared with values at exhaustion \((P = 0.026, d_z = 1.439)\).

Diastolic arterial pressure (Fig. 6C) during muscle occlusion was higher than preexercise values only at exhaustion \((P = 0.006, d_z = 0.971)\). MAP (Fig. 6D) was higher during muscle occlusion at exhaustion \((P = 0.006, d_z = 1.339)\) compared with preexercise values but recovered after 3 min \((P = 0.172, d_z = 0.470)\). MAP during muscle occlusion after 3 min of recovery was lower than MAP at exhaustion \((P = 0.006, d_z = 1.241)\).
occlusion at exhaustion during the OLDEexh session (6.24 ± 2.83 vs. 2.93 ± 2.11, P = 0.036, d = 1.189).

DISCUSSION

The aim of study 1 was to describe central fatigue and other central alterations of neuromuscular function following exhaustive high-intensity OLDE. This is the first study reporting an increase in cortical excitability and CSP, and a decrease in spinal excitability at exhaustion following exhaustive high-intensity OLDE. As expected, central fatigue and changes in corticospinal parameters induced by exhaustive high-intensity OLDE were greater shortly after exhaustion than after 3 min of recovery. The aim of study 2 was to use MAP and leg muscle pain during muscle occlusion as markers of feedback from group III-IV muscle afferents. As expected, these markers demonstrate that exhaustive high-intensity OLDE significantly increases feedback from group III-IV muscle afferents. Furthermore, our results suggest that, after 3 min of recovery, this afferent feedback is no longer significant. When integrating the results of both studies, the present investigation suggests that the observed increase in CSP and decrease in spinal excitability are strongly associated with feedback from group III-IV muscle afferents. However, central fatigue (i.e., an exercise-induced decrease in voluntary activation level) was only weakly associated with feedback from group III-IV muscle afferents as demonstrated by the persistence of central fatigue despite no significantly higher leg muscle pain and MAP during muscle occlusion after 3 min of recovery. This finding suggests that additional mechanisms must play a significant role in the central fatigue induced by exhaustive high-intensity OLDE.

Physiological and Perceptual Responses to Exhaustive High-Intensity OLDE

As observed in previous studies, high-intensity OLDE performed to exhaustion induced significant increases in blood lactate, perception of effort and leg muscle pain, and EMG activity of the vastus lateralis muscle (7, 56). Additionally, MAP and heart rate also increased during exhaustive high-intensity OLDE.

We monitored changes in oxygenation of the vastus lateralis muscle via near-infrared spectroscopy. Vastus lateralis muscle deoxyhemoglobin signal continued to increase until 20% of the time-to-exhaustion test, and then plateaued, with no change in total hemoglobin. This early increase and plateau suggest an increase in oxygen extraction that is then held constant until exhaustion. This early alteration in vastus lateralis muscle oxygenation may be associated with the development of peripheral fatigue that occurs within the first 40% of high-intensity self-paced isokinetic exercise (23).

Muscle Fatigue and Peripheral Fatigue Following Exhaustive High-Intensity OLDE

Exhaustive high-intensity OLDE induced significant muscle fatigue, as demonstrated by the decrease in MVC torque shortly after exhaustion and after 3 min of recovery. The decrease in MVC torque measured shortly after exhaustion in the present study (~40%) is greater than that demonstrated by Cheng and Rice (~25%; see Ref. 13) following OLDE performed at maximal contraction velocity. The difference between both studies is likely due to the fact that their subjects did not reach volitional exhaustion but were stopped once the contraction velocity was reduced by 35%. Contrary to Cheng and Rice (13), the isometric MVC torque in our study partially recovered after 3 min. This recovery was associated with a recovery in peripheral fatigue (e.g., doublet amplitude evoked at rest), confirming some recovery in skeletal muscle function (23). Our findings also support the existence of low-frequency fatigue following exhaustive dynamic exercise (18, 23). Indeed, only torque amplitude evoked by high-frequency stimulation (doublet at 100 Hz), and not by single stimulation, recovered after 3 min.

Central Fatigue Following Exhaustive High-Intensity OLDE

To the best of our knowledge, only one study (54) demonstrated a significant decrease in voluntary activation level measured within 2.5 min after cessation of exhaustive high-intensity OLDE. Our finding that voluntary activation level partially recovers 3 min after exhaustion suggests that this typical time delay between cessation of dynamic exercise and the start of neuromuscular testing may lead to an underestimation of the extent of central fatigue induced by dynamic exercise such as OLDE (7, 56) and cycling exercise (e.g., see Ref. 4). Nevertheless, contrary to these previous studies, we found a significant decrease in voluntary activation level after 3 min of recovery. Our ability to detect persistent central fatigue 3 min after exhaustive high-inten-
sity OLDE may be explained by 1) the use of high-frequency paired stimulation (100 Hz) to overcome the negative effect of low-frequency fatigue on force production and 2) the fact that we used electrical stimulation and not magnetic stimulation to induce the superimposed and potentiated doublet. Despite that both magnetic and electrical stimulation are known to be valid for neuromuscular testing (65), some studies assessing neuromuscular function following exhaustive dynamic exercise with magnetic stimulation were unable to stimulate at supramaximal intensity (stimulation performed at a near plateau of resting twitch and M-wave; e.g., see Refs. 4 and 5). Therefore, because the excitation threshold of nerve fibers increases with fatigue (11), these studies may have underestimated the magnitude of knee extensor muscle fatigue.

Several studies used the RMS_{MVC}/RMS_{M} EMG ratio to quantify the amount of central fatigue following prolonged dynamic exercise (for review, see Ref. 48) or isometric muscle contractions (e.g., Ref. 51). In contrast to previous studies showing similar changes in voluntary activation level and RMS_{MVC}/RMS_{M} EMG ratio following isometric contraction of the knee extensor muscles (e.g., Ref. 51), we did not find a decrease in the RMS_{MVC}/RMS_{M} EMG ratio either shortly after exhaustive high-intensity OLDE or after 3 min of recovery. This result confirms that EMG signal is not a reliable index of central motor drive (21). Therefore, as recently reminded, assessment of central fatigue should be performed via the twitch interpolation technique (26).

Cortical and Spinal Excitability Following Exhaustive High-Intensity OLDE

Our findings provide the first evidence that high-intensity OLDE performed to exhaustion significantly decreases spinal excitability while increasing supraspinal excitability. Shortly after exhaustion, MEP_{area}/M_{area} ratio presented an increase of ~30%, whereas the CMEP_{area}/M_{area} ratio decreased by ~40% compared with preexercise levels. Contrary to the MEP_{area}/M_{area} ratio, the CMEP_{area}/M_{area} ratio fully recovered after 3 min. The MEP results differ from those obtained following intermittent submaximal isometric contractions performed until exhaustion (30, 32) or task failure (defined as a decrease in MVC force of 35%; see Ref. 37). In the studies previously mentioned, the authors found both an unchanged MEP (30, 32) and a decrease in corticospinal excitability (37). Interestingly, Jubeau et al. (36) and Temesi et al. (63) found an increase in MEP following prolonged cycling and running exercise. Therefore, taking the findings of these studies together, it seems that changes in corticospinal excitability of the knee extensor muscles might be specific to the muscle contraction performed. Moreover, the 50% decrease in CMEP_{area}/MEP_{area} ratio shortly after exhaustion also suggests that increases in cortical excitability are likely to be underestimated. Indeed, MEP may be influenced by fatigue-related changes in responsiveness of the motoneuron pool, as is the case in the present study (i.e., decrease in CMEP). The relatively short time course of recovery in cortical and spinal excitability could be a factor in the previously reported lack of significant changes in corticospinal excitability following exhaustive cycling exercise (e.g., see Ref. 28).

An increase in CSP has been suggested to reflect an increase in excitability of inhibitory GABAergic interneurons (25). To the best of our knowledge, only one study (63) demonstrated an increase in CSP (at suboptimal transcranial magnetic stimulation intensity) following prolonged running exercise, and only one study following intermittent isometric exercise performed until exhaustion (32). Our findings present the first experimen-
tal evidence that exhaustive OLDE induces an increase in CSP. However, caution has to be taken in CSP interpretation, since CSP may reflect impaired motoneuron responsiveness rather than intracortical inhibition (46). Therefore, because the increase in CSP and its recovery were associated with impaired motoneuron responsiveness and its recovery, the present study limits the conclusions on whether the observed increase in CSP reflects an increase in cortical inhibition, a decrease in motoneuron responsiveness, or a combination of both phenomena.

Feedback from Group III-IV Muscle Afferents Following Exhaustive High-Intensity OLDE

As expected, muscle occlusion preexercise (in the absence of exercise-induced metabolites) induced an increase in MAP and leg muscle pain compared with resting values (with no muscle occlusion). This increase in MAP and leg muscle pain during preexercise muscle occlusion is likely to be caused by degradation of adenosine triphosphate and increase in bradykinin and reactive oxygen species in the muscle milieu during the muscle occlusion, inducing feedback from group III-IV muscle afferents (14, 16). Therefore, indirect assessment of exercise-induced changes in feedback from group III-IV muscle afferents must be compared between pre- and postexercise muscle occlusion and not between resting (no muscle occlusion) and postexercise muscle occlusion.

Both MAP and leg muscle pain during postexercise muscle occlusion increased shortly after exhaustion and returned to preexercise values after 3 min of recovery. Moreover, MAP and leg muscle pain significantly decreased during the 3-min recovery. Therefore, our results suggest a strong feedback from group III-IV muscle afferents only shortly after exhaustion and not after 3 min of recovery. The decrease in feedback from group III-IV muscle afferents is likely to be explained by a decrease in exercise-induced metabolites in the muscle milieu during the recovery period. This hypothesis is supported by our near-infrared spectroscopy data. Indeed, near-infrared spectroscopy can be used as an indirect index of oxidative metabolism (33). The higher O$_2$Hb and Hb diff after 3 min of recovery compared with exhaustion is suggestive of changes in exercise-induced metabolites in the muscle. Indeed, O$_2$Hb is known to be correlated with regulatory metabolites (ADP and PCr) of oxidative phosphorylation (33). However, interpretation of the O$_2$Hb signal is complicated by contaminant increases in tHb following the exhaustive exercise. Previous studies using microdialysis and biopsies demonstrated that metabolite concentration in the muscle milieu following dynamic exercise is known to quickly decrease (41, 58), providing further support to the decrease in feedback from group III-IV muscle afferents observed after 3 min of recovery in the present study.

Association Between Feedback from Group III-IV Muscle Afferents and Central Alterations of Neuromuscular Function

By integrating the results of studies 1 and 2, we also investigated qualitatively the association between central alterations of neuromuscular function and feedback from group III-IV muscle afferents. The concomitant increase in leg muscle pain and MAP during muscle occlusion and decrease in voluntary activation level shortly after exhaustion is consistent with the hypothesis that feedback from group III-IV muscle afferents might induce a reduction in the capacity of the central nervous system to fully recruit the active muscles during an MVC (for review, see Ref. 25). Our findings on the recovery time course of central fatigue are of particular importance in the interpretation of previous studies, which proposed feedback from group III-IV muscle afferents as an important contributor to the inhibition of central motor drive (e.g., Ref. 3). Indeed, the persistent decrease in voluntary activation level after 3 min recovery occurred despite no significantly higher leg muscle pain and MAP during muscle occlusion, two markers of feedback from III-IV muscle afferents (12, 15, 22). The persistence of central fatigue after 3 min of recovery confirms that mechanisms other than feedback from group III-IV muscle afferents significantly contribute to central fatigue (for review, see Ref. 25). For example, alterations in brain dopamine (47) or brain glycogen concentration (44) might be important contributors to the decrease in voluntary activation level observed following dynamic exercise.

Our results on central fatigue suggest that the cause and effect relationship between feedback from group III-IV muscle afferents and inhibition of the central motor drive needs to be established more firmly. Indeed, in one of the few experimental studies on the knee extensor muscles to date, Graven-Nielsen et al. (31) found a decrease of 20% in MVC torque of the knee extensor muscles following injection of hypertonic saline solution (known to induce afferent feedback from the injected muscles) in the rectus femoris muscle. This decrease in MVC torque occurred in the absence of peripheral alterations, suggesting a causal link between feedback from group III-IV muscle afferents and central fatigue. However, because the authors did not measure voluntary activation level, this causal link remains unclear. Furthermore, Hilty et al. (34) failed to demonstrate an effect of spinal blockade of afferent feedback on MVC of the knee extensor muscles after fatiguing isometric exercise. At first glance, the results of Hilty et al. (34) seem to argue against the causal association between feedback from group III-IV muscle afferents and neuromuscular fatigue (i.e., exercise-induced decline in MVC force/torque). However, the authors measured MVC force 7 min after cessation of exercise (34). Our results clearly suggest that, after such a long time delay, feedback from group III-IV muscle afferents is no longer significant. Therefore, further investigations are required to establish the cause and effect relationship between feedback from group III-IV muscle afferents and impairments in MVC force/torque and voluntary activation level.

The present study demonstrates complete recovery of the CMEP$_{area}$/M$_{area}$ ratio after 3 min, suggesting that feedback from group III-IV muscle afferents is likely to decrease the responsiveness of the motoneuron pool innervating the knee extensor muscles. Similar to MAP and leg muscle pain during muscle occlusion (i.e., both markers of feedback from group III-IV muscle afferents), the CSP increased only shortly after exhaustion and was fully recovered after 3 min. These parallel changes in metaboreflex, leg muscle pain, and CSP suggest that feedback from group III-IV muscle afferents might cause the lengthening of the CSP. This hypothesis has received experimental support from a spinal blockade study by Hilty et al. (34). These authors found no increase in CSP following isometric knee extension exercise when subjects received injection of intrathecal fentanyl, an anesthetic known to block.
feedback from group III-IV muscle afferents from the working muscles.

Limitations

The results of the first study describe the extent of central fatigue and changes in corticospinal excitability following exhaustive high-intensity OLDE. However, because CMEP in the lower limbs can be elicited only during submaximal contraction for most subjects (62), our data do not provide any information on the resting corticospinal excitability. Furthermore, because MEP/angle and CMEP/angle ratio was not matched and consequently activated a different proportion of the motoneuron pool, further studies matching MEP and CMEP amplitude are required. However, because MEP increased and CMEP decreased (antagonistic responses), we are confident that future studies matching MEP and CMEP amplitude will strengthen the results of the present study.

The second study demonstrated a recovery in MAP and leg muscle pain during muscle occlusion after 3 min of recovery. Because both MAP and leg muscle pain in the absence of central motor command are known to reflect central integration of feedback from group III-IV muscle afferents, our results suggest that muscle occlusion can be used to indirectly assess feedback from group III-IV muscle afferents in humans. However, further studies need to investigate the validity and reliability of this new methodology by comparing the recovery in MAP and leg muscle pain during muscle occlusion with the concentration of exercise-induced metabolites in the muscle milieu.

Perspectives and Significance

The findings of the present study suggest that the alterations in spinal excitability and CSP induced by high-intensity OLDE are associated with an increase in afferent feedback at exhaustion, whereas central fatigue does not fully recover even when significant afferent feedback is no longer present. Nevertheless, the cause and effect relationship between feedback from group III-IV muscle afferents and central fatigue still needs to be established. The exercise model and new integrative methodology used in the present investigation provide some tools to perform various experimental manipulations (e.g., spinal blockade of afferent feedback from the working muscles) to test whether a cause and effect relationship exists between feedback from group III-IV muscle afferents, central fatigue, and corticospinal excitability in humans.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES


