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ORIGINAL ARTICLE

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Contralateral versus ipsilateral protective effect against muscle damage of the elbow flexors and knee extensors induced by maximal eccentric exercise

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Abstract

The present study compared the ipsilateral repeated bout effect (IL-RBE) and contralateral repeated bout effect (CL-RBE) of the elbow flexors (EF) and knee flexors (KF) for the same interval between bouts to shed light on their mechanisms. Fifty-two healthy sedentary young (20–28 years) men were randomly assigned to the IL-EF, IL-KF, CL-EF, and CL-KF groups ($n = 13$/group). Thirty maximal eccentric contractions of the EF were performed in IL-EF and CL-EF, and 60 maximal eccentric contractions of the KF were performed in IL-KF and CL-KF, with a 2-week interval between bouts. Changes in muscle damage markers such as maximal voluntary contraction (MVC) torque, muscle soreness, and plasma creatine kinase activity, and proprioception measures before to 5 days post-exercise were compared between groups. Changes in all variables were greater ($p < 0.05$) after the first than second bout for all groups, and the changes were greater ($p < 0.05$) for the EF than KF. The changes in all variables after the second bout were greater ($p < 0.05$) for the CL than IL condition for both EF and KF. The magnitude of the average protective effect was similar between CL-EF (33%) and CL-KF (32%), but slightly greater ($p < 0.05$) for IL-EF (67%) than IL-KF (61%). These demonstrate that the magnitude of CL-RBE relative to IL-RBE was similar between the EF and KF (approximately 50%), regardless of the greater muscle damage for the EF than KF. It appears that the CL-RBE is more associated with neural adaptations at cerebrum, cerebellum, interhemispheric inhibition, and coricospinal tract, but the IL-RBE is induced by additional adaptations at muscles.

KEYWORDS

creatine kinase, cross-education effect, delayed onset muscle soreness, eccentric exercise, elbow flexors, knee extensors, muscle strength, proprioception, protective effect

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1 | INTRODUCTION

The magnitude of muscle damage induced by eccentric exercise is reduced when the same exercise is repeated within several weeks in the same muscle (ipsilateral) as well as in the homologous muscle of the contralateral limb. This phenomenon is referred to as the ipsilateral repeated bout effect (IL-RBE) and contralateral repeated bout effect (CL-RBE), respectively.[1]

Our previous study[1] showed that the CL-RBE was evident when the right and left arm bouts of maximal eccentric exercise of the elbow flexors (EF) were separated by 1 day (changes in muscle damage indices were reduced by 53% on average), 1 week (55%), or 4 weeks (34%), but not within 12 h or 8 weeks. Our subsequent study[2] demonstrated that the CL-RBE was also observed for the knee flexors (KF), lasting for 1 week (48%) but not for 4 weeks. It appears that the magnitude of the CL-RBE is comparable between EF (55%) and KF (48%) for the same time interval (i.e., 1 week), but the duration of the CL-RBE is longer for EF than KF. Previous studies reported that a single bout of eccentric exercise-induced muscle damage was significantly greater for the EF than KF.[3,4] Thus, it might be that the magnitude of the CL-RBE is different between EF and KF. This warrants the comparison of the CL-RBE between EF and KF using the same interval between bouts when muscle damage was fully recovered from the initial exercise bout (e.g., 2 weeks) in the same study.

It is important to note that the aforementioned studies included the IL-RBE condition in which two bouts of 30 maximal eccentric contractions of EF[1] or 60 maximal eccentric contractions of KF[2] were performed by the same limb for the first and second bouts with a 2-week interval between bouts. However, the 2-week interval between bouts was not included in the CL-RBE conditions in those studies,[1,2] and no previous study has compared the IL-RBE and CL-RBE in the same interval between bouts. To accurately compare the magnitude of CL-RBE to IL-RBE, it is necessary to set the same interval between bouts.

The mechanisms underpinning the IL-RBE and CL-RBE are not clear, although a combination of neural adaptations, muscle–tendon complex behavior changes, extracellular matrix (ECM) structural remodeling, and modified inflammatory responses has been proposed.[5] It is interesting that the magnitude of the cross-education effect on increases in muscle strength is approximately 35% (95% CI: 20.9%–49.3%) of the ipsilateral trained limb.[6] Green and Gabrial[7] reported that the magnitude of the cross-education effect ranged from 48% to 77% (the ratio between the nontrained and trained muscle strength gain) among nonclinical populations. It is reasonable to postulate that the mechanisms of the CL-RBE are similar to those of the cross-education effect. Investigating the ratio of the magnitude of change in muscle damage markers between the CL-RBE and IL-RBE may shed light on potential mechanisms of the CL-RBE.

Impairment of proprioception affects motor control, leading to injuries during exercise or everyday life activities.[8] Some studies reported that proprioception, such as position sense (PS), was impaired following eccentric exercise that induced muscle damage.[8–11] Only three studies have investigated the IL-RBE on proprioception.[8,10,11] For example, Paschalis et al.[8] reported that changes in PS and joint reaction angle (JRA) after maximal eccentric exercise of the KF were significantly smaller and recovered faster after the second bout compared to the first bout that was performed by the same muscle 4 weeks earlier. In contrast, Da Silva et al.[11] found no significant difference in PS of knee joint between the first and second bouts of submaximal eccentric exercise of the same KF separated by 1 week. Thus, clarifying whether the repeated bout effect exists for proprioception markers is necessary. Moreover, to the best of our knowledge, no previous study has investigated the CL-RBE on PS and JRA. It is interesting to investigate if the magnitude of the RBE on the proprioception markers is different from that on other muscle damage markers, and any difference exists in the magnitude between IL-RBE and CL-RBE.

The present study therefore investigated the magnitude of the IL-RBE and CL-RBE of the EF and KF for muscle damage and proprioceptive markers, and compared the IL-RBE and CL-RBE over the same time interval between the first and second exercise bouts (i.e., 2 weeks) for each muscle, as well as between the EF and KF. We hypothesized that the magnitude of muscle damage and proprioception markers of the CL-RBE in relation to the IL-RBE would be similar between EF and KF, although the magnitude of muscle damage would be greater for EF than KF. We also hypothesized that the changes in muscle damage and proprioception markers in the CL-KF group following the second bout would be significantly smaller than the CL-EF group.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

Sedentary young men ($n = 52$) who had no musculoskeletal injuries of the upper and lower extremities were recruited for this study from the university population. Each participant provided informed consent to participate in the

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study that had been approved by the University Research Ethics Committee (Taiwan). The study was conducted in conformity with the policy statement regarding the use of human subjects by the Declaration of Helsinki. Their mean (±SD) age, height, and body mass were 21.0 ± 1.8 years, 171.6 ± 5.6 cm, and 65.5 ± 7.2 kg, respectively.

The participants were placed into one of the four groups (n = 13/group); ipsilateral elbow flexor (IL-EF), contralateral elbow flexor (CL-EF), ipsilateral knee flexor (IL-KF), and contralateral knee flexor (CL-KF) groups. Similarities in the average baseline peak maximal voluntary concentric contraction torque (MVC) of the EF or the KF between IL-EF and CL-EF, or IL-KF and CL-KF groups were taken into consideration when assigning participants to study groups.

The IL-EF and IL-KF groups performed the two bouts of maximal isokinetic (30°/s) eccentric contractions (EC1, EC2) of the EF and the KF using the nondominant arm and leg, respectively, separated by 2 weeks. Limb dominance was determined based on the arm and leg that each participant used to throw and kick a ball, respectively.[9] For the CL-EF and CL-KF groups, six or seven participants used their dominant or nondominant arm or leg for the first bout, and nondominant or dominant arm or leg for the second bout. Thus, the CL-EF and CL-KF groups performed the EC1 of the EF (CL-EF group) and KF (CL-KF group) with one limb and performed the subsequent bout using the opposite limb (EF or KF) 2 weeks later. No significant (p < 0.05) differences in age, height, body mass, and baseline MVC torque were observed between the groups.

The sample size was estimated using the data from our previous study on the CL-RBE of the EF.[1] On the basis of an expected 10% difference in MVC torque recovery at 1 day post-exercise between the ipsilateral and the contralateral arms (the effect size of 0.8), with α level of 0.05, and a power (1 − β) of 0.80, it was estimated that at least 12 participants per group were necessary (G*Power 3.1.9.2, Heinrich-Heine-Universitat Dusseldorf; http://www.gpower.hhu.de/). Thus, considering participant attrition and estimation error, 13 participants for each group were recruited in the present study.

A familiarization session was conducted 3–5 days prior to EC1, in which participants experienced the measurements of muscle soreness, range of motion (ROM), upper or lower limb circumference (CIR), muscle hardness, echo intensity of ultrasound transverse images (EI), position sense (PS), joint reaction angle to release (JRA), and performed submaximal (30%, 50%, 80%) and maximal voluntary concentric contractions (MVC) of the EF or KF. The investigator demonstrated the eccentric exercise, but no eccentric contractions of the EF and KF were performed by the participants as a few eccentric contractions could confer some protective effect.[5]

2.2 | Maximal eccentric exercise (EC)

All participants performed two bouts of maximal eccentric exercise (EC1 and EC2) on an isokinetic dynamometer (Biodex System 3 Pro; Biodex Medical Systems). Based on our previous study showing that 30 maximal eccentric contractions resulted in significantly less muscle damage for KF than EF,[3] to intend to induce similar extent of muscle damage between EF and KF, the number of eccentric contractions was doubled for the KF. Thus, EC1 and EC2 consisted of five sets of six maximal eccentric contractions for the EF but 10 sets of six maximal eccentric contractions for the KF at the angular velocity of 30°/s. In each exercise, the elbow or knee joint was forcibly extended from 90° to a fully extended position by the dynamometer, while each participant was asked to maximally resist against the elbow or knee extending motion. Participants were in a seated position for the EF exercise and in a prone position for the knee flexor exercise.[2,12] Each contraction lasted for 3 s and was repeated every 10 s, and a 2-min rest was given between sets. After each contraction, the isokinetic dynamometer passively brought the participant's limb back to the flexed position at the angular velocity of 9°/s, which provided a 10-s rest between contractions. The peak torque and work for each contraction was calculated using the Biodex Medical Systems (Biodex Medical Systems, Inc.) software. The average value from each set was used for analysis.

2.3 | Dependent variables

The dependent variables consisted of MVC torque, ROM, CIR, muscle hardness, muscle soreness, EI, plasma CK activity, PS, JRA, and index of protection. All measures except plasma CK activity were taken from the exercised limb, and blood samples for CK measures were taken from the non-exercised arm. MVC torque and ROM measures were taken immediately before, immediately after, and 1, 2, 3, 4, and 5 days following each eccentric exercise bout. Other measures were taken at all time points shown above except immediately post-exercise. The test–retest reliability of the dependent variables indicated by the coefficient of variation (CV) was shown to be smaller than 9.9% in our previous studies performed in the same laboratory and by the same investigators.[9,12,13]

2.3.1 | MVC torque

MVC torque was measured on the same isokinetic dynamometer in the same position as that described for the eccentric exercise. MVC torque was measured at the

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angular velocity of 60°/s (1.05 rad/s) for the range of motion of 140° for the EF (0°–140°, 0–2.45 rad) and elbow extensors (EE; 140°–0°) for three continuous contractions for both directions.[3] MVC torque of the KF and knee extensors (KE) was measured using the same isokinetic dynamometer in the same position as that described for the exercise, at an angular velocity of 60°/s for the range of motion of 120° for the KF (0°–120°) and the KE (120°–0°) for three continuous contractions for both directions.[9,12] The EE and KE MVC torque measures were included to examine the effect of the eccentric exercise on antagonist muscles. Verbal encouragement was provided during each test. The highest value of the three trials of each test were used for analysis.

2.3.2 | Range of motion

The range of motion (ROM) of the elbow or knee joint was determined as the difference in the joint angles between maximal voluntarily flexion (FANG) and extension (EANG) measured using a manual goniometer.[1–3] Briefly, for the knee joint ROM measurement, FANG was measured when the participant attempted to flex the knee joint to touch the heel to the hip, and EANG was determined when the participant attempted to extend the knee joint as much as possible while keeping the involved leg in parallel with the opposing leg in a standing position. Regarding the elbow joint ROM, FANG were measured as the participant attempted to flex the elbow joint to touch the shoulder, and EANG were determined when the participant attempted to fully extend the elbow joint. Three measurements were taken for FANG and EANG, and the mean value of each was used to calculate ROM.

2.3.3 | Limb circumference

The circumference of the upper arm was measured at the midportion of the upper arm between the acromion process of the clavicle and the lateral epicondyle of the humerus with the participant in standing position, the arm relaxed at the side, using a Gulick tape measure.[3] Upper thigh circumference was measured midway between the trochanterion (top of the femur) and tibiale laterale (top of the tibia).[3] The measurements were taken three times by the same investigator and the mean of the three measures was used for statistical analysis.[3]

2.3.4 | Muscle hardness

As increased muscle hardness (or muscle stiffness) is also one of the indirect markers of muscle damage,[14] muscle hardness was measured using a tissue hardness algometer (OE-220, Ito Co. Ltd.) at the midportion of the biceps brachii or the long head of biceps femoris. The biceps brachii muscle hardness was measured as each participant lay supine with the testing arm was extended and relaxed on an exam table.[12] The biceps femoris muscle hardness was measured as each participant lay prone with the testing leg extended and relaxed on an exam table.[3] The algometer quantified the amount of tissue displacement applied by the probe onto the site. Three measures were taken and the mean value was used for further analysis.[12]

2.3.5 | Muscle soreness

Muscle soreness of the EF or KF of the exercised limb was quantified using a visual analog scale (VAS) that had a 100-mm continuous line with "not sore at all" on one side (0-mm) and "very, very sore" on the other side (100-mm). The participant was asked to rate their perceived soreness on the VAS scale as the muscles were passively extended through the same ROM that was used for the MVC measures.[1,12]

2.3.6 | Echo intensity

According to our previous studies,[1,3] ultrasound images of the exercised muscles were taken using a Ultrasound System with a 7.5-MHz linear probe (Terason Co.). The probe was placed at the midway of the biceps brachii or the long head of biceps femoris as described previously for the limb circumference measurements. Participants were seated in a chair with the forearm on a padded table at the shoulder angle of 80° and an elbow joint angle of 170° for EF measures. For KF measures, participants lay prone with the hip, knee, and ankle joint angles of 0° (i.e., neutral position). Transverse images were obtained from the same sites over time, and all images were saved in a computer (HP Workstation xw4400). The saved images were analyzed with image analysis software (ULT File Reader for Windows, Broadsound Co.), and the mean echo intensity (EI) of a histogram of gray scale (0: black, 256: white) was calculated for a region of interest (ROI: $2 \times 2 = 4\,cm^2$) that was set approximately 5 mm adjacent to the humerus for the biceps brachii and the long head of biceps femoris. The relative change in the echo intensity from the pre-exercise value was calculated.

2.3.7 | Plasma CK activity

A 5-ml venous blood sample was withdrawn by standard venipuncture technique from the cubital fossa region of

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the non-exercised arm and centrifuged for 10 min to extract plasma. Plasma samples were stored at −80°C until analyses. Plasma CK activity was assayed spectrophotometrically by an automated clinical chemistry analyzer (Model 7080, Hitachi, Co. Ltd.) using a commercially available test kit.[9]

2.3.8 | Position sense and joint reaction angle

Position sense (PS) and joint reaction angle (JRA) measures from our previous studies were employed in the current investigation.[9,15] Each participant was seated and blindfolded for both PS and JRA testing in the same position used for the MVC torque measures on the isokinetic dynamometer. For PS, the investigator positioned the testing arm and leg of each participant to 45° (0.78 rad), maintained position for 10 s, and returned it passively to a full elbow or knee extension (0° = 0 rad) respectively. The participant was then instructed to stop the elbow or knee flexion movement at 20°/s by pressing a stop button with the hand of the opposite limb at the perceived target angle. Regarding JRA, the tested arm and leg of the participant was passively moved by the investigator from 90° (0.79 rad) elbow and knee flexion to a target angle (i.e., 45°) slowly (approximately 20°/s), then the tested arm and leg was stopped and fully relaxed at a target angle for 5–10 s, when it reached the target angle shown on the computer screen, the investigator would then suddenly release the lever arm without warning. The participant was instructed to stop the lever arm as soon as they could after the investigator released the lever arm. The difference between the target angle and the actual angle (PS) or the angle at stopping (JRA) was recorded, respectively. The time between trials for each test was 10 s, and 3-min of rest were provided between PS and JRA measurements. The difference from the target angle value was the mean value of the two closest to the reference angle among four trials, and this value was used for analysis.

2.4 | Index of protection

Based on our previous studies[2,12] showing that 2 days post-exercise time point or peak changes reflected the magnitude of the repeated bout effect better, and the magnitude of the protective effect (index of protection) was calculated using the values at 2 days post-exercise for MVC torque and ROM, and peak values for other measures by the following equation: (EC1 − EC2)/EC1 × 100.[2] For example, if the responses were the same between EC1 and EC2, it was considered as no protection (the index is 0%), and an index of 50% would show that the changes in the dependent variables were 50% smaller after EC2 than EC1.

2.5 | Statistical analyses

A Shapiro–Wilk test was used to check the normality assumption of the data, which demonstrated that normality assumption was met for all variables in the present study. All dependent variables before each exercise bout were compared between the groups by a one-way analysis of variance (ANOVA). Changes in peak torque and work during each EC were also compared between the groups (i.e., IL-EF vs. CL-EF, IL-KF vs. CL-KF) over sets using a mixed-design of two-way ANOVA. Changes in the dependent variables over time were compared between EC1 and EC2 by a mixed-design using two-way ANOVA for IL-EF versus CL-EF, and IL-KF versus CL-KF groups, respectively. When ANOVA found a significant interaction effect, a Tukey's post-hoc test was performed. The magnitude of repeated bout effect among the IL-EF, CL-EF, IL-KF, and CL-KF groups were compared by a one-way ANOVA, and followed by a Tukey's post-hoc test. The magnitude of repeated bout effect between the ipsilateral (i.e., IL-EF and IL-KF) and contralateral (i.e., CL-EF and CL-KF) groups were compared by a *t*-test. Eta-squared (η^2) values were calculated as measures of effect size, and ~0.02 was considered a small effect, ~0.13 a medium effect, and >0.26 as a large effect.[16] The data are presented as mean ± standard deviation (SD), unless otherwise stated. Statistical significance was set at $p \leq 0.05$.

3 | RESULTS

3.1 | Baseline measurements

No significant differences ($p > 0.05$) in the baseline values of any of the dependent variables existed between the IL-EF and CL-EF, and IL-KF and CL-KF groups before EC1 and EC2 (Table 1). When comparing EF and KF, MVC, ROM, and CIR before EC1 were significantly ($p < 0.05$) smaller in EF (IL-EF and CL-EF) than KF (IL-KF and CL-KF), but EI, muscle hardness, PS, and JRA were significantly ($p < 0.05$) greater for EF than KF.

3.2 | Exercise

The average peak torque (PT) and total work (TW) generated during exercise was similar ($p > 0.05$) between EC1 and EC2 for the IL-EF (EC1: PT: 42.1 ± 7.4 Nm, TW: 1411 ± 381 J; EC2: PT: 36.8 ± 7.8 Nm, TW: 1453 ± 315 J) and

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TABLE 1 Baseline values (means ± SD) before the first (EC1) and second (EC2) bouts of maximal eccentric exercise of the elbow flexors (EF) or the knee flexors (KF) for the ipsilateral (IL-EF, IL-KF) and contralateral (CL-EF, CL-KF) groups for maximal voluntary concentric (MVC) torque of the elbow or knee flexors (MVC-flex) and extensors (MVC-ext), range of motion (ROM) of the elbow or knee joint, upper arm or upper thigh circumference (CIR), muscle soreness (SOR) assessed by the 100-mm visual analog scale, muscle hardness assessed by an algometer, plasma creatine kinase (CK) activity, ultrasound echo intensity of biceps brachii and brachialis, or long head of biceps femoris in transverse images (EI), position sense (PS), and joint reaction angle (JRA).

Variable	Bout	IL-EF	CL-EF	IL-KF	CL-KF
MVC-flex (Nm)	EC1	33.9 ± 4.6	32.8 ± 3.6	71.4 ± 14.2	70.5 ± 12.1
	EC2	34.0 ± 5.2	33.1 ± 5.4	72.8 ± 13.1	71.1 ± 13.1
MVC-ext (Nm)	EC1	32.5 ± 4.3	31.9 ± 2.6	127.3 ± 13.7	124.3 ± 14.8
	EC2	33.0 ± 4.5	31.6 ± 2.0	126.5 ± 13.5	128.7 ± 17.5
ROM (^{o})	EC1	147.3 ± 5.2	145.7 ± 3.8	112.7 ± 3.6	112.2 ± 4.5
	EC2	146.8 ± 5.5	145.2 ± 4.2	112.4 ± 3.3	112.3 ± 4.0
CIR (mm)	EC1	260.8 ± 24.9	259.2 ± 16.9	494.3 ± 30.0	493.2 ± 35.0
	EC2	260.4 ± 24.9	260.3 ± 15.7	495.0 ± 29.2	493.6 ± 34.8
SOR (mm)	EC1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	EC2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Hardness (N/cm^2)	EC1	51.2 ± 4.3	50.4 ± 1.8	35.9 ± 4.8	38.4 ± 4.2
	EC2	50.7 ± 3.6	50.3 ± 2.8	37.3 ± 6.5	37.1 ± 4.7
CK (IU/L)	EC1	122.8 ± 9.8	128.2 ± 9.7	123.9 ± 7.1	122.6 ± 14.0
	EC2	124.9 ± 10.7	131.6 ± 10.8	125.0 ± 13.7	125.4 ± 18.6
EI (A.U.)	EC1	102.1 ± 20.7	109.2 ± 12.2	77.3 ± 7.4	79.7 ± 9.5
	EC2	106.4 ± 113.7	114.8 ± 14.0	77.1 ± 6.2	83.4 ± 6.5
PS (^{o})	EC1	46.5 ± 1.9	47.7 ± 1.7	50.1 ± 2.8	49.0 ± 2.8
	EC2	46.3 ± 1.5	46.9 ± 2.8	48.9 ± 2.8	48.0 ± 2.4
JRA (^{o})	EC1	39.5 ± 2.1	39.2 ± 1.7	37.1 ± 2.7	35.8 ± 2.2
	EC2	41.7 ± 1.4	39.9 ± 1.5	37.5 ± 2.4	36.2 ± 2.4

Note: No significant ($p > 0.05$) difference was evident for all variables between EC1 and EC2 for IL-EF and CL-EF, or IL-KF and CL-KF, and between IL-EF and CL-EF as well as IL-KF and CL-KF.

the CL-EF (EC1: PT: 40.1 ± 5.8 Nm, TW: 1350 ± 211 J; EC2: PT: 39.6 ± 4.6 Nm, TW: 1302 ± 224 J), as well as the IL-KF (EC1: PT: 71.5 ± 14.3 Nm, TW: 4754 ± 730 J; EC2: PT: 74.4 ± 11.5 Nm, TW: 4957 ± 863 J) and CL-KF (EC1: PT: 69.7 ± 19.1 Nm, TW: 4576 ± 955 J; EC2: PT: 69.6 ± 21.0 Nm, TW: 4875 ± 1104 J). However, the average PT and TW produced during EC1 and EC2 was significantly ($p < 0.05$) smaller for the IL-EF and CL-EF groups compared to IL-KF and CL-KF groups.

3.3 | Changes in the dependent variables after EC1 and EC2

3.3.1 | EF

All variables changed significantly ($p < 0.05$) after EC1 and EC2 for the IL-EF and CL-EF groups, but the extent of changes in all variables after EC2 was significantly (interaction effect: $p < 0.05$) smaller than that of EC1 for both groups (Figures 1 and 2 and Table 2). The changes in all variables after EC2 were significantly (interaction effect: $p < 0.05$) smaller for the IL-EF than CL-EF group, although the changes after EC1 were not different between groups (Figures 1 and 2 and Table 2).

3.3.2 | KF

Similar to EF, both IL-KF and CL-KF groups showed significant ($p < 0.05$) changes in all variables after EC1 and EC2, and the changes were significantly ($p < 0.05$) smaller after EC2 than EC1 without difference (interaction effect: $p > 0.05$) between IL-KF and CL-KF groups for EC1 (Figures 1 and 2 and Table 2). The changes in all variables after EC2 for IL-EF was significantly (interaction effect: $p < 0.05$) smaller than CL-EF (Figures 1 and 2 and Table 2).

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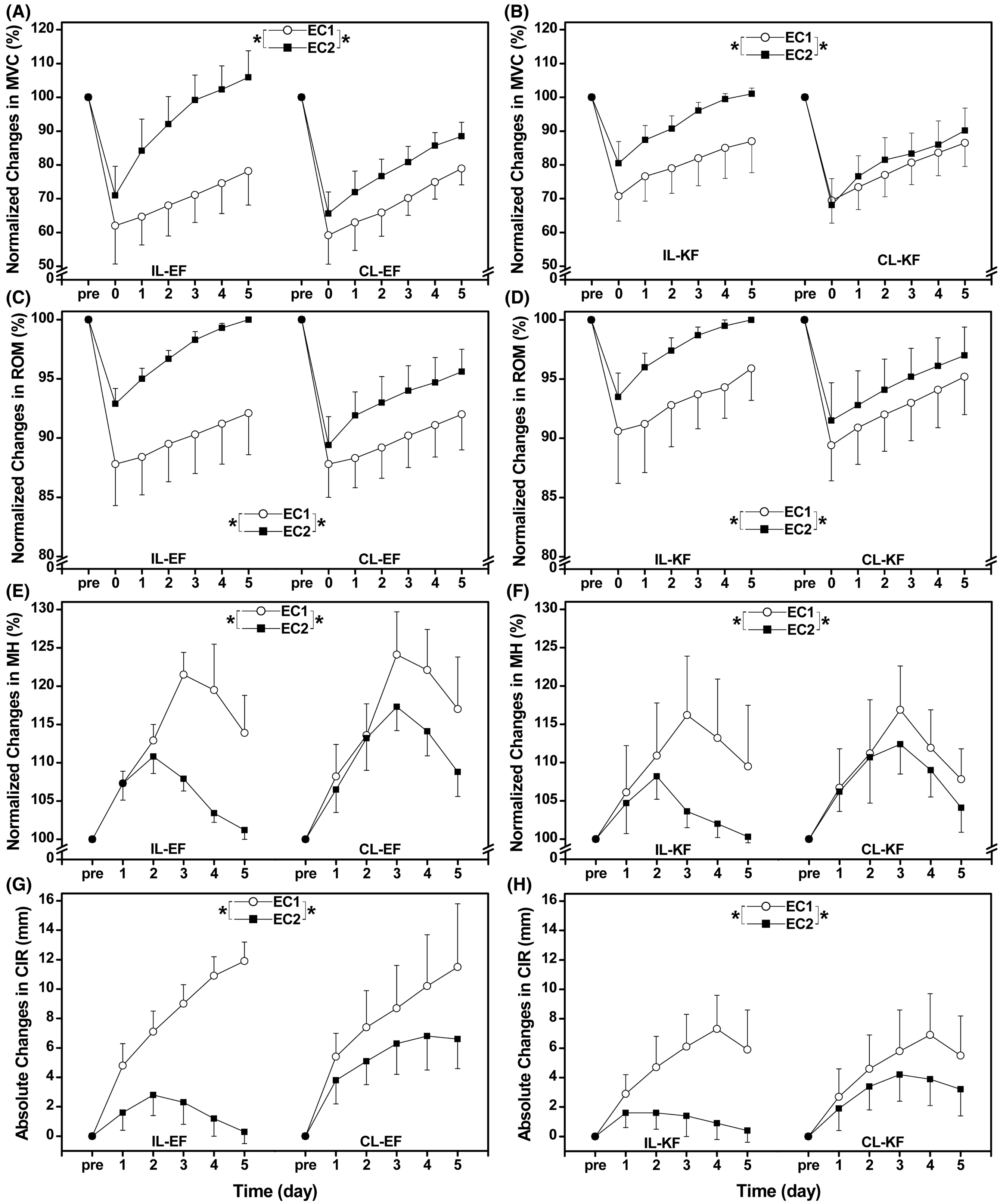

FIGURE 1 Normalized changes (means ± SD) in maximal concentric contraction (MVC) torque (A, B), range of motion (ROM; C, D), and muscle hardness (MH; E, F), and absolute changes in upper limb circumference (CIR; G, H) before (pre), immediately after (0), and 1, 2, 3, 4, and 5 days after the first (EC1) and second bouts (EC2) of maximal eccentric contractions of the elbow flexors (EF: A, C, E, G) and knee flexors (KF: B, D, F, H) performed by the ipsilateral limb (IL-EF, IL-KF) and contralateral limb (CL-EF, CL-KF). *Indicates a significant ($p < 0.05$) interaction effect by mixed design two-way ANOVA.

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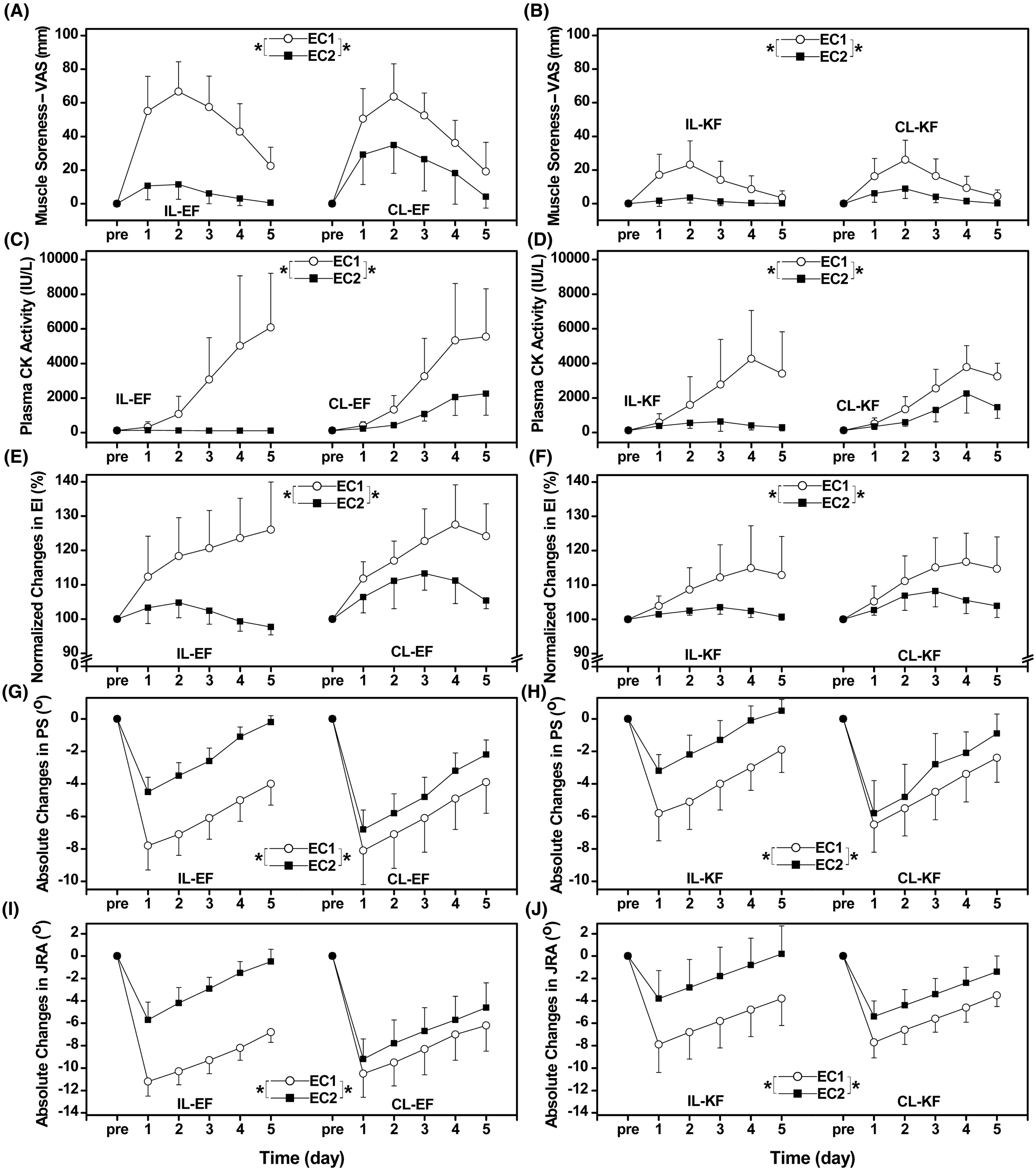

FIGURE 2 Changes (means ± SD) in muscle soreness (A, B) and plasma creatine kinase (CK) activity (C, D), normalized changes in echo intensity (EI) of B-mode ultrasound transverse images (E, F), and absolute changes in position sense (PS; G, H) and joint reaction angle to release (JRA) from the pre-exercise value (I, J) before (pre), and 1, 2, 3, 4, and 5 days after the first (EC1) and second (EC2) bouts of maximal eccentric contractions of the elbow (EF: A, C, E, G, I) and knee flexors (KF: B, D, F, H, J) performed by the ipsilateral limb (IL-EF, IL-KF) and contralateral limb (CL-EF, CL-KF). *Indicates a significant ($p < 0.05$) interaction effect by mixed design two-way ANOVA.

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TABLE 2 Summary results of mixed design two-way analysis of variance (F, p, and η^2 values) for comparison between the ipsilateral and contralateral repeated bout groups of the elbow flexors (IL-EF vs. CL-EF) or the knee flexors (IL-KF vs. CL-KF) for changes in maximal voluntary concentric contraction torque (MVC), range of motion (ROM), limb circumference (CIR), muscle hardness (Hardness), muscle soreness (SOR), plasma creatine kinase activity (CK), echo intensity of the ultrasound transverse images (EI), position sense (PS), and joint reaction angle (JRA) before, immediately after, and 1–5 days after the first (EC1) and second (EC2) maximal eccentric exercise bout.

	EC1			EC2		
IL-EF versus CL-EF						
MVC	F=0.333	p=0.918	η^2=0.014	F=16.907	p<0.001	η^2=0.413
ROM	F=0.019	p=0.956	η^2=0.001	F=20.279	p<0.001	η^2=0.458
CIR	F=0.832	p=0.529	η^2=0.034	F=38.986	p<0.001	η^2=0.619
Hardness	F=0.853	p=0.515	η^2=0.034	F=44.207	p<0.001	η^2=0.648
SOR	F=0.351	p=0.881	η^2=0.014	F=8.739	p<0.001	η^2=0.267
CK	F=0.223	pp=0.952	η^2=0.009	F=30.820	p<0.001	η^2=0.562
EI	F=0.818	p=0.539	η^2=0.033	F=10.789	p<0.001	η^2=0.310
PS	F=0.128	p=0.986	η^2=0.005	F=20.094	p<0001.	η^2=0.456
JRA	F=1.697	p=0.140	η^2=0.066	F=25.780	p<0.001	η^2=0.518
IL-KF versus CL-KF						
MVC	F=1.605	p=0.096	η^2=0.114	F=11.653	p<0.001	η^2=0.327
ROM	F=0.446	p=0.847	η^2=0.018	F=10.003	p<0.001	η^2=0.294
CIR	F=0.114	p=0.989	η^2=0.005	F=17.165	p<0.001	η^2=0.417
Hardness	F=0.376	p=0.864	η^2=0.015	F=15.575	p<0.001	η^2=0.394
SOR	F=0.353	p=0.879	η^2=0.015	F=4.155	p=0.002	η^2=0.148
CK	F=0.177	p=0.971	η^2=0.007	F=21.320	p<0.001	η^2=0.470
EI	F=0.259	p=0.035	η^2=0.011	F=4.954	p<0.001	η^2=0.171
PS	F=0.578	p=0.717	η^2=0.024	F=7.824	p<0.001	η^2=0.246
JRA	F=0.149	p=0.980	η^2=0.006	F=3.800	p=0.003	η^2=0.137

Abbreviations: F, F-value; p, p-value; η^2, eta-squared.

3.3.3 | EF versus KF

As shown in Figures 1 and 2, the extent of changes in all variables except muscle soreness after EC1 and EC2 were significantly smaller (interaction effect: $p<0.05$) for KF (IL-KF and CL-KF) than EF (IL-EF and CL-EF). Muscle soreness following EC2 was not significantly different ($p=0.244$, $\eta^2=0.054$) between IL-EF and CL-KF (Figure 2A,B).

3.3.4 | IL versus CL

As shown in Figure 3, the average index of protection of all nine variables was significantly greater ($p\leq0.001$) for IL-EF (67±3%) than other three groups (CL-EF, IL-KF, and CL-KF). IL-KF (61±6%) was greater ($p<0.001$) than both CL-EF (33±6%) and CL-KF (32±6%), without a significant ($p=0.428$) difference between CL-EF and CL-KF. When pooling the results of the ipsilateral (IL-EF and IL-KF) groups and the contralateral (CL-EF and CL-KF) groups, the average index of protection of all nine variables in the ipsilateral condition was 64±6%, which was significantly ($p\leq0.001$) greater than that of the contralateral condition (32±6%).

4 | DISCUSSION

The current study compared the IL-RBE and CL-RBE in the upper and lower limbs over the same time interval between bouts (i.e., 2 weeks) to test the hypothesis that the magnitude of the CL-RBE and IL-RBE would be similar between EF and KF, although the changes in muscle damage and proprioception markers following the first and second eccentric exercise bouts would be significantly smaller for KF than EF. The results showed that changes in all variables following the first eccentric exercise and all variables except for muscle soreness following the second bout were significantly smaller for KF than EF in both IL and CL conditions (Figures 1 and 2). In addition, the index of protection was similar between EF and KF, and the magnitude of CL-RBE relative to IL-RBE was approximately 50% for both EF and KF (Figure 3). These results appeared to be in line with the hypothesis.

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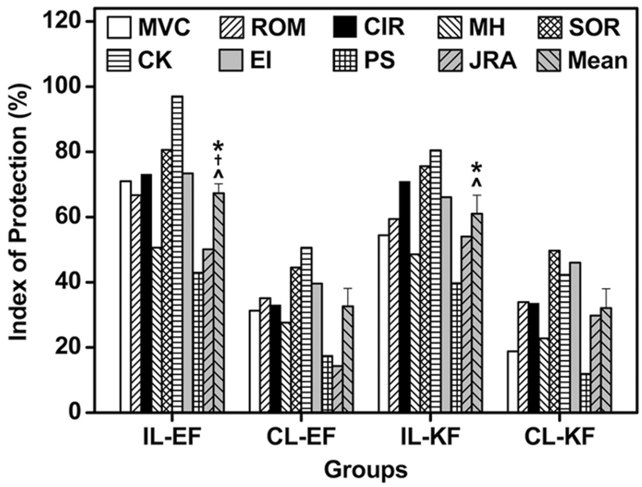

FIGURE 3 Index of protection for maximal voluntary concentric contraction (MVC) torque of the elbow (EF) and knee flexors (KF), range of motion (ROM), upper limb circumference (CIR), muscle hardness (MH), muscle soreness (SOR), plasma creatine kinase (CK) activity, echo intensity of B-mode ultrasound transverse images (EI), position sense (PS), and joint reaction angle to release (JRA), and the average and standard deviation of the nine variables (mean) for the ipsilateral (IL-RBE) and contralateral repeated bout effect (CL-RBE) groups of the elbow (IL-EF, CL-EF) and knee flexors (IL-KF, CL-KF). The index was based on the comparison to the changes after the bout of their own the first bout of maximal eccentric exercise (EC1), which was calculated by the formula; (Change in the first exercise bout condition of each own group − Change in IL-EF/KF or CL-EF/KF group)/(Change in the first exercise bout for each group) × 100%. The "Change" in the formula refers to the magnitude of the change from the baseline at two days post-exercise for MVC and ROM, maximal change from the baseline for CIR, MH, SOR, CK, EI, PS, and JRA. *Significant ($p < 0.05$) difference from the CL-EF group by a t-test. †Significant ($p < 0.05$) difference from the IL-KF group by a t-test. ^Significant ($p < 0.05$) difference from the CL-KF group by a t-test.

In the current study, changes in the dependent variables following the first bout of maximal eccentric contractions of the EF and KF (Figures 1 and 2) were similar to those reported in previous studies.[2,9,13] For the current study participants, baseline values (Table 1) and their changes after the first exercise bout (Table 2 and Figures 1 and 2) were similar between IL and CL conditions for both EF and KF. In addition, average peak torque and total work for the first and second eccentric exercise bouts were consistent for the EF as well as the KF groups. Changes in all variables were smaller after the second exercise bout when compared to the first bout for all groups (Figures 1 and 2 and Table 2), thus demonstrating the repeated bout effect.

Previous research has shown that the extent of muscle damage after unaccustomed eccentric exercise is greater for the EF than KF.[3,4] In the present study, changes in muscle damage and proprioception markers after the first eccentric exercise bout were also greater for the EF than KF (Figures 1 and 2). Muscles involved in knee flexion have relatively larger pennation angle when compared to the biceps brachii and brachialis.[17,18] Muscle size and muscle fiber type composition may also influence the susceptibility to muscle damage.[18–20] It has been shown that Type II fibers are more susceptible to eccentric exercise-induced muscle damage than Type I fibers.[20] Johnson et al.[21] reported that biceps brachii (Type I: 46%, Type II: 54%) consisted of more Type II fibers than biceps femoris (Type I: 67%, Type II: 33%). Importantly, no previous study has compared EF and KF eccentric exercise for the magnitude of the repeated bout effect in the same study. How muscles are used in daily activities, differences in muscle length changes during the eccentric contractions, muscle architecture, muscle size, and fiber type composition may all contribute to the observed differences between EF and KF.

It has been shown that eccentric contractions in one limb can result in a repeated bout effect in the contralateral limb (i.e., CL-RBE), and this phenomenon occurs in the arms and in the legs.[1,2] The current study was the first to examine the IL-RBE and CL-RBE in the upper and lower limbs over the same time interval between eccentric exercise bouts (i.e., 2 weeks). The magnitude of the RBE was greater in the IL than the CL condition as demonstrated by the larger index of protection for the IL-EF (67%) and IL-KF (61%), when compared with the CL-EF (33%) and CL-KF (32%) for both EF and KF (Figure 3). This level of index of protection for IL-RBE in the present study was similar to that of previous studies in which the IL-RBE was investigated for the EF[1,13] and KF[2] with a 2-week interval between bouts.

The mechanisms underpinning the CL-RBE have not been clearly elucidated, nevertheless we postulate that CL-RBE may be largely a function of acute neural adaptations similar to those seen in the cross-education effect. Cross-education is a phenomenon where an increase in the strength of the contralateral (untrained) limb is increased following training in the ipsilateral (trained) limb.[6,22,23] Frazers et al.[24] described that the potential sites of adaptations in the cross-education included changes in brains (supplementary motor area, primary motor cortex, middle temporal gyrus, interior temporal gyrus, occipital lobe, and cerebellum), interhemispheric inhibition, spinal cord, motoneuron, and muscles. The cross-education effect on improved strength is most likely due to neural adaptations[22–25] and the motor cortex is a primary site of the adaptations.[24,25] It is possible that the cross-education of muscular strength is induced by changes within cortical motor and non-motor regions, including increased corticospinal excitability, reduced cortical inhibition, reduced interhemispheric inhibition, and changes in voluntary activation.[24–26]

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Tsuchiya et al.[27] compared muscle fiber activation between the first and second bout of eccentric exercise of the EF performed by the ipsilateral arm or contralateral arm using transverse relaxation time (T2) of magnetic resonance imaging (MRI). They reported that the T2 immediately after the second exercise bout was longer for the ipsilateral (+20.3%) and contralateral (+20.5%) conditions when compared with the first bout (+11.8%), suggesting an increase in muscle fiber activation in the IL-RBE and CL-RBE. In addition, Kidgell et al.[26] have shown that eccentric exercise training modulated corticospinal excitability and inhibition of the untrained limb to a greater extent than concentric training. Others reported acute neural responses to eccentric contractions that support neural modifications that could contribute to the CL-RBE.[28,29] Current evidence suggests that spinal and supraspinal neural mechanisms primarily account for the CL-RBE. Thus, it may be that a single bout of eccentric exercise with one limb acutely modulates neural output (i.e., agonist/antagonist activation, motor unit recruitment properties) to the opposite limb which attenuates the magnitude of muscle damage following subsequent bouts of eccentric contractions (i.e., CL-RBE) and then with repeated stimuli over time (i.e., resistance training) the cross-education effect can result in increased strength of the contralateral homologous muscle.

It should be noted that other factors may contribute to the CL-RBE. Koltzenburg et al.[30] proposed that the contralateral effect may mediated by circulating factors such as breakdown products from the damaged nerve or denervated tissue that could induce changes in contralateral neuronal system. Hardee et al.[31] reported that repeated bouts of eccentric exercise could attenuate systematic effect of interleukin-6 (IL-6) in an animal model. Hyldahl et al.[5] have stated that alteration to biochemical signaling and/or immune responses of systemic effect is one of potential contributing factors of the CL-RBE. It has also been shown that brain cytokines (e.g., interleukin-1β) increase after downhill running in animal studies.[32,33] These suggest that inflammatory responses could also induce the systemic effects and affect central nervous system. It may be that the first eccentric exercise bout induced such systemic responses sufficient to attenuate muscle damage induced by the subsequent bout performed by the same and opposite limbs.

As the magnitude of the CL-RBE was approximately 50% of that of the IL-RBE, it may be that the IL-RBE and CL-RBE share the similar neural mechanisms, but IL-RBE has additional peripheral responses contributing to the 50% greater protective effect. For example, changes in muscle mechanical properties such as passive muscle stiffness and remodeling of the intermediate filament system,[34] and structural remodeling of the ECM such as tenascin C are likely associated with the IL-RBE.[5] Sidky et al.[35] reported that the three to six bouts of 50 maximal eccentric contractions of in vivo model significantly increased dystrophin (136%), β-sarcoglycan (40%), and junctophilin (65%) in the anterior crural muscles of C57BL/6 female mice, and attenuated the decrease in post-exercise isometric torque by 15%–24%. It is likely that peripheral adaptations such as these may contribute to the IL-RBE, leading to the greater magnitude of IL-RBE to CL-RBE.

Previous studies reported that PS and JRA were impaired after an acute bout of eccentric exercise of the EF or KF, and participants placed (i.e., PS) or stopped (i.e., JRA) the elbow or knee joint at a more extended position.[4,8,9] To the best of our knowledge, this was the first study to investigate the CL-RBE on proprioceptive markers (i.e., PS and JRA). Changes in PS and JRA after the second exercise bout were significantly smaller than those after the first bout for both IL-RBE and CL-RBE conditions (Figures 1 and 2). The index of protection was smaller for the CL-RBE than IL-RBE condition for both EF (PS: 17% vs. 43%, JRA: 14% vs. 50%) and KF (PS: 12% vs. 40%, JRA: 30% vs. 54%) as shown in Figure 3. However, the magnitude of CL-RBE relative to IL-RBE of both EF (PS: 41%, JRA: 29%) and KF (PS: 29%, JRS: 55%) was not largely different from that of other measures (Figure 3). This may suggest that the mechanisms of the repeated bout effect on proprioception are not different from those on other measures. Paschalis et al.[8] speculated that the proprioceptors (such as muscle spindles and tendon organs) detected stimuli generated by not only muscle itself but also exteroceptors such as cutaneous receptors like Ruffni endings.[36] Muscle spindles contribute to position sense and movement of the limbs,[37] and the rise in passive tension after eccentric exercise can mechanically unload muscle spindles.[38] Unloading of muscle spindles can lower their passive discharge rates leading participants to lengthen their muscles more by extending the elbow and knee joints.[39] Given the fact that eccentric exercise increased muscle circumference and passive stiffness/hardness (Figure 1E–H), these may increase the sensitivity of the receptors, which may have led the participants to adopt a more extended position. It is interesting that these affect the contralateral limb, although the magnitude of the effect is less when compared to the effects on the ipsilateral limb.

The current study is limited in that only young sedentary healthy men were used as participants, hence it is not known whether the results of the current investigation are applicable for other populations (e.g., women, elderly). In addition, it is well established that muscle damage responses to eccentric contractions are different among elbow and knee flexors and extensors (arm and leg) muscles.[3] However, the current investigation only focused on

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the elbow and knee flexors, thus the current results may not be generalizable to other muscles (e.g., knee extensors, plantar flexors). Lastly, the current investigation was descriptive in nature. A more mechanistic design (e.g., transcranial magnetic stimulation, muscle biopsies, measures of protein regulation, measures of systematic responses, and/or inflammatory response) in future studies may elucidate the mechanisms underpinning the CL-RBE and IL-RBE.

In conclusion, the results of the present study better demonstrated that the magnitude of CL-RBE relative to IL-RBE was similar between the EF and KF (approximately 50%), although muscle damage was significantly greater for the EF than KF for both bouts. Further studies investigating the mechanisms underpinning the CL-RBE and IL-RBE are warranted.

5 | PERSPECTIVE

Muscle mass and function decline after a period of inactivity such as immobilization due to an injury. Exercise of the immobilized muscle after recovery that involves eccentric contractions would likely induce DOMS.[12] The discomfort of DOMS may discourage an individual from adhering to a rehabilitative exercise program. The current study better demonstrated that peak DOMS was reduced by approximately 50% when the contralateral limb muscle performed the same eccentric exercise at 2 weeks after the initial exercise performed by the opposite limb (Figure 3). As immobilization makes muscle more susceptible to eccentric exercise-induced muscle damage and impaired proprioception,[12] it is a good strategy to perform eccentric exercise of the non-immobilized limb first before performing eccentric exercise of the immobilized limb. We have shown that ipsilateral exercise has a positive effect on the contralateral limb and may serve as a potential therapeutic intervention for offsetting the effects of unilateral inactivity. Indeed, unilateral eccentric exercise training of the non-immobilized arm prevented muscle strength decreases in the immobilized arm demonstrating a cross-education effect.[12,23] The remarkable cross-education effect associated with eccentric contractions may serve as useful tool in an orthopedic rehabilitation strategy.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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