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Impact of Eccentric versus Concentric Cycling Exercise on Neuromuscular Fatigue and Muscle Damage in Breast Cancer Patients

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ABSTRACT

HUCTEAU, E., J. MALLARD, C. BARBI, M. VENTURELLI, R. SCHOTT, P. TRENSZ, C. PFLUMIO, M. KALISH-WEINDLING, X. PIVOT, F. FAVRET, G. P. DUCROCQ, S. P. DUFOUR, A. F. PAGANO, and T. J. HUREAU. Impact of Eccentric versus Concentric Cycling Exercise on Neuromuscular Fatigue and Muscle Damage in Breast Cancer Patients. *Med. Sci. Sports Exerc.*, Vol. 56, No. 11, pp. 2103–2116, 2024. **Introduction:** This study investigated the magnitude and etiology of neuromuscular fatigue and muscle damage induced by eccentric cycling compared with conventional concentric cycling in patients with breast cancer. **Methods:** After a gradual familiarization protocol for eccentric cycling, nine patients with early-stage breast cancer performed three cycling sessions in eccentric or concentric mode. The eccentric cycling session (ECC) was compared with concentric cycling sessions matched for power output (CON_{power}; 80% of concentric peak power output, 95 ± 23 W) or oxygen uptake ($CON_{\dot{V}O_2}$; 10 ± 2 mL·min·kg^{-1}). Preexercise to postexercise changes (30-s through 10-min recovery) in knee extensor maximal voluntary contraction force (MVC), voluntary activation, and quadriceps potentiated twitch force (Q_{tw}) were quantified to determine global, central, and peripheral fatigue, respectively. Creatine kinase and lactate dehydrogenase activities were measured in the plasma before and 24 h after exercise as markers of muscle damage. **Results:** Compared with CON_{power} (−11% ± 9%) and $CON_{\dot{V}O_2}$ (−5% ± 5%), the ECC session resulted in a greater decrease in MVC (−25% ± 12%) postexercise ($P < 0.001$). Voluntary activation decreased only in ECC (−9% ± 6% postexercise, $P < 0.001$). The decrease in Q_{tw} was similar postexercise between ECC and CON_{power} (−39% ± 21% and −40% ± 16%, $P > 0.99$) but lower in $CON_{\dot{V}O_2}$ ($P < 0.001$). The CON_{power} session resulted in twofold greater $\dot{V}O_2$ compared with the ECC and $CON_{\dot{V}O_2}$ sessions ($P < 0.001$). No change in creatine kinase or lactate dehydrogenase activity was reported from preexercise to 24 h postexercise. **Conclusions:** The ECC session induced greater neuromuscular fatigue compared with the concentric cycling sessions without generating severe muscle damage. ECC is a promising exercise modality for counteracting neuromuscular maladaptation in patients with breast cancer. **Key Words:** CENTRAL AND PERIPHERAL FATIGUE, CHEMOTHERAPY TREATMENT, ECCENTRIC CONTRACTION, EXERCISE INTOLERANCE, MUSCLE SORENESS

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In oncology, exercise is considered as medicine (1) for fighting treatment-related side effects, such as skeletal muscle deconditioning (2) and exacerbation of neuromuscular fatigue (3,4). However, contrasting results and moderate benefits of exercise interventions on physical condition have been reported in patients with breast cancer (5–7). These discrepancies are likely explained by the absence of specific exercise guidelines for each cancer type (8,9), leading to the large diversity of exercise modalities, intensities, durations, and frequencies utilized in clinical studies (10).

Given the need to counteract severe neuromuscular alterations in the face of documented exercise intolerance from breast cancer diagnosis to the end of chemotherapy treatment (11,12), eccentric cycling may be an exercise modality of particular interest in this population. Indeed, exercise in the eccentric mode (i.e., lengthening contractions) is characterized by greater force production per muscle fiber, resulting in lower

muscle activation and metabolic demand for a given power output than in the concentric mode (13). Therefore, eccentric cycling drastically reduces metabolic demand compared with conventional concentric cycling, which offers an opportunity to increase muscle mechanical stimuli (14–16), and *in fine*, the neuromuscular training stimuli.

To date, no study has investigated the effects of eccentric cycling in patients with breast cancer. Although the cardiorespiratory, circulatory, and neuromuscular responses to eccentric versus concentric cycling exercise have been previously described in healthy participants (14,16–18), the consequences of eccentric cycling on neuromuscular fatigue etiology are not documented in patients with breast cancer. Given the pivotal role of neuromuscular fatigue in subsequent training-induced neuromuscular adaptations (19–21), it is necessary to identify the magnitude and etiology of neuromuscular fatigue, which can occur from a central origin (i.e., a failure of the central nervous system to voluntarily activate the muscle) (22) and/or peripheral origin (i.e., structural and biochemical changes within the active muscle leading to an attenuated force response to neural output) (23). The consequences of eccentric cycling might differ in patients with breast cancer undergoing chemotherapy compared with their healthy counterparts because of their strong physical deconditioning (2) resulting from muscular (24,25) neural (3,4) and cardiorespiratory (11) limitations.

Although eccentric cycling offers unique and interesting characteristics, including by leading less pain and perceived effort when perfomed at similar power output (18), lengthening of contracting muscle fibers can induce muscle damage associated with severe local inflammation (26–28). In patients with breast cancer, it is critical to limit the systemic consequences associated with severe muscle damage in this vulnerable population (29). Interestingly, muscle soreness and damage can be prevented by familiarization sessions to eccentric cycling (30). Thus, muscle soreness and damage induced by an eccentric cycling session need to be investigated in patients with breast cancer to evaluate its safety and feasibility before its implementation in a training program.

The present study aimed to investigate the magnitude and etiology of neuromuscular fatigue and muscle damage induced by eccentric cycling exercise, compared with conventional concentric cycling, in patients with early breast cancer. To achieve these goals, eccentric and concentric cycling exercises were performed at either similar power output, matching mechanical stimuli but leading to different metabolic demands or at similar oxygen consumption level ($\dot{V}O_2$), matching metabolic demands but leading to different mechanical stimuli. We hypothesized that eccentric cycling induces greater neuromuscular fatigue than concentric cycling performed at similar power output or $\dot{V}O_2$.

METHODS

Patients

Nine women from the Institute of Cancerology Strasbourg Europe (ICANS) were included in the present study (NCT05166148). All patients provided written informed consent before enrollment, and the study was conducted in accordance with the Declaration of Helsinki and received approval from the National Ethics Committee (2021-A01624-37). The inclusion criteria were as follows: French-speaking, nonpregnant, ≥18 yr old, Scarff–Bloom–Richardson grades I–III, early-stage breast cancer, and a World Health Organization performance status of 0–2 within 1 yr after completion of (neo)adjuvant taxane-based chemotherapy. Women were excluded if they had psychiatric, musculoskeletal, or neurological disorders. The patient characteristics are shown in Table 1.

Experimental Design

Each patient performed 10 visits at the Cancerology Institute within a period of 5 wk.

$\dot{V}O_2$ assessment. Patients performed an incremental cycle ergometer test until exhaustion, which has been validated in breast cancer patients (31), to determine maximal oxygen uptake ($\dot{V}O_{2max}$) and concentric peak power output. After a 2-min warm-up at 25 W and 60 rpm, the exercise intensity reached 40 W and was increased by 10 W every minute until exhaustion. After a 10-min recovery period, a second constant test (105% of peak power at 60 rpm) until exhaustion was then performed to ensure that the patients reached $\dot{V}O_{2max}$ (32). The mean durations of the incremental and the constant tests were 9.2 ± 2.6 and 2.3 ± 0.3 min, respectively. If the difference in $\dot{V}O_2$ between the incremental test and the constant test was ≤2.1 mL·min·kg^{-1}, the $\dot{V}O_2$ was considered to be maximal (33). For every patient, the differences in peak $\dot{V}O_2$ between the incremental test and the constant test were equivalent (23.4 ± 6.0 vs 23.8 ± 5.7 mL·min·kg^{-1}, respectively; $P < 0.001$ for equivalence test).

Familiarization sessions. Four visits, separated by 2–3 d of recovery, were implemented to familiarize the patients with eccentric cycling. Each familiarization session consisted of three bouts of eccentric cycling interspersed with no more than

TABLE 1. Participants' characteristics.

Participants' Characteristics (n = 9)	
Characteristics (mean ± SD)	
Age (yr)	53 ± 13
Body mass (kg)	76 ± 27
Height (cm)	165 ± 1
Body mass index (kg/m^2)	28 ± 8
Incremental test (mean ± SD)	
$\dot{V}O_{2max}$ (mL·min·kg^{-1})	23 ± 6
HR_{max} (bpm)	167 ± 13
PPO (W)	121 ± 25
Tumor stage (n)	
2	3
3	6
Tumor SBR grade (n)	
II	7
III	2
Tumor type (n)	
Luminal (A/B)	6
HER2+++	3
Treatment setting (n)	
Adjuvant	5
Neoadjuvant	4

HER2, human epidermal growth factor receptor 2; PPO, concentric peak power output; SBR, Scarff–Bloom–Richardson.

3 min of passive recovery. Exercise workload and duration were progressively increased within and between familiarization sessions. During visit 1, patients performed three 2-min bouts of eccentric cycling. Patients were asked to apply a low resistance to acquire the specific coordination required in eccentric cycling. Cadence was progressively increased from 40 to 60 rpm during visit 1 and then kept at 60 rpm for all the following sessions (34). During visit 2, patients performed 2 min of eccentric cycling at 50% of concentric peak power output, followed by 3 min at 50% of concentric peak power output and 3 min at 60% of concentric peak power output. During visit 3, patients performed 6 min of eccentric cycling at 60% of concentric peak power output, followed by 3 min at 65% of concentric peak power output and 3 min at 70% of concentric peak power output. During visit 4, patients performed 6 min of eccentric cycling at 70% of the concentric peak power output, followed by 6 min at 75% of the concentric peak power output and 4 min at 80% of the concentric peak power output. After each familiarization session (24 and 48 h postexercise), patients reported thigh muscle soreness (detailed hereinafter).

Experimental cycling sessions. Each patient performed three experimental sessions as follows: eccentric, high-intensity concentric, and low-intensity concentric cycling exercise. Each experimental session was also associated with assessments 24 h postexercise. Eccentric session (ECC) and high-intensity concentric session (CON_{power}) were performed at similar power output, fixed at 80% of the concentric peak power. ECC and low-intensity concentric ($CON_{\dot{V}O_2}$) sessions were performed at similar $\dot{V}O_2$ level. The order of the sessions was pseudo-randomized among the patients, given that the $CON_{\dot{V}O_2}$ session needed to be performed after the ECC session.

Experimental Cycling Protocol

The cycling protocol consisted of three 6-min cycling bouts separated by 3 min of recovery in order to provide a high-intensity interval training session that is tolerable by our population of patients with cancer (35).

All patients carried out the experiment protocol as follows: 1) preexercise assessments, 2) exercise task, 3) postexercise assessments, and 4) 24-h postexercise assessments. Before exercise, blood samples were collected, and neuromuscular testing was performed (detailed hereinafter). The cycling sessions were performed on a semirecumbent ergometer both for eccentric (Cyclus II—Recumbent; RBM Electronics, Leipzig, Germany) and concentric (Ergoselect 600; Ergoline GmbH, Bitz, Germany) cycling. The seat position of each ergometer was adjusted to each patient's morphology and kept constant during all sessions. Patients were required to perform the exercise task, which consisted of three 6-min cycling bouts at 60 rpm separated by 3 min of recovery. Neuromuscular function was evaluated during each recovery period at 30 s and 2 min, as well as postexercise at 30 s, 2 min, 3 min, 5 min, 10 min, and 24 h. At the end of each exercise bout, the rate of perceived exertion was evaluated using the Borg CR-10 scale. Blood samples (detailed hereinafter) were collected 24 h postexercise to estimate systemic muscle damage. Muscle soreness (detailed hereinafter) was evaluated at 24 and 48 h postexercise.

Neuromuscular Protocol

Patients were first familiarized with isometric knee extensor contractions and the associated experimental procedures. Neuromuscular assessment of the knee extensor muscles was conducted before, between, and after the cycling bouts using a standardized set of contractions. In each set, patients performed a 3-s maximal voluntary isometric contraction (MVC), and stimulation was applied both during (superimposed twitch (SIT)) and 1 s after (potentiated resting twitch) each MVC to assess the voluntary activation and contractile properties of the knee extensors, respectively. For each set, strong verbal encouragement was given. Corticospinal excitability was measured immediately after the potentiated twitch. Three transcranial magnetic stimulations were delivered during a submaximal voluntary isometric contraction corresponding to 20% of each patient's maximal EMG-RMS output (obtained from MVC). At preexercise, six sets separated by 30 s of recovery were used to ensure potentiation. Additional sets were performed if the variability of the MVC exceeded 5%. The same standardized set was used for the evaluation of neuromuscular function between bouts and postexercise.

Data Acquisition and Analysis

Neuromuscular function

Force and electromyographic activity. Patients were tested in a seated position with the hip and knee joints fixed at 100° and 90°, respectively (where 180° represents full extension), and aligned in the frontal axis. The lower right leg was strapped above the ankle to an ergometer connected to a calibrated force transducer (Force sensor kit; Chronojump, Barcelona, Spain). Surface electromyography (EMG) recording electrodes (Ag-AgCl, 32 × 32 mm) were placed over the vastus lateralis (VL), vastus medialis (VM), rectus femoris (RF), and biceps femoris (BF) according to the SENIAM guidelines (36). EMG recordings were bandpass filtered (10 Hz–1 kHz) and amplified with an isolated differential amplifier (Octal Bio Amp; AD Instruments, Colorado Springs, CO). EMG and mechanical signals were collected simultaneously at a sampling rate of 2000 Hz using LabChart Software (AD Instruments, version 8.1.13). EMG muscle activity was recorded during MVC and during cycling exercise. Muscle activation of the VL, VM, and RF was calculated with the root mean square (RMS) of the EMG signals. During MVC, the RMS was determined over a 500-ms window surrounding the peak force and normalized to the muscle action potential (M_{max}) amplitude (VL RMS$\cdot M_{max}^{-1}$, VM RMS$\cdot M_{max}^{-1}$, and RF RMS$\cdot M_{max}^{-1}$) to estimate central motor drive. During cycling, VL, VM, and RF muscle activation was calculated by the RMS of each burst using a custom-made MATLAB software

algorithm (MATLAB R2019b; MathWorks, Natick, MA, USA). The signal was then averaged every 30 s and normalized to the RMS signal recorded during preexercise MVCs ($VL_{\%MVC}$, $VM_{\%MVC}$, and $RF_{\%MVC}$).

Electrical femoral nerve stimulation. A constant–current high-voltage (400 V) stimulator (DS7-AH; Digitimer Ltd., Hertfordshire, UK) was used to generate rectangular electrical impulses (200 μs) and evoke knee extensor contractions from the femoral nerve. The cathode (32-mm diameter, CF3200 models; Valu Trode, Axelgaard, Denmark) was positioned over the inguinal space on the femoral nerve, and the anode (90 ×50 mm, Valu Trode, 895240 models) was positioned in the gluteal fold. A recruitment curve was obtained to determine the optimum stimulation intensity. The stimulation intensity was increased by 10 mA from 50 mA until a plateau in the single quadriceps twitch peak force (Q_{tw}) and compound M_{max} were achieved. The maximal intensity was reached when no improvement in Q_{tw} and M_{max} was observed despite increasing stimulation intensity. A supramaximal stimulation intensity (i.e., 120% of the maximal stimulation intensity) was then used to guarantee the complete recruitment of motor units during all neuromuscular assessments.

Q_{tw} was calculated as the force amplitude between the baseline signal and the highest force value of the evoked potentiated twitch. The following parameters of potentiated resting twitch, which are indicators of muscle contractile properties, were also calculated: contraction time (CT), which is the time from the start of the contraction to Q_{tw}; half relaxation time (HRT), which is the time from Q_{tw} to 50% decline in Q_{tw}; and maximal rate of force development (MRFD), which is the highest positive derivative of the torque for an interval of 10 ms. Voluntary activation was calculated using the amplitude of the SIT, and Q_{tw}, using the following formula: voluntary activation (%) = $[1 - (SIT \div Q_{tw})] \times 100$.

Transcranial magnetic stimulation. Transcranial magnetic stimulations were generated using a magnetic stimulator (Magstim 200^2; The Magstim Company Ltd., Dyfed, UK) and a double-cone coil (diameter of 130 mm). Intensities are expressed as a percentage and function of the maximum output intensity (1.4 T). Stimulations were applied to the left motor cortex to evoke motor-evoked potentials (MEPs) in the right knee extensor muscle with the current flowing posteriorly to the anterior direction. The coil position was determined by applying stimulations at 50% of the maximal intensity during isometric contraction at a constant level of EMG (20% EMG-RMS registered from the knee extensor MVC, which corresponds to 28% ± 5% of the MVC). The optimal position was determined as the position that elicited the greatest MEP in the VL and the lowest in the BF (<15% of the raw VL MEP amplitude) (37); the position was marked directly on the scalp with a medical marker for reproducibility during the experimental session. The stimulation intensity for neuromuscular assessments was determined by the active motor threshold method. The active motor threshold was the minimum stimulus intensity that produced a minimal EMG response (more than 50 μV in three out of five consecutive trials) during 20% EMG-RMS isometric contraction. The stimulator intensity was set to 120% of the active motor threshold to ensure a clear MEP (37). The MEP peak-to-peak amplitudes were measured between the maximum and minimum values. Corticospinal excitability showed great reproducibility using three transcranial magnetic stimulations (preexercise ICC for MEP amplitudes in VL: 0.89 (95% confidence interval (CI), 0.71–0.96), VM: 0.90 (95% CI, 0.74–0.97), and RF: 0.91 (95% CI, 0.76–0.98)). The three MEP amplitudes were normalized to the concomitant M_{max} ($MEP \cdot cM_{max}^{-1}$) for the VL, VM, and RF and averaged together.

Cardiorespiratory assessments

Gas exchange and heart rate (HR) were measured at rest and during each bout of cycling using a portable metabolic cart (Cortex Metamax 3B; Cortex Biophysik GmbH, Leipzig, Germany). Before each exercise session, the pneumotachograph was calibrated with a 3-L calibration syringe (Model 5530; Hans Rudolph, Kansas City, MO). The gas analyzers were calibrated with reference gases of known O_2 and CO_2 concentrations (15% O_2 and 5% CO_2). $\dot{V}O_2$ and HR were averaged every 30 s.

Muscle soreness

Thigh muscle soreness was quantified 24 and 48 h after the familiarization sessions to eccentric cycling and experimental sessions, using a visual analog scale ranging from 0 to 10 (where 0 indicates "no pain," and 10 indicates "worst pain imaginable") after three standing up from a sitting position on a chair.

Blood parameters

Venous blood samples were drawn at rest before each exercise protocol session and after 24 h. Blood samples were collected in 2 × 4-mL ethylenediaminetetraacetic acid tubes. The blood samples were immediately centrifuged (10 min at 2000*g*), and the plasma was collected and stored at −80°C. Assessments of creatine kinase (CK) (Sigma-Aldrich assay kit, MAK116) and lactate dehydrogenase (LDH; Sigma-Aldrich assay kit, MAK066) activities were subsequently performed in 96-well plates using a spectrophotometer (Varioskan LUX, Thermo Fisher Scientific) according to the manufacturer's instructions.

Statistical Analysis

The sample size calculation was based on a previous investigation documenting the decrease in knee extensor MVC after an eccentric cycling session in older adults (38). Assuming an effect size of 1.4, an α risk of 0.05, and a β risk of 0.95, the sample size required was $n = 9$ (G*Power, version 3.1.9.4).

All the statistical tests were performed with Statistica 10 (Stat-Soft, Inc., Tulsa, OK, USA), and the graphs were generated with GraphPad Prism version 8 software (GraphPad Software, San Diego, CA, USA). The data are presented as the means ± SD. The Shapiro–Wilk test and the Levene test were

used to check for the normality and variance homogeneity of the data, respectively. The two-one-sided *t*-test was used to test the equivalence in peak $\dot{V}O_2$ between the incremental test and the constant test using a 90% CI. Two-way ANOVAs with repeated measures (condition–time) were used to compare neuromuscular indices using absolute data (i.e., MVC, RMS·M_{max}^{-1}, voluntary activation, Q_{tw}, CT, HRT, MRFD, M_{max}, and MEP·cM_{max}^{-1}), biomarkers of muscle damage (CK and LDH activities), thigh muscle soreness, and rate of perceived exertion. Three-way ANOVAs with repeated measures (condition–bouts–time) were used to compare muscle activation ($VL_{\%MVC}$, $VM_{\%MVC}$, and $RF_{\%MVC}$) and cardiorespiratory parameters ($\dot{V}O_2$ and HR) during cycling. In particular, statistical analyses of the cardiorespiratory parameters were performed during the steady state (i.e., last 3 min of each cycling bout). Multiple comparison analysis was performed with Tukey's HSD *post hoc* test when a significant difference was found in the ANOVAs. Statistical significance was set at $P < 0.05$.

RESULTS

Baseline values and settings for the experimental cycling conditions. At rest, there were no significant differences among the three experimental cycling conditions in neuromuscular indices (MVC, RMS·M_{max}^{-1}, voluntary activation, Q_{tw}, CT, HRT, MRFD, M_{max}, and MEP·cM_{max}^{-1}), cardiorespiratory indices ($\dot{V}O_2$ and HR), or plasma biomarkers (CK and LDH; Supplemental Table 1, Supplemental Digital Content, Baseline values, http://links.lww.com/MSS/D58).

By design, the power output was not different between the ECC (95 ± 23 W) and CON_{power} (95 ± 23 W, $P = 0.999$) sessions but was lower in the $CON_{\dot{V}O_2}$ (29 ± 12 W, $P < 0.001$) session. Moreover, $\dot{V}O_2$ was similar between the ECC session (10 ± 2 mL·min·kg^{-1}, 43% ± 8% of $\dot{V}O_{2max}$) and $CON_{\dot{V}O_2}$ session (10 ± 2 mL·min·kg^{-1}, 42% ± 9% of $\dot{V}O_{2max}$, $P = 0.940$) but were greater in the CON_{power} session (20 ± 5 mL·min·kg^{-1}, 85% ± 7% of $\dot{V}O_{2max}$, $P < 0.001$).

Neuromuscular fatigue. The neuromuscular indices are presented Figure 1 and Table 2. A significant condition–time interaction effect was found for MVC ($P < 0.001$). Although significant reductions were evidenced in the ECC and CON_{power} sessions (−25% ± 12% vs −11% ± 9% 30 s postexercise, respectively; $P < 0.001$), MVC remained unchanged compared with preexercise throughout the $CON_{\dot{V}O_2}$ session (Fig. 1A). The ECC session resulted in a greater decrease in MVC compared with the $CON_{\dot{V}O_2}$ and CON_{power} sessions after each bout ($P < 0.001$). This greater reduction in MVC between conditions persisted during the early recovery period documented from 30 s to 10 min postexercise ($P < 0.001$). Moreover, the MVC remained depressed 24 h postexercise compared with preexercise in the ECC session (−17% ± 8%, $P < 0.001$), but it was recovered in the CON_{power} session ($P = 0.376$). The two-way ANOVA did not reveal any significant effect on VL, VM, and RF RMS·M_{max}^{-1} during MVC.

A significant condition–time interaction effect was found for voluntary activation ($P < 0.001$; Fig. 1B). Voluntary activation decreased only in the ECC session after the third bout of exercise, reaching −9% ± 6% at 30 s postexercise and −16% ± 9% at 3 min postexercise ($P < 0.001$). Voluntary activation was fully recovered 24 h postexercise in the ECC session ($P = 0.981$).

A significant condition–time interaction effect was found for Q_{tw} ($P < 0.001$; Fig. 1C). Compared with baseline, the Q_{tw} decreased during exercise in the three cycling conditions ($P < 0.001$). Compared with $CON_{\dot{V}O_2}$ session, the ECC session resulted in a greater decrease in Q_{tw} after the second and third exercise bouts ($P < 0.001$), and this difference persisted throughout the 10-min recovery period ($P < 0.001$). The ECC session resulted in a lower decrease in Q_{tw} compared with the CON_{power} session at 30 s after the first bout only (−17% ± 10% vs −36% ± 13%, respectively; $P < 0.001$). No difference between the two conditions was found from the second exercise bout to the 10-min recovery period ($P > 0.889$). Although the Q_{tw} remained lower than the preexercise value 24 h after ECC (−14% ± 7%, $P < 0.001$), it fully recovered in the CON_{power} ($P = 0.940$) and $CON_{\dot{V}O_2}$ sessions ($P = 0.999$). The Q_{tw} properties (i.e., CT, HRT, and MRFD) are provided in Table 2. Although only a significant time effect was reported for CT ($P < 0.001$), a significant condition–time interaction effect was found for HRT ($P < 0.001$) and MRFD ($P < 0.001$).

The VL, VM, and RF muscle activations during cycling are presented in Figure 2. A significant condition–time interaction effect was found for VL, VM, and RF $RMS_{\%MVC}$ ($P < 0.001$). The ECC session resulted in lower muscle activation compared with the CON_{power} session (VL $RMS_{\%MVC}$, $P = 0.008$; VM $RMS_{\%MVC}$, $P = 0.006$; and RF $RMS_{\%MVC}$, $P = 0.026$) but higher muscle activation compared with $CON_{\dot{V}O_2}$ session (VM $RMS_{\%MVC}$ and RF $RMS_{\%MVC}$, both $P < 0.001$). The VL $RMS_{\%MVC}$ and VM $RMS_{\%MVC}$ significantly increased between the first and third bouts only in the ECC session ($P < 0.001$). A significant condition–time interaction effect was found for M_{max} in the VL, VM, and RF ($P < 0.001$; Table 2). M_{max} decreased only in the ECC and recovered 24 h postexercise in the VL, VM, and RF.

A significant time effect was found for corticospinal excitability in the VL and RF MEP·cM_{max}^{-1} ($P < 0.001$ and $P = 0.019$, respectively; Table 2).

Cardiorespiratory responses to exercise. The cardiorespiratory indices are presented in Figure 3. A significant condition–time interaction effect was found for $\dot{V}O_2$ ($P < 0.001$; Fig. 3A). $\dot{V}O_2$ increased over time from the first to the third bout during the three experimental conditions ($P < 0.001$).

A significant condition–bout–time interaction effect was found for HR ($P = 0.032$; Fig. 3B). The ECC session resulted in a lower HR during exercise compared with the CON_{power} session (107 ± 12 bpm corresponding to 64% ± 5% of maximal heart rate (HR_{max}) vs 143 ± 15 bpm corresponding to 89% ± 4% of HR_{max}) and a higher HR compared with the $CON_{\dot{V}O_2}$ session

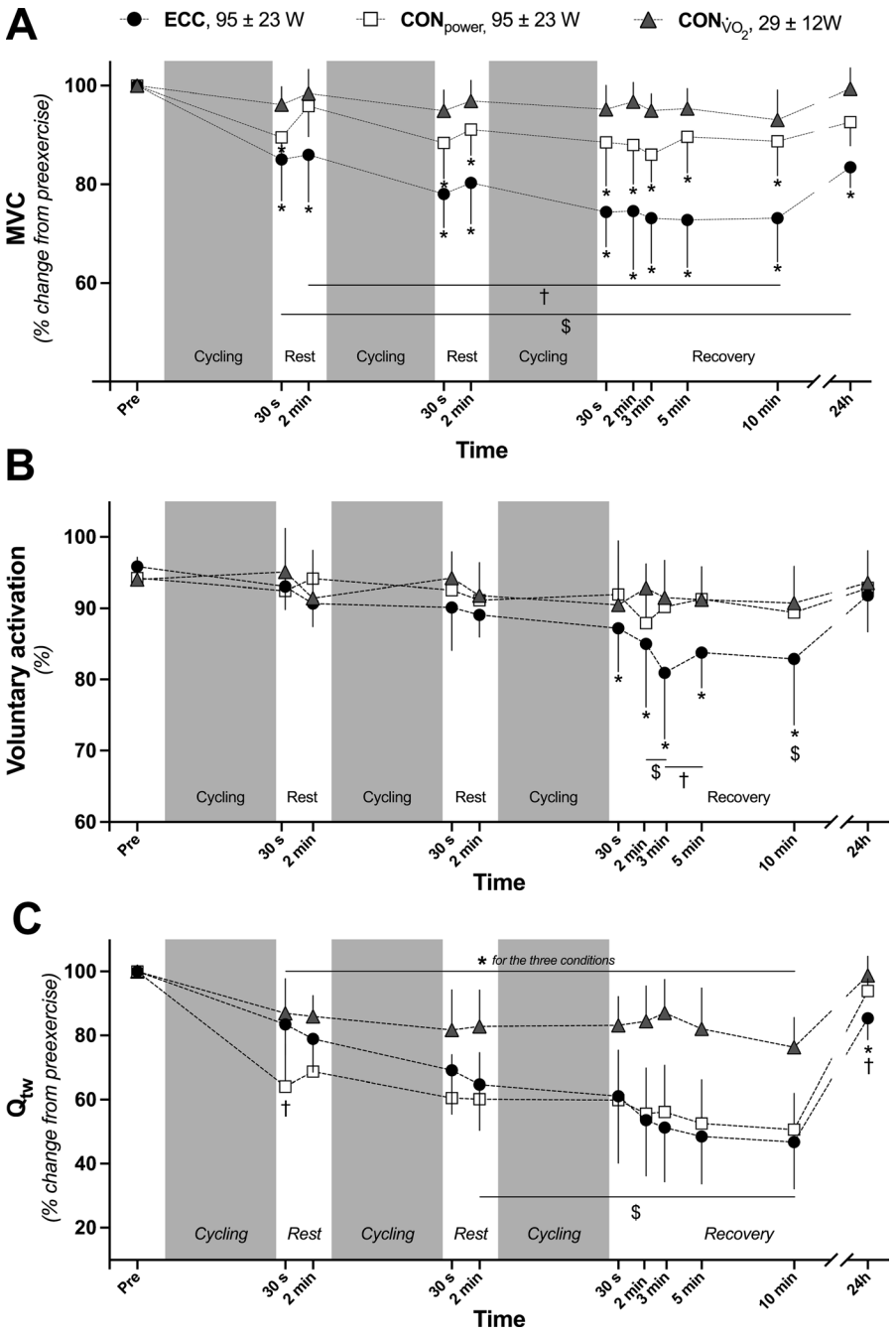

FIGURE 1—Exercise-induced changes in neuromuscular function during exercise and recovery. A, Maximal voluntary contraction (MVC) expressed in relative units. Voluntary activation (B) and (C) quadriceps potentiated twitch force (Q_{tw}) expressed in relative units. Variables were assessed preexercise, after each exercise bout, and postexercise up to 24 h. The data are presented as the mean ± SD (n = 9). * Significant difference from preexercise, $P < 0.05$. †Significant difference between ECC and CON_{power}, $P < 0.05$. $Significant difference between ECC and $CON_{\dot{V}O2}$, $P < 0.05$. The eccentric cycling sessions (ECC) are represented by black circles. The concentric cycling exercise sessions performed at the same power output as that of the ECC sessions (CON_{power}) are represented by white squares. The concentric cycling exercise sessions performed at the same O_2 consumption level as that of the ECC sessions ($CON_{\dot{V}O2}$) are represented by gray triangles.

(96 ± 14 bpm corresponding to 57% ± 5% of HR_{max}). The HR increased over time from the first to the third bout during the three experimental conditions ($P < 0.001$).

Rate of perceived exertion and muscle soreness. The rates of perceived exertion are presented in Table 3. Significant time ($P < 0.001$) and condition ($P < 0.001$) effects were found for the rate of perceived exertion. Compared with the ECC session, the rate of perceived exertion was greater in the CON_{power} session ($P = 0.042$) but lower in the $CON_{\dot{V}O_2}$ session ($P < 0.001$).

The thigh muscle soreness is presented in Table 4. A significant condition effect was found for thigh muscle soreness

TABLE 2. Neuromuscular function of quadriceps before, during, and after exercise in the eccentric and concentric cycling sessions.

		Postbout 1		Postbout 2		Postbout 3					
	Preexercise	30 s	2 min	30 s	2 min	30 s	2 min	3 min	5 min	10 min	24 h
CT (ms)											
ECC	108 ± 9	112 ± 11	111 ± 13	108 ± 13	106 ± 7	110 ± 12	107 ± 6	113 ± 13	123 ± 33	101 ± 7	109 ± 12
CON_{power}	110 ± 11	110 ± 15	110 ± 11	111 ± 11	117 ± 23	113 ± 15	115 ± 16	115 ± 20	116 ± 19	110 ± 10	112 ± 12
$CON_{\dot{V}O2}$	110 ± 10	112 ± 12	114 ± 11	112 ± 12	114 ± 9	108 ± 12	113 ± 10	113 ± 12	111 ± 13	114 ± 12	104 ± 5
HRT (ms)											
ECC	77 ± 21	37 ± 11*,**	38 ± 9*,**	33 ± 6*,**,***	36 ± 9*	28 ± 8*,***	35 ± 8*	32 ± 8*,***	33 ± 6*	36 ± 12*	78 ± 14
CON_{power}	75 ± 30	93 ± 50	67 ± 37	69 ± 32	56 ± 30	45 ± 30*	50 ± 28	43 ± 24*	55 ± 54	42 ± 20*	74 ± 36
$CON_{\dot{V}O2}$	86 ± 22	59 ± 28*	58 ± 20*	65 ± 30	57 ± 25*	70 ± 36	54 ± 23*	60 ± 30	60 ± 15	57 ± 13*	88 ± 23
MRFD ($N \cdot s^{-1}$)											
ECC	4180 ± 1074	3626 ± 1094**,***	3313 ± 1170*	2920 ± 1117*	2611 ± 1004*	2538 ± 1227*	2192 ± 932*,***	2027 ± 950*,***	1851 ± 793*,***	1826 ± 839*,***	3378 ± 748**
CON_{power}	4389 ± 1398	2686 ± 1195*	2955 ± 1207*	2513 ± 1178*	2486 ± 1161*	2591 ± 1240*	2325 ± 1132*	2321 ± 1109*	2214 ± 1063*	2082 ± 892*	4208 ± 983
$CON_{\dot{V}O2}$	4037 ± 1390	3460 ± 1143	3533 ± 1130	3313 ± 1201	3338 ± 1218	3330 ± 1103	3135 ± 1261	3338 ± 1096*	3163 ± 1182*	2971 ± 1084*	4027 ± 1172
VL (M_{max}·mV)											
ECC	11.3 ± 4.1	10.7 ± 3.6	10.2 ± 3.6*,**	10.4 ± 3.3**	10.3 ± 3.3*,**	10.2 ± 3.3*	10.2 ± 3.3*	10.2 ± 3.3*	10.2 ± 3.4*	10.2 ± 3.5*	10.8 ± 4.9
CON_{power}	10.7 ± 4.5	11.4 ± 4.1	11.4 ± 4.1	11.5 ± 4.2	11.5 ± 4.2	11.2 ± 4.8	11.0 ± 4.4	11.0 ± 4.4	10.6 ± 4.3	10.4 ± 4.4	10.6 ± 4.7
$CON_{\dot{V}O2}$	10.8 ± 4.6	10.6 ± 4.3	10.6 ± 4.3	10.8 ± 4.5	10.7 ± 4.4	10.8 ± 4.2	10.7 ± 4.2	10.7 ± 4.2	10.5 ± 4.2	10.4 ± 4.2	12.4 ± 4.7
VM (M_{max}·mV)											
ECC	12.7 ± 4.6	11.3 ± 3.7	10.4 ± 4.3*,**	10.3 ± 3.7**	10.8 ± 3.3*,**	10.3 ± 3.6*	10.6 ± 3.3*	10.8 ± 3.5*	10.5 ± 3.5*	10.6 ± 3.6*	12.4 ± 4.6
CON_{power}	11.8 ± 4.4	11.6 ± 5.5	11.8 ± 5.7	11.2 ± 5.0	11.4 ± 4.4	10.8 ± 5.9	9.9 ± 5.2	10.3 ± 5.0	9.5 ± 5.0	9.6 ± 4.8	11.6 ± 4.9
$CON_{\dot{V}O2}$	12.0 ± 5.4	11.4 ± 5.4	11.6 ± 5.1	11.4 ± 5.4	11.6 ± 5.0	11.6 ± 5.0	11.5 ± 4.8	11.5 ± 4.9	11.5 ± 4.6	11.3 ± 4.7	12.4 ± 4.7
RF (M_{max}·mV)											
ECC	4.0 ± 1.4	3.7 ± 1.2	3.5 ± 1.0	3.4 ± 1.1*,**	3.5 ± 1.1**	3.4 ± 1.2*	3.5 ± 1.0	3.5 ± 1.0	3.5 ± 1.0	3.4 ± 1.1*	4.1 ± 1.1
CON_{power}	4.1 ± 1.3	4.0 ± 1.5	4.0 ± 1.3	4.1 ± 1.0	4.1 ± 1.0	4.0 ± 1.2	3.8 ± 1.1	3.8 ± 1.2	3.7 ± 1.2	3.7 ± 1.3	3.8 ± 1.5
$CON_{\dot{V}O2}$	4.2 ± 1.3	3.9 ± 1.1	3.9 ± 1.2	3.9 ± 1.3	3.9 ± 1.4	3.8 ± 1.2	3.9 ± 1.2	3.9 ± 1.2	3.8 ± 1.2	3.8 ± 1.2	4.4 ± 1.3
VL (RMS·M_{max}^{-1}·a.u.)											
ECC	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
CON_{power}	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
$CON_{\dot{V}O_2}$	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01
VM (RMS·M_{max}^{-1}a.u.)											
ECC	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.03	0.05 ± 0.02	0.04 ± 0.01	0.04 ± 0.02	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
CON_{power}	0.04 ± 0.01	0.05 ± 0.03	0.05 ± 0.03	0.06 ± 0.04	0.04 ± 0.01	0.09 ± 1.3	0.07 ± 0.07	0.06 ± 0.06	0.07 ± 0.06	0.07 ± 0.07	0.05 ± 0.05
$CON_{\dot{V}O2}$	0.05 ± 0.02	0.06 ± 0.06	0.04 ± 0.01	0.05 ± 0.02	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.06 ± 0.07
RF (RMS·M_{max}^{-1}·a.u.)											
ECC	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.06 ± 0.2
CON_{power}	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.02	0.06 ± 0.01	0.06 ± 0.01
$CON_{\dot{V}O2}$	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.02	0.07 ± 0.02
VL (MEP·cM_{max}^{-1}·a.u.)											
ECC	0.19 ± 0.08	0.19 ± 0.08	0.19 ± 0.08	0.20 ± 0.11	0.23 ± 0.09	0.22 ± 0.08	0.25 ± 0.09	0.24 ± 0.10	0.26 ± 0.11	0.26 ± 0.12	0.22 ± 0.11
CON_{power}	0.24 ± 0.11	0.21 ± 0.09	0.22 ± 0.09	0.18 ± 0.07	0.21 ± 0.08	0.24 ± 0.09	0.26 ± 0.08	0.28 ± 0.10	0.27 ± 0.08	0.29 ± 0.07	0.23 ± 0.09
$CON_{\dot{V}O2}$	0.21 ± 0.06	0.20 ± 0.07	0.22 ± 0.09	0.22 ± 0.10	0.25 ± 0.14	0.23 ± 0.10	0.25 ± 0.08	0.24 ± 0.06	0.22 ± 0.08	0.25 ± 0.09	0.22 ± 0.05
VM (MEP·cM_{max}^{-1}·a.u.)											
ECC	0.19 ± 0.11	0.21 ± 0.10	0.22 ± 0.12	0.21 ± 0.13	0.23 ± 0.11	0.22 ± 0.12	0.25 ± 0.13	0.24 ± 0.13	0.27 ± 0.14	0.27 ± 0.15	0.22 ± 0.11
CON_{power}	0.25 ± 0.12	0.33 ± 0.28	0.29 ± 0.15	0.26 ± 0.18	0.25 ± 0.11	0.47 ± 0.57	0.46 ± 0.42	0.47 ± 0.47	0.45 ± 0.30	0.46 ± 0.38	0.25 ± 0.12
$CON_{\dot{V}O2}$	0.30 ± 0.20	0.43 ± 0.63	0.30 ± 0.21	0.32 ± 0.26	0.19 ± 0.21	0.29 ± 0.16	0.30 ± 0.14	0.30 ± 0.13	0.25 ± 0.10	0.30 ± 0.16	0.25 ± 0.08
RF (MEP·cM_{max}^{-1}·a.u.)											
ECC	0.29 ± 0.12	0.31 ± 0.09	0.29 ± 0.09	0.29 ± 0.11	0.34 ± 0.14	0.31 ± 0.10	0.32 ± 0.14	0.32 ± 0.12	0.34 ± 0.15	0.34 ± 0.17	0.29 ± 0.11
CON_{power}	0.34 ± 0.15	0.34 ± 0.15	0.35 ± 0.11	0.29 ± 0.09	0.32 ± 0.11	0.31 ± 0.07	0.40 ± 0.13	0.43 ± 0.13	0.41 ± 0.14	0.44 ± 0.14	0.40 ± 0.24
$CON_{\dot{V}O2}$	0.33 ± 0.09	0.31 ± 0.13	0.31 ± 0.14	0.32 ± 0.13	0.33 ± 0.16	0.37 ± 0.13	0.37 ± 0.15	0.39 ± 0.12	0.36 ± 0.12	0.37 ± 0.15	0.33 ± 0.13

The data are presented as the means ± SD ($n = 9$).
*Significant difference from preexercise, $P < 0.05$.
**Significant difference from CON_{power}, $P < 0.05$.
***Significant difference from $CON_{\dot{V}O2}$, $P < 0.05$.

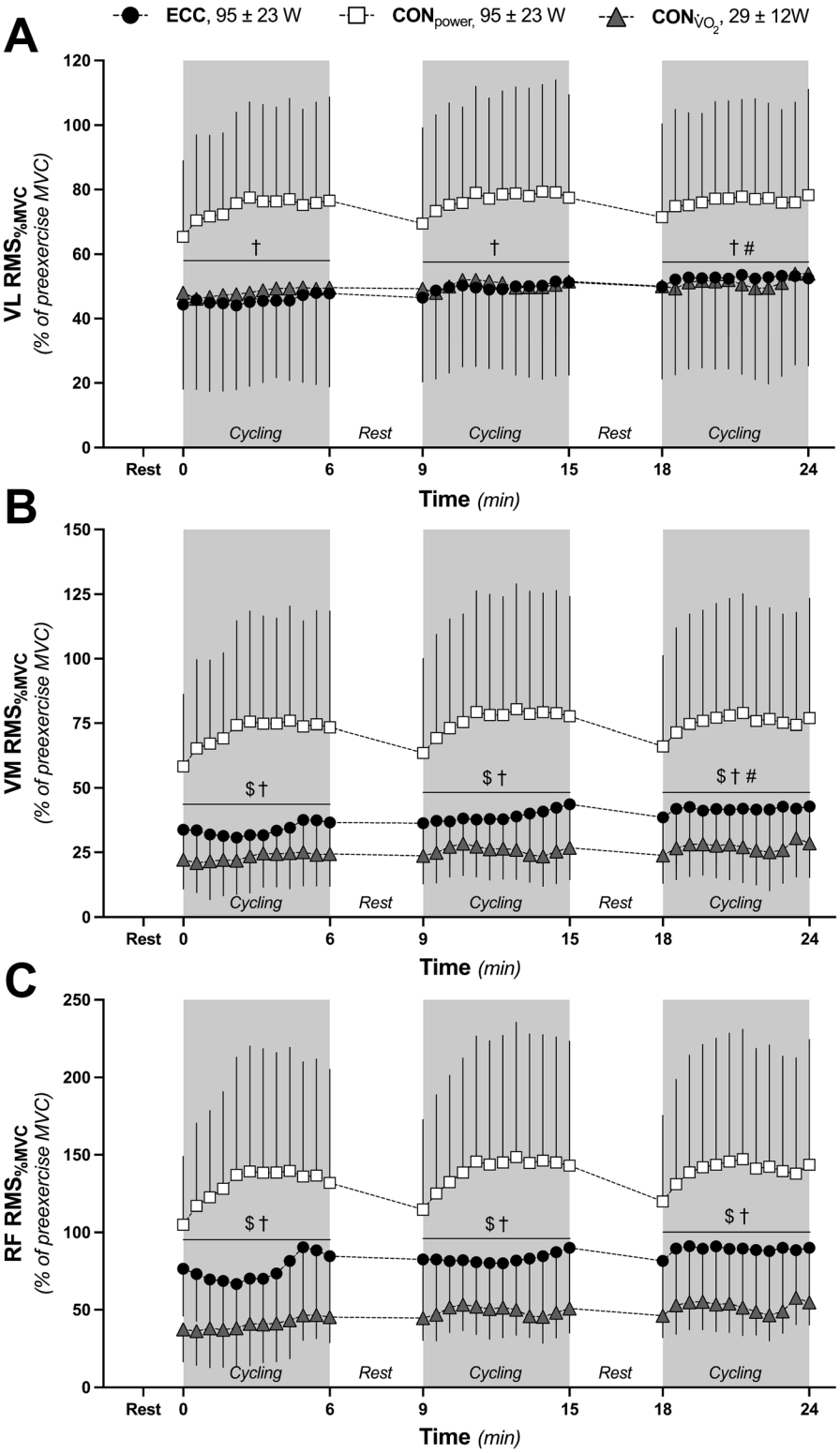

FIGURE 2—Muscle activation during exercise. Vastus lateralis, VL (A), vastus medialis,VM (B), and rectus femoris, RF (C) muscle activations are normalized to the root mean square (RMS) recorded during preexercise MVCs and expressed as a percentage from preexercise. The data are presented as the mean ± SD ($n = 9$). †Significant difference between ECC and CON_{power}, $P < 0.05$. $Significant difference between ECC and $CON_{\dot{V}O2}$, $P < 0.05$. #Significant difference from the first bout in ECC session, $P < 0.05$. The eccentric cycling sessions (ECC) are represented by black circles. The concentric cycling exercise sessions performed at the same power output as that of the ECC sessions (CON_{power}) are represented by white squares. The concentric cycling exercise sessions performed at the same O_2 consumption level as that of the ECC sessions ($CON_{\dot{V}O2}$) are represented by gray triangles.

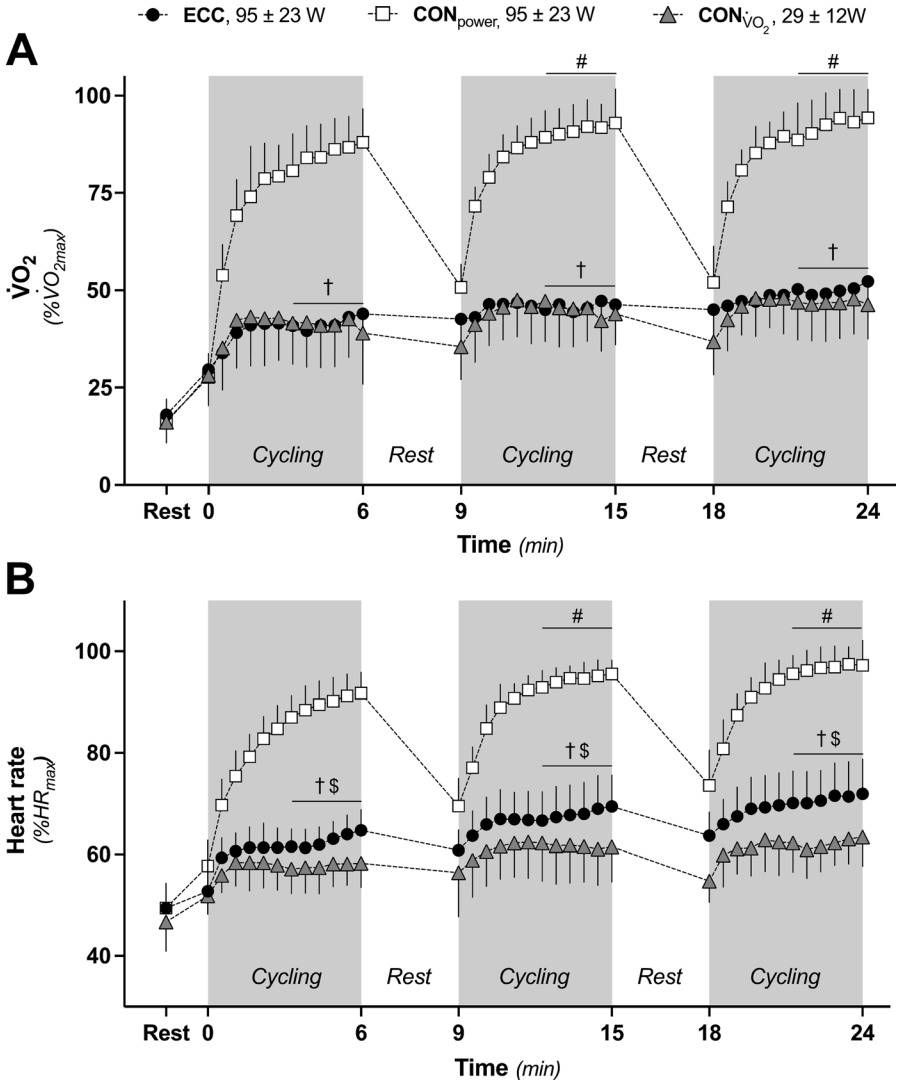

FIGURE 3—O_2 consumption normalized to $\dot{V}O_{2max}$ (A), and heart rate (HR) normalized to HR_{max} (B) responses during cycling exercise. Statistical analyses were performed during the steady state (i.e., the last 3 min of each cycling bout). The data are presented as the mean ± SD (n = 9). †Significant difference between ECC and CON$_{power}$, $P < 0.05$. $Significant difference between ECC and CON$_{\dot{V}O2}$, $P < 0.05$. #Significant difference from the first bout in the three conditions, $P < 0.05$. The eccentric cycling sessions (ECC) are represented by black circles. The concentric cycling exercise sessions performed at the same power output as that of the ECC sessions (CON$_{power}$) are represented by white squares. The concentric cycling exercise sessions performed at the same O_2 consumption level as that of the ECC sessions (CON$_{\dot{V}O2}$) are represented by gray triangles.

($P = 0.002$). The thigh muscle soreness measured 24 and 48 h postexercise was greater in the ECC session than in the CON$_{power}$ ($P = 0.002$) and CON$_{\dot{V}O_2}$ ($P < 0.001$) sessions.

Muscle damage. The plasma biomarker levels are presented in Figure 4. Two-way ANOVA did not reveal any significant effects on CK (Fig. 4A) or LDH (Fig. 4B) activity.

DISCUSSION

The present study investigated the magnitude and etiology of neuromuscular fatigue induced by eccentric cycling exercise (ECC) in patients with early breast cancer. These results were compared with those of conventional concentric cycling exercises performed either at similar power output (matching mechanical stimuli but with different metabolic stimuli (CON$_{power}$)) or at similar $\dot{V}O_2$ levels (matching metabolic stimuli but with different mechanical stimuli (CON$_{\dot{V}O_2}$)). Using plasma biomarkers, subsequent muscle damage induced by these exercise sessions was quantified. As hypothesized, ECC induced greater neuromuscular fatigue than concentric

TABLE 3. Rate of perceived exertion assessed using the Borg CR-10 scale at the end of each cycling bout in the three experimental conditions.

	Bout 1	Bout 2	Bout 3
ECC	3.2 ± 1.6*,**	3.8 ± 1.6**	4.3 ± 1.7*,**,***
CON$_{power}$	4.4 ± 2.0	4.7 ± 1.1	5.4 ± 1.2
CON$_{\dot{V}O2}$	0.7 ± 0.7	1.0 ± 0.9	1.4 ± 0.8

The data are presented as the mean ± SD (n = 9).
*Significant difference from CON$_{power}$, $P < 0.05$.
**Significant difference from CON$_{\dot{V}O2}$, $P < 0.05$.
***Significant difference from bout 1, $P < 0.05$.

TABLE 4. Thigh muscle soreness assessed with a visual analog scale 24 and 48 h after the familiarization sessions and experimental conditions.

	Familiarizations to Eccentric			
	Session 1	Session 2	Session 3	Session 4
24 h postexercise	1.2 ± 0.9	1.6 ± 1.5	2.1 ± 1.9	2.0 ± 2.2
48 h postexercise	1.0 ± 1.5	1.2 ± 1.6	2.3 ± 2.1	1.1 ± 1.5

	Experimental Sessions		
	ECC	CON_{power}	$CON_{\dot{V}O_2}$
24 h postexercise	2.1 ± 2.1*,**	0.2 ± 0.6	0.0 ± 0.0
48 h postexercise	2.0 ± 1.8*,**	0.5 ± 0.8	0.0 ± 0.0

The data are presented as the mean ± SD (n = 9).
*Significant difference from CON_{power}, $P < 0.05$.
**Significant difference from $CON_{\dot{V}O2}$, $P < 0.05$.

cycling, regardless of matching for power output or $\dot{V}O_2$. Specifically, the greater magnitude of neuromuscular fatigue in the ECC session was primarily due to central mechanisms. In addition, the CK and LDH activities did not change under any of the experimental conditions, indicating the efficacy of the familiarization protocol before ECC in limiting the systemic consequences associated with muscle damage in patients with early breast cancer.

Neuromuscular responses to eccentric versus concentric cycling. The present results demonstrated that ECC session induced greater neuromuscular fatigue throughout exercise and up to 24 h postexercise than concentric cycling sessions, including when conditions were matched for power output (i.e., ECC vs CON_{power}, Fig. 1), in patients with breast cancer. The difference in "global" neuromuscular fatigue (Fig. 1A) between ECC and concentric exercises was explained by mechanisms of central origin from 0.5 to 10 min postexercise (discussed in the next paragraph, Fig. 1B) and by mechanisms of peripheral origin 24 h postexercise (Fig. 1C). However, the observation of similar levels of peripheral fatigue between the ECC and CON_{power} sessions during the early recovery period (i.e., from 0.5 to 10 min postexercise) did not necessarily imply a similar etiology. Indeed, the CON_{power} session was associated with greater metabolic demand compared with the ECC session, as evidenced by greater $\dot{V}O_2$

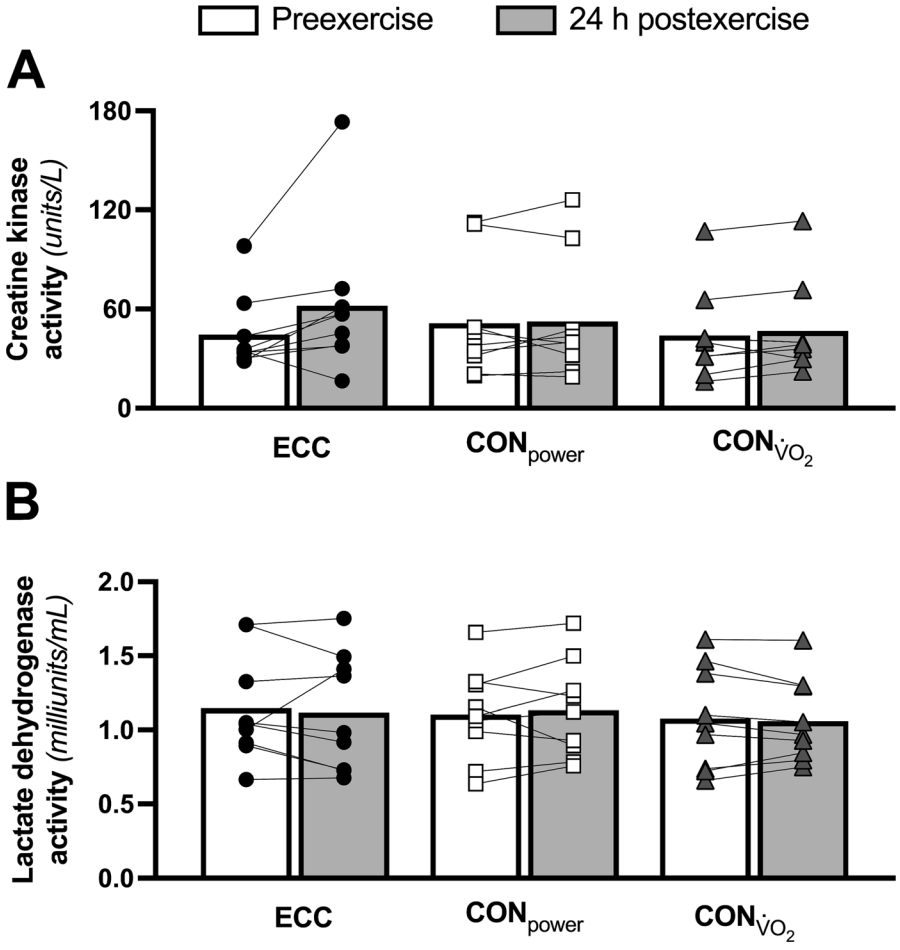

FIGURE 4—Changes in plasma biomarkers of muscle damage from preexercise to 24 h postexercise. Creatine kinae (CK) activity (A) and lactate dehydrogenase (LDH) activity (B). For every index, bars correspond to mean group data, and dots, squares, and triangles correspond to individual data (n = 9). Individual values are presented. The eccentric cycling sessions (ECC) are represented by black circles. The concentric cycling exercise sessions performed at the same power output as that of the ECC sessions (CON_{power}) are represented by white squares. The concentric cycling exercise sessions performed at the same O_2 consumption level as that of the ECC sessions ($CON_{\dot{V}O2}$) are represented by gray triangles.

levels (~twofold greater, Fig. 3) and greater muscle activation (Fig. 2) recorded throughout the exercise session, suggesting greater intramuscular metabolic perturbation. In contrast, peripheral fatigue was partially explained by alterations in membrane excitability in the ECC session, as evidenced by significant decreases in the quadriceps M_{max} (39), and resulting from overstretching of the sarcomeres during lengthening contractions (26). At similar $\dot{V}O_2$, the greater peripheral fatigue observed in the ECC session compared with the $CON_{\dot{V}O_2}$ session was explained by the high mechanical constraint characterizing the eccentric contraction mode and leading to structural disruption of sarcomeres (40). Interestingly, observation of greater neuromuscular fatigue in ECC compared with CON_{power} in the present study contracts with a previous investigation performed in healthy participants (18). This discrepancy between studies might be explained by the population of interest but also by the exercise duration and intensity that plays an important role in neuromuscular fatigue magnitude and etiology (41,42). This emphasizes how the results might be specific, and therefore limited, to its characteristics and context.

In addition to the characterization of the level of neuromuscular fatigue postexercise, the present study also documented its kinetics during the three cycling bouts. Although the decrease in "global" (ΔMVC) and peripheral fatigue was quite linear from the first to the third bout in ECC, their development kinetics were as fast (ΔMVC) or faster (ΔQ_{tw}) after the first bout in CON_{power}, despite no significant change thereafter until the last bout (Fig. 1). These results indicate that different kinetics during exercise can lead to similar values at exercise termination (peripheral fatigue), providing important insights for exercise training prescriptions.

After a 24-h recovery period, a significant magnitude of peripheral fatigue remained only in the ECC session. Given that M_{max} fully recovered at that time, a failure in membrane excitability was excluded, which indicated that factors located beyond the sarcolemma were responsible for the reduction in force output (43). More precisely, the reduction in MRFD observed at 24 h postexercise in the ECC session suggested alterations in excitation–contraction coupling (44).

Why is central fatigue exacerbated during eccentric cycling compared with power-matched concentric cycling?. The present findings supported central fatigue as a primary cause of the greater neuromuscular fatigue observed in the ECC session compared with the concentric cycling sessions. Indeed, voluntary activation decreased only in the ECC session, which is supported by a previous study showing central fatigue following eccentric, but not concentric, knee extensor contractions in healthy participants (45).

In the present study, voluntary activation was reduced in the ECC session despite no change in corticospinal excitability during any exercise condition. This result suggests that inhibition occurred upstream rather than downstream of the motor cortex (46,47). This idea is also supported by fMRI studies showing differences in cortical activity and brain functional connectivity between eccentric and concentric exercises (48). However, it is important to consider that the lack of a net effect on corticospinal excitability did not necessarily imply the absence of change (49), which is consistent with studies showing that central alterations also occur at the spinal level during eccentric exercise (50,51). Moreover, when transcranial magnetic stimulations were delivered during the cycling exercise, a lower corticospinal excitability associated with a longer silent period were observed in eccentric compared with concentric mode performed at the same power output (17). Finally, it is important to note that corticospinal excitability was tested in the present study using one stimulation intensity before and after fatiguing exercise and not through an input–output (dose–response) curve (52) that might have been more sensitive.

The differences in central fatigue between eccentric and concentric cycling might be explained, at least in part, by greater stimulation of group III/IV muscle afferent feedback, which can inhibit voluntary activation without any alteration in corticospinal excitability (53,54). Indeed, group III/IV muscle afferents are triggered by various signals, such as thermal, mechanical, metabolic, or nociceptive stimuli (55), and they project from skeletal muscles to the central nervous system to promote central fatigue during intense exercise in order to restrict peripheral fatigue (56,57). Previous findings have demonstrated that eccentric exercise is associated with exacerbated core and muscle temperature elevation (~ + 1°) at a given $\dot{V}O_2$ (58) or power output (59) compared with concentric exercise. Importantly, a 1° increase in temperature is sufficient to activate group III/IV muscle afferents, as evidenced in animal models (60,61). Moreover, it was demonstrated that an increase in core temperature throughout exercise (reaching a peak change of +2°) promotes central fatigue in humans (62). Additionally, the activation of group III/IV muscle afferents is presumably specific to the contraction mode (63). For example, tendon stretching has been shown to activate a different population of mechanosensitive group III muscle afferents than isometric contraction in decerebrated cats (64). The role of nociceptive stimuli in triggering group III/IV muscle afferents should also be considered. Although the *systemic* ECC-induced pain/inflammation process is not immediate but delayed from hours to days after exercise (65,66), *intramuscular* bradykinin and prostaglandin concentrations can increase during exercise (67,68). The increase in the levels of these two proinflammatory hormones, which directly activate group III/IV muscle afferents (69,70), was likely greater during ECC than during concentric exercise. In contrast, greater activation of group III/IV muscle afferents due to greater metabolic stimuli (i.e., perturbations) was unlikely given the lower metabolic demand during the ECC session compared with the CON_{power} session. Taken together, although speculative, differences in thermal, mechanical, and hormonal stimuli might explain the greater central fatigue observed in the ECC session than in the concentric cycling exercise sessions and its persistence during the early phase of recovery.

Clinical considerations and future directions. Although neuromuscular fatigue is a key stimulus for chronic adaptations to training (19–21), the eccentric cycling session, which led to a greater magnitude of neuromuscular fatigue

postexercise compared with the conventional concentric cycling sessions, seems to be particularly appropriate for counteracting the neuromuscular alterations characterizing patients with early breast cancer treated with chemotherapy (2,3). Moreover, ECC session is associated with greater mechanical constraints per skeletal muscle fiber compared with CON_{power} session (71), as evidenced in the present study by the lower muscle activation for a given power output in ECC session compared with CON_{power} session (Fig. 2). Interestingly, muscle hypertrophy is directly stimulated by mechanical constraint per fiber (72); therefore, eccentric exercise leads to greater development of muscle mass and force than concentric exercise (73–75). Taken together, these findings indicate that eccentric cycling is a promising exercise modality in patients with breast cancer suffering from skeletal muscle atrophy (12).

Although eccentric cycling is often associated with severe muscle damage (26,28,65), the present study showed that gradual familiarization sessions can minimize this undesirable consequence, as evidenced by very low thigh muscle pain reported by patients 24 and 48 h postexercise (2/10 on a visual analog scale). These results are supported by the findings of a previous study performed in healthy participants with muscle soreness assessed 24 and 48 h after eccentric cycling exercise (30). Familiarization sessions likely prevent systemic muscle damage given that repetitions of eccentric contractions have been shown to reduce CK activity in a subsequent session and to protect the muscle against lesions induced by the eccentric contraction mode (28). The present study revealed no change in CK or LDH activity from preexercise to 24 h postexercise in the ECC session, indicating that no major muscle damage (i.e., no systemic effect) was induced by the exercise session (76). This observation is important in the context of early breast cancer, as patients are already vulnerable (77), and this vulnerability should not be exacerbated with exercise interventions. Interestingly, we documented low to moderate ratings of perceived exertion in eccentric cycling (Table 3), which is consistent with a previous study showing less perceived effort exertion in eccentric compared with concentric cycling performed at similar power output in healthy participants (18). Moreover, the observation of no adverse events throughout the study following ECC session supported the feasibility and safety of ECC for patients with early breast cancer.

Despite the absence of systemic consequences, it is important to note that the observation of an ~17% decrease in MVC suggested local muscle damage (78). Although such stimuli may trigger muscle adaptations to training (79), this substantial decrease in MVC 24 h post-ECC also suggested caution in determining the weekly training frequency for eccentric cycling sessions in patients with early breast cancer. The next step will be to conduct a randomized controlled trial investigating the chronic effects of an eccentric versus concentric cycling training program prescribed during chemotherapy treatment in patients with breast cancer.

CONCLUSIONS

The present study conducted in patients with early breast cancer demonstrated that eccentric cycling induced greater neuromuscular fatigue than concentric cycling performed either at similar power output or at similar $\dot{V}O_2$ level. Specifically, the present findings supported central fatigue as a primary cause of the greater neuromuscular fatigue observed in eccentric cycling exercise compared with concentric cycling exercise. When matched for power output, the metabolic demand was twofold lower in eccentric compared with concentric cycling. Moreover, eccentric cycling performed after a familiarization protocol was not associated with the development of severe muscle damage in patients with early breast cancer. Taken together, eccentric cycling may be an interesting exercise modality for providing a strong neuromuscular stimulus while limiting the implication of impaired cardiorespiratory function characterizing patients with breast cancer.

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