Effects of resistance training at different intensities of load on cross-education of muscle strength

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Effects of resistance training at different intensities of load on cross-education of muscle strength

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Draft

Abstract

The objectives of this study were 1) to compare the extent of cross-transfer of high- versus low-load unilateral resistance training performed with external pacing of the movement (URTEP) and 2) to compare the time course of the two approaches. Fifty subjects were randomized to one of the following three groups: G80 [two sets at 80% and two sets at 40% of one maximum repetition (1RM), 1 concentric second and 3 eccentric seconds controlled by a metronome]; G40 (four sets at 40% of 1 RM, 1s and 3s controlled by a metronome); or CG (control group). At week 1, the G80 increased the elbow flexion 1RM ($P<0.05$) in contralateral arm. At week 4, both G80 and G40 increased the elbow flexion 1RM ($P<0.05$) in contralateral arm. However, a greater 1RM gain was observed in the G80 than in the G40 ($P<.05$). Thus, although higher-load URTEP seems to enhance the cross-education effect when compared to lower-load URTEP, the cross-education of dynamic strength can be achieved in the two approaches after four weeks. Many patients would benefit from cross-education of muscle strength through URTEP, even who are unable to exercise with high loads and in short periods of immobilization.

Keywords: Contralateral adaptations; Unilateral strength training; electromyography; Cross-Education; Cross-transfer; Strength training

Novelty bullets: (1) Unilateral resistance training promotes cross-education of dynamic muscle strength. (2) However, higher-load resistance training enhances the effects of cross-education of muscle strength.

INTRODUCTION

Cross-education or the cross-transfer effect is a neural adaptation that occur in untrained homologous and contralateral muscles after unilateral training, increasing the strength of the untrained muscles (Frazer et al. 2018; Ruddy and Carson 2013). Adaptations in cortical motor and non-motor regions, altering the neural drive to the contralateral muscles have been implicated in the underlying mechanisms of cross-education (Frazer et al. 2018; Ruddy and Carson 2013). Unilateral resistance training has been considered an effective strategy to promote cross-education of muscle strength (Colomer-Poveda et al. 2019; Frazer et al. 2018; Manca et al. 2017). Interestingly, a great variation in training stimuli (i.e. type, load, contraction type, and external pacing and velocity of movement) and magnitude of the cross-education effect on muscle strength has been reported (Colomer-Poveda et al. 2019; Frazer et al. 2018; Green and Gabriel 2018). Particularly, augmentation of activity in the ipsilateral and contralateral primary motor cortex, accompanied by elevation in the excitability of corticospinal output projections is observed in unilateral tasks that demand maximal levels of motor output (Hendy et al. 2017; Perez and Cohen 2008; Ruddy and Carson 2013). Indeed, Othman et al showed that low-load unilateral resistance training may be inadequate to induce an increase in contralateral muscle strength, particularly in elbow flexion (Ben Othman et al. 2018). For this reason, unilateral resistance training has preferably been performed with a higher intensity of load (> 50% of maximum muscle strength) to promote cross-education of muscle strength (Carroll et al. 2006; Cirer-Sastre et al. 2017; Colomer-Poveda et al. 2019). In this regard, many patients are unable to perform an exercise with high loads [(e.g., osteoarthritis, patellofemoral pain, stroke, hypertension (Frazer et al. 2018; Giles et al. 2017; Ruddy and Carson 2013; Sharman et al. 2015)] and, therefore, would not benefit from unilateral resistance training due to the need for high loads.

On the other hand, it has been shown that unilateral movement repetition in the absence of skill acquisition, even with higher intensity of load, may be inadequate to induce changes in ipsilateral corticospinal excitability (Leung et al. 2015) and contralateral muscle strength (Munn et al. 2005). Therefore, learning appears to be a necessary step to drive neuroplastic changes in the cortical regions, promoting cross-education of muscle strength (Leung et al. 2015; Ruddy and Carson 2013). In this sense, results from recent studies have shown that dynamic eccentric, when compared to dynamic concentric or static unilateral voluntary muscle contractions (Colomer-Poveda et al. 2019; Howatson et al. 2011; Uematsu et al. 2010), and externally paced movements (Colomer-Poveda et al. 2019; Leung et al. 2015, 2018) leading to greater increases in the excitability of the ipsilateral primary motor cortex and reductions in short-interval intracortical inhibition after both, acute and chronic unilateral resistance training. Therefore, if dynamic eccentric contraction and externally paced movements lead to greater activation of the ipsilateral brain areas, following the cross-activation model it is possible that dynamic low-load unilateral resistance training with external pacing of the movement (controlling eccentric contraction) could serve as a training stimulus for ipsilateral cortex adaptations and promote an increase in contralateral muscle strength.

Neural changes and ability to produce muscular strength and motor skill in the trained limb that previously occur following resistance and motor skill training, respectively, are rapid (first week of training) (Del Balso and Cafarelli 2007; Karni et al. 1998; Mason et al. 2020; Siddique et al. 2020). However, whether these adaptations (e.g., muscle strength) are transferred to the untrained arm at the same rate as that manifested in the trained arm remains uncertain. There are very limited data regarding the time course of cross-limb strength improvements during short-term unilateral muscle strength training. Some studies have observed different time points in the onset of muscle strength increase of the contralateral muscle to the training limb after high-intensity isometric unilateral resistance training. Carr et

al. (Carr et al. 2019), Hortobagyi et al. (Hortobagyi et al. 2011), and Barss et al. (Barss et al. 2018) reported a significant increase in isometric strength of the untrained muscle after two, three, and four weeks of unilateral isometric strength training, respectively. The different time points in the onset of muscle strength increase may suggest that factors other than the intensity of load may be responsible for the different rates at which these adaptations (e.g., muscle strength) manifest for the untrained, contralateral limb. Whereas Carr et al. provided visual force feedback and instructed the participant to produce force rapidly at contraction onset, the other studies did not report such training stimuli. Nevertheless, whether unilateral resistance training when planning to take into account training stimuli (i.e., dynamic eccentric unilateral voluntary muscle contractions and different strategies of pacing the movement with external auditory signal (Colomer-Poveda et al. 2019; Leung et al. 2015; Munn et al. 2005; Ruddy and Carson 2013)) may produce an early increase (i.e., in the first week of training) in muscle strength of (untrained) contralateral limb is uncertain.

Moreover, a progressive increase in strength of the contralateral muscle has been reported after the initial phase of high-load unilateral resistance training. It is possible that, in the later phase, higher-load unilateral resistance training promotes a greater increase in the strength of contralateral muscle than lower-load unilateral resistance training due to greater stimuli on cross-activation of the corticomotor pathway (Colomer-Poveda et al. 2019; Frazer et al. 2018; Ruddy and Carson 2013). Therefore, the objectives of this study were 1) to compare the extent of cross-transfer of high- versus low-load unilateral resistance training (dynamic) performed with external pacing of the movement (URTEP), and 2) to compare the time course of the two approaches.

METHODS

Experimental Approach to the Problem

In studies on cross-education of muscle function, more control can be achieved by randomizing subjects into groups (Carroll et al. 2006). To determine the contralateral effect of the URTEP, we used one of the three options suggested by Carroll et al 2006. According to Carroll et al 2006, a “possibility is to compare the strengths of untrained limbs of trained and untrained subjects after adjusting for baseline strength in an analysis of covariance.” (Carroll et al. 2006). Therefore, this randomized controlled study was a parallel, between-group design that included two groups that received unilateral dynamic resistance training (higher or lower intensity of load) and a control group that did not receive resistance training (Figure 1). First, participants were invited to take part in a day in which they were familiarized with resistance exercise on the Scott bench (dumbbell Scott curl). After a 48-hour interval, the one repetition maximum (1 RM) test was performed. After a 48-hour interval, a retest of 1 RM was performed. The 1RM test and retest were performed to eliminate intra-individual variability and reduce possible biases in increased strength by learning the tests. After 48h of 1RM retest, the maximum voluntary isometric contraction (MVIC) test was performed (three attempts were performed). When both arms were evaluated (Figure 1), the right arm was evaluated before the left one.

Following these assessments, we used a Medcalc® tool (Create random group) to assign cases to random groups. Each volunteer was randomized (taking into account gender: block randomization) into the three training groups: Low-load resistance training (G40), high-load resistance training (G80), and the control group (Edgcumbe et al.). All the individuals were right-handed. However, the volunteer’s arms were randomized (taking into account the side: left or right) in the trained arm or transfer arm. Thus, a similar number of dominant and non-dominant arms were allocated to the training arm or transfer arm. In the control group (no exercise), the volunteer’s arms were also randomized in the training control arm or transfer control arm.

In the training groups, each volunteer performed a dynamic URTEP (isoinertial) with only one arm (training arm). G40 or G80 performed dynamic URTEP (dumbbell Scott curl), three times per week, for four weeks. After one week of dynamic URTEP, 1RM and MVIC tests were performed again (both tests were separated by 48 hours) solely in the transfer arm and transfer control arm. After four weeks of dynamic URTEP, the 1RM and MVIC tests were performed again (both tests were separated by 48 hours) in all arms. All assessments and training sessions were performed by a physiotherapist.

All individuals performed all training sessions and assessments at the same time of day (afternoon or evening) to eliminate possible variations of the day. All evaluations were carried out in a laboratory with temperature ($\sim 21^{\circ}\text{C}$) and noise controls.

Subjects

This study was approved by the local ethics committee (n. 73681617.0.0000.5154) and all participants were informed about the research procedures and signed an informed consent form before participation.

A priori sample calculation was performed before starting the study. The sample size was calculated using G*Power software (version 3.1.9.2). The effect size was based on the cross-education of dynamic muscular strength reported in a meta-analysis ($d = 0.65$) (Green and Gabriel 2018). However, we decided to use a smaller effect ($d = 0.40$) to ensure a sample of sufficient size. The conversion from d to η^2 (eta squared) was performed using the formula suggested by Fritz et al (Fritz et al. 2012): $\eta^2 = \frac{d^2}{d^2 + 4}$. The power analysis demonstrated that at least 16 participants are needed for each group to detect a η^2 of 0.036 (effect size $f = 0.19$, test family f , repeated measures, within-between interaction). The alpha error was defined as 0.05 with a power of 80%, correlation among repeated measures of 0.6, and non-sphericity correction of 1.0.

Recruitment was carried out through social media, pamphlets, and invitations distributed in places with a large flow of people. Fifty healthy and right-handed participants (26 women, 24 men aged 19–41 years) volunteered to participate in the study and met the inclusion criteria. Inclusion criteria were: the volunteers had to be free of orthopedic and neurological diseases; had controlled blood pressure and glycemia; were untrained (did not engage in exercise programs over the last 6 months, neither recreational nor professionally); non-smoker; and did not take any medicine. Inclusion criteria were identified by a physiotherapist who administered an anamnesis.

Since there is evidence that there is no difference in the occurrence of cross-transfer between the young and elderly (Bemben and Murphy 2001; Ehsani et al. 2014; Hester et al. 2019), we chose to form a sample comprising only young adults (from 19 to 41 years), in a way that become as homogeneous as possible.

Procedures

Dynamic strength - One repetition maximum test (1RM)

The dynamic strength of elbow flexion was evaluated using the 1RM test on the Scott bench (dumbbell Scott curl). The seat height was adjusted according to each subject's height and the subject's shoulder was positioned at 50 degrees of flexion. The test was performed with an elbow flexion range of motion from 30 to 120 degrees. A goniometer was used to measure joint angles. Then, to ensure the exact 90 degrees range of motion, a “piece of string” was positioned at the exact distance that the individual could extend and flex the elbow. Two rulers (millimeters) were positioned at both sides of the Scott bench to mark the position of the piece of string (Figure 2a). The same marks were used in all assessments and training to eliminate possible biases in movement range alteration. The contralateral arm was positioned similarly to the test arm but remained at rest.

Before the 1 RM test, a warm-up was performed using a subjective load with approximately 15 repetitions of ~30% of 1RM. After 1.5-min of rest, the load was increased, and twelve repetitions were performed with a subjective load of ~50 % of 1RM. After 1.5-min of rest, the load was increased, and five repetitions were performed with a subjective load of ~80 % of 1RM. After 3 to 5-min. of rest, the load was considerably increased, and the subjects were encouraged to overcome resistance using full motion. When the load was overestimated or underestimated, the subjects rested for 3 to 5-min. before a new attempt was performed with a lower or higher load, respectively. This procedure was performed to find the equivalent load of 1RM, which ranged between 2 and 5 attempts. Attempts were conducted with verbal encouragement from the evaluator, in a standardized way, inspiring the individual to perform maximum strength. The load that was adopted as the maximum load was the load used for the last time the exercises were performed with no more than one repetition by the subject.

Two tests (test and retest) of 1RM were performed with a 48-hour interval between the tests. However, the higher value was used for comparison between groups. The intraclass correlation coefficient for the test and retest of 1 RM of transfer arms ($n = 50$ arms) was 0.992 (CI95%: 0.996 - 0.982). The technical error of measurement (TEM) was 0.45 kg (CI95%: 0.34 kg - 0.55 kg).

Isometric strength - *Maximum voluntary isometric contractions (MVIC)*

The isometric strength of elbow flexion was evaluated by the MVIC. The MVIC was collected by a load cell, Metrolog brand, model SD20- analog; LP3D-TV4J serial; sensor: Alfa ZX500 load cell (S / N 1154470). The load cell was attached to a support on the wall. The traction was transferred to the load cell by a cable. The cable passed through a pulley to avoid an angular effect of force on a load cell. The cable was positioned to provide a 90-degree angle with the forearm. On the Scott bench, volunteers' elbows and shoulders were positioned to

provide 90- and 50-degree angles, respectively (Figure 2b). While testing one arm, the other arm remained stabilized, using a belt extended along the device. The trunk was also stabilized.

In MVIC elbow flexor tests, the acquisition rate was performed every 1.57 millisecond. The software smoothed the data. Three MVIC of elbow flexion (5 seconds each) were performed for the same arm, with two minutes of rest between them. Data extraction was performed offline by Software SD20 Datalogger v4.0. To obtain the final MVIC (in kg.f) used for statistical analysis of the comparison between groups, the maximum strength registered by the equipment in each contraction was considered (the highest strength value of the 3168 acquisitions made in the 5 seconds of each MVIC), then the average of the highest values of the three contractions was calculated. The data were analyzed offline. The intraclass correlation coefficient for the three MVIC of transfer arms ($n = 50$ arms) was 0.977 (CI95%: 0.960 - 0.987). The technical error of measurement between the highest and lowest values was 2.23 kg (CI95%: 1.62 kg – 2.84 kg).

Surface electromyography

The evaluation of muscle activation was performed by the recording of electromyographic signals, the surface electromyography (sEMG), of the biceps brachii (and also the biceps brachii contralateral to determine irradiation) and triceps brachii muscles (antagonist), during the CVIM and 1RM tests. In order to analyze the sEMG data of the 1 RM tests, we considered the contraction before the failure (the only complete one). For the sEMG analysis of the MVIC tests (the MVIC test was performed 48 hrs after 1 RM test), we used the average of the three contractions.

The equipment used was the Miotoll Uro 200/400 [Miotec® biomedical equipment], with four channels (gain of 100x, 14-bit A / D converter, 2000 Hz acquisition rate, common-mode rejection ratio of 110dB, noise level < 2 low significative bit, and 20pF//1010 ohm input

impedance) and an entry for a reference electrode. Initially, the skin was prepared by shaving the hair, cleaning it with alcohol and skin abrasion, following the recommendations of SENIAM (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles) (SENIAM 2017). The location of the sensor on the muscle was the line between the medial acromion and the fossa cubit at 1/3 from the fossa cubit, in which the subject had his/her elbow flexed at a 90 ° angle and the dorsal side of the forearm was horizontally down (Hermens et al. 1999). The sensor location was confirmed by palpation of the muscle belly using the manual muscle strength test (Kendall et al. 2005). In each muscle, a pair of adhesive and disposable electrodes (Ag/AgCl: 44mm long, 21mm wide, 20mm between poles/Double Trace brand/Double Trace model LH-ED4020) were used. The reference electrode was placed on the medial malleolus of the left leg, also using adhesive electrodes. All electrodes were affixed with anti-allergenic microporous tape.

After positioning the electrodes, a 20-second resting collection was performed to check for the presence of electrical and electromagnetic noise. To do this, a collection was made using a computer, the Myosystem electromyograph and the load cell disconnected from the power grid and disconnected cell phones. This procedure is necessary because electrical or electromagnetic signals generate noise in the electromyography signal (De Luca et al. 2010). Each pair of electrodes was connected to the same electromyography channel for all collections (baseline, week 1 and week 4).

After data collection, signal processing was performed using the Miotec Suit 1.0 software in which the window (region) of the signal to be processed was defined. This window was bounded between the beginning and the end of the contraction (1 RM and MVIC). sEMG signals were rectified and smoothed using the root mean (Jiang et al.) squared with a 20ms smoothing window. sEMG signals were analyzed considering their amplitude peak. The bandpass filter (4th order butterworth) from 10 Hz to 500 Hz in addition to the 60 Hz filter

(notch) for the electrical network was performed to eliminate noise (De Luca et al. 2010). A collection in maximum voluntary isometric contractions of 3 seconds was performed 5 minutes before the start of each 1 RM test just to normalize the sEMG data of 1RM (Not part of the MVIC calculation). For the sEMG of MVIC test (performed 48 hrs after 1 RM test), we used the non-normalized RMS peak value.

Inter-limb transfer

The magnitude of inter-limb transfer (how much of the training effect was transferred to the untrained limb) was calculated in all volunteers as suggested by Green and Gabriel (Green and Gabriel 2018).

$$\text{Inter-limb Transfer} = (\text{untrained arm \% gain} / \text{trained arm \% gain}) \times 100$$

Negative inter-limb transfer values were considered zero.

Strength training protocol

The subjects underwent isoinertial dynamic URTEP (elbow flexion) on the Scott bench with dumbbell for four weeks, 3 times a week, on Mondays, Wednesdays and Fridays. Only one arm of each volunteer performed the resistance training protocol. During the training, the contralateral arm remained at rest and was extended on the Scott bench.

The G40 group performed four series of 15 repetitions at 40% of 1 RM and the G80 group consisted of 4 series, the first with 15 repetitions at 40% of 1 RM, the second with 8 repetitions at 80% of 1RM, the third equal to the first and the last with 7 repetitions at 80% of 1RM. The repetitions were done in this way to equalize the training volumes between groups G40 and G80. The load was increased by 5% after the second week (load progression).

In both groups, the strategies of pacing the movement were 1 concentric second and 3 eccentric seconds controlled by an external auditory signal (metronome). Two minutes of rest

were allowed between sets. The range of motion of the elbow during training was 30 ° to 120 °. The range of motion was guaranteed by a goniometer and a piece of string that limits the movement between 30 ° to 120 °. The piece of string offered no resistance or movement assistance.

The training was done individually, with a scheduled time, in a covered court used only for research, without interference from music or other noise.

Statistical analysis

Data were presented as means and standard deviation or confidence interval of 95% (CI95%). To verify the effect of the groups (GC, G40, and G80), time (baseline[pre], after one week [inter] and after 4 weeks [post]) and group versus time interaction, we used the mixed ANOVA. The effects were analyzed with confounding variables as covariates (age, sex, and trained arm side) in Mixed-ANOVA. Afterwards, ANCOVA, correcting the gains (delta, Δ) by the baseline values, age, sex, and trained arm side, was used to compare the group. Levene and Mauchly tests were used to verify homogeneity of variances and specificity assumption, respectively. The LSD was used as post hoc analysis.

To determine whether a change in the dynamic strength of the untrained arm across the intervention (pre and post) within the individual was associated with the change in isometric strength of the untrained arm across the intervention, we used multiple regression as recommended by Bland and Altman (Bland and Altman 1995).

The reliability analysis of the test and retest of 1RM and MVIC was made by the intraclass correlation coefficient, by the two-way mixed model and absolute agreement (single measure). Technical errors of measurement (TEM) were calculated by using the following formula: $\sqrt{\Sigma d^2/2n}$ (where “d” is the estimated difference between measures and “n” is the

number of participants). The standard error of the measure (Van Cutsem et al.) was calculated as $SEM = SD \times \sqrt{1-ICC}$. CI95% of TEM was calculated as $TEM \pm (1.96 \times SEM)$.

The program used for statistical analysis was SPSS statistics version 23. The statistical model was interpreted using the P-value (< 0.05) and CI95%.

RESULTS

There were 8 women and 9 men in the CG; 8 women and 8 men in the G40 and 8 women and 9 men in the G80. Concerning the arm side that performed the training, in GC and G80, 9 subjects trained the dominant arm and 8 the non-dominant one and in the G40 group, 8 individuals trained the dominant arm and 8 the non-dominant arm. The average age (years) of the subjects was similar between the groups, in which 29.6 ± 6.4 were in the CG, 27.0 ± 3.7 in the G40, and 27.8 ± 3.9 in the G80. Weight (kg) and height (cm) were 70.8 ± 14.9 and 155.6 ± 47.3 in the CG, 67.4 ± 9.3 and 167.2 ± 7.6 in the G40, and 70.6 ± 14.9 and 168.2 ± 8.0 in the G80, respectively. Schooling (time of study in years) was 15.5 ± 3.8 in the CG, 15.3 ± 1.8 in the G40, and 14.8 ± 1.6 in the G80.

Transfer arm adaptations

The values (means and standard deviation) of 1RM, MVIC, and sEMG amplitude at baseline, week 1, and week 4 are shown in Table 1. The statistical model (Mixed ANOVA) revealed $P < 0.05$ for the time by group interaction in the tests of 1RM [$F(4) = 18.9$ and $P < 0.001$] and MVIC [$F(4) = 4.4$ and $P = 0.003$] and sEMG amplitude during the 1RM [$F(4) = 4.8$ and $P = 0.002$]. The post hoc analysis revealed ($P < 0.05$) that after one week of URTEP the 1RM increased in the G40 e G80, but not in the CG. After four weeks of URTEP, only the G80 increased 1RM when compared to week 1. The MVIC increased only the G80 in week 4 when compared to baseline. The sEMG amplitude during the 1RM test increased as early as week 1

in the G80, while in the G40 only in week 4. There was no effect of time by group interaction in the MVIC test for sEMG amplitude.

1RM change scores (means and CI95%) at week 1 and week 4 are shown in Figure 3A. At week 1, the statistical model (ANCOVA and post hoc) revealed [$F(2) = 13.1$, $P < 0.001$, $\eta^2 = 0.36$, and observed power = 1.0] that 1RM change scores were higher in the G80 and G40 than the CG, with no difference between the trained groups [GC = -0.2 kg (CI95%: -0.7 – 0.2 kg), G40 = 0.8 kg (CI95%: 0.4-1.3 kg) and G80 = 1.4 kg (CI95%: 1.0 -1.8 kg)]. However, only the G80 produced an increase in dynamic strength (CI95%: 1.0 -1.8 kg) in the untrained arm that did not cross the upper limit of the TEM confidence interval (0.55kg). At week 4, ANCOVA [$F(2) = 30.8$, $P < 0.001$, $\eta^2 = 0.51$, and observed power = 1.0] and post hoc revealed that 1RM change score was higher in the G80 than in the G40 and CG. Also, 1RM change score was higher in the G40 than in the CG. [GC = -0.2 kg (CI95%: -0.6 – 0.3 kg), G40 = 1.1 kg (CI95%: 0.7-1.6 kg) and G80 = 2.2 kg (CI95%: 1.8 -2.6 kg)].

sEMG amplitude change scores (MVIC %) at week 1 and week 4 are shown in Figure 3B. At week 1, the statistical model (ANCOVA) revealed [$F(2) = 0.9$, $P = 0.414$, $\eta^2 = 0.13$] that there was no difference in sEMG amplitude change scores among groups [GC = 0.8 % (CI95%: -16.5 – 18.1 %), G40 = 9.1 % (CI95%: -7.1 – 25.2 %) and G80 = 17.7 % (CI95%: 1.4 – 34.0 %)]. However, only the G80 produced an increase in sEMG amplitude change (CI95%: 1.4 – 34.0 %) in the untrained arm that did not cross value zero. At week 4, ANCOVA [$F(2) = 3.3$, $P = 0.047$, and observed power = 0.6] and post hoc revealed that sEMG amplitude change scores were higher in the G80 and G40 than the CG, with no difference between the trained groups [GC = -9.9 % (CI95%: -28.0 – 8.0 %), G40 = 19.1 % (CI95%: 2.2 – 35.9 %) and G80 = 20.7 % (CI95%: 3.7 – 37.7 %)].

Sex effect on transfer arm adaptations

Sex effect on sEMG amplitude and 1RM change scores (means and CI95%) at week 1 and week 4 are shown in Figure 4 A. At week 1, the statistical model (ANCOVA) revealed no interaction [$F(2) = 1.2$, $P = 0.302$, $\eta^2 = 0.06$] between sex and group in the 1 RM changes [GC: men = -0.3 kg (CI95%: -1.1 – 0.5 kg) and women = -0.1 kg (CI95%: -0.8 – 0.5 kg), G40: men = 1.0 kg (CI95%: 0.4 - 1.7 kg) and women = 0.6 kg (CI95%: -0.1 - 1.3 kg), and G80: men = 1.8 kg (CI95%: 1.1 – 2.5 kg) and women = 1.0 kg (CI95%: 0.3 – 1.7 kg)]. At week 4, ANCOVA [$F(2) = 3.9$, $P = 0.028$, $\eta^2 = 0.16$, and observed power = 0.67] and post hoc revealed that 1RM change score was higher in the men than in the women at both intensities of load (G40 and C80) [GC: men = -0.1 kg (CI95%: -0.8 – 0.7 kg) and women = -0.3 kg (CI95%: -0.9 – 0.3 kg), G40: men = 1.6 kg (CI95%: 1.0 – 2.3 kg) and women = 0.7 kg (CI95%: 0.0 - 1.3 kg), and G80: men = 3.1 kg (CI95%: 2.4 – 3.8 kg) and women = 1.4 kg (CI95%: 0.7 – 2.0 kg)].

There was no interaction ($P > 0.05$) between sex and group on the change scores of 1RM sEMG amplitude (MVIC %) (figure 4 B) and isometric strength at weeks 1 and 4.

Trained arm adaptations

The statistical model (Mixed ANOVA) revealed $P < 0.001$ [$F(2) = 46.8$] for the time by group interaction in the 1RM test. The post hoc analysis revealed ($P < 0.05$) that after four weeks of URTEP the 1RM increased in the G40 e G80, but not in the CG. ANCOVA revealed [$F(2) = 46.5$, $P < 0.001$, $\eta^2 = 0.61$, and observed power = 1.0] that 1RM change scores were different among the groups. 1RM change score was higher in the G80 than in the G40 and CG. Also, 1RM change score was higher in the G40 than in the CG. [GC = -0.4 kg (CI95%: -0.9 – 0.1 kg), G40 = 1.5 kg (CI95%: 1.1 – 2.0 kg) and G80 = 2.7 kg (CI95%: 2.3 – 3.2 kg)].

The statistical model (Mixed ANOVA) revealed $P < 0.001$ [$F(2) = 46.8$] for the time by group interaction in the test of MIVC. The post hoc analysis revealed ($P < 0.05$) that after four weeks of URTEP the MIVC increased in the G40 e G80, but not in the CG. ANCOVA revealed

[$F(2) = 8.2$, $P = 0.001$, $\eta^2 = 0.22$, and observed power = 0.95] that MIVC change scores were different among the groups. MIVC change score was higher in the G80 and G40 than in the CG, with no difference between the trained groups [GC = -1.5 kg (CI95%: -3.1 – 0.05 kg), G40 = 2.1 kg (CI95%: 0.5 – 3.7 kg) and G80 = 2.6 kg (CI95%: 1.1 – 4.1 kg)].

Sex effect on trained arm adaptations

ANCOVA [$F(2) = 7.8$, $P = 0.001$, $\eta^2 = 0.28$, and observed power = 0.94] and post hoc revealed that 1RM change score was higher in the men than in the women only in the G80 [GC: men = -0.0 kg (CI95%: -0.7 – 0.7 kg) and women = -0.7 kg (CI95%: -1.3 – -0.1 kg), G40: men = 1.9 kg (CI95%: 1.2 – 2.5 kg) and women = 1.2 kg (CI95%: 0.6 - 1.9 kg), and G80: men = 4.1 kg (CI95%: 3.4 – 4.8 kg) and women = 1.5 kg (CI95%: 0.8 – 2.2 kg)]. There was no interaction ($P > 0.05$) between sex and group on the isometric strength change scores.

Magnitude of inter-limb transfer

The magnitude of inter-limb transfer was significantly higher in the G80 when compared to the G40 in 1RM (G80: $95.3 \pm 7.7\%$ vs. G40: $62.6 \pm 12.0\%$, difference = 32.6 %, 95% CI: 4.5 % to 60.6 % and $P = 0.023$) and also in MVIC (G80: $119.86 \pm 4.12\%$ vs. G40: $32.39 \pm 6.67\%$, difference = 87.46 %, 95% CI: 43.86% - 116.01%).

Correlation between 1RM and MVIC gains in the Untrained arm

In one week, the 1RM gain in the untrained arm was not significantly associated with the MVIC gain in the untrained arm ($B = 0.165$, 95% CI: -0.002; 0.331, $R^2 = 0.11$ and $P = 0.053$). However, in four weeks, the 1RM gain in the untrained arm was significantly associated with the MVIC gain in the untrained arm ($B = 0.384$, 95% CI: 0.225; 0.542, $R^2 = 0.43$ and $P < 0.001$).

Correlation between muscle strength gains of the trained and the untrained arm.

One RM gain in the untrained arm was significantly associated with the 1RM gain in the trained arm in the G80 ($R^2=0.95$; $P<0.001$), G40 ($R^2=0.55$; $P=0.001$), men ($R^2=0.85$; $P<0.001$), and women ($R^2=0.76$; $P<0.001$). Also, MVIC gain in the untrained arm was significantly associated with the MVIC gain in the trained arm in the G80 ($R^2=0.64$; $P<0.001$), men ($R^2=0.28$; $P=0.002$) and women ($R^2=0.23$; $P=0.011$), but no in the G40 ($R^2=0.002$; $P=0.882$).

Change of antagonist activation during 1RM

There was no change [Mixed ANOVA, group by time interaction: $F(4) = 1.3$, $P = 0.253$] in the sEMG amplitude (μV) of antagonist muscle (triceps brachii) during the 1RM test at baseline and after one and four weeks of URTEP (CG: baseline = 221.7 ± 98.2 , week 1 = 216.7 ± 88.7 and week 4 = 218.1 ± 84.4 ; G40: baseline = 241.3 ± 148.5 , week 1 = 295.4 ± 140.3 and week 4 = 304.7 ± 120.7 ; G80: baseline = 188.9 ± 110.6 , week 1 = 170.4 ± 113.4 and week 4 = 194.6 ± 64.7).

DISCUSSION

This study sought 1) to investigate the extent of cross-transfer of high- vs low-load URTEP and 2) to compare the time course of the two approaches. The main findings show that low-load URTEP may promote cross-education of muscle strength in the later phase (four weeks). This is important because many patients who are unable to exercise with high loads [e.g., osteoarthritis, patellofemoral pain, stroke, and hypertension] would benefit from cross-education of muscle strength with low-load URPEP (Frazer et al. 2018; Giles et al. 2017; Ruddy and Carson 2013; Sharman et al. 2015). However, high-load URTEP seems to promote cross-

education of muscle strength in the early phase (one week). This is important because even in short periods of immobilization, high-load URTEP can be effective in promoting cross-education and preventing loss of muscle strength (Frazer et al. 2018; Ruddy and Carson 2013). Moreover, the use of high loads seems to enhance the cross-education of muscle strength in four weeks of dynamic resistance training (Frazer et al. 2018; Ruddy and Carson 2013).

We observed an increase in muscle strength of the contralateral to the trained arm (transfer arm) after one and four weeks of URT in the low-load URTEP (G40). However, this difference was higher than the upper limit of TEM (0.55 kg) only at week four. As TEM helps to indicate the minimum necessary difference above the evaluator's repeated measurement error, we have strong evidence to accept increased muscle strength only after 4 weeks of low-load URTEP. The observed increase was 8.6% in muscle strength of the transfer arm in the low-load URTEP. This value of cross-education is lower than the recent estimates of 12% reported by Manca et al. (Manca et al. 2017) and 18% by Green and Gabriel (Green and Gabriel 2018). This may be due to the lower load used in the G40 because the magnitude of cross-activation of the corticomotor pathway is associated with the intensity of load of the unilateral contraction (Perez and Cohen 2008). Indeed, in the current study, the high-load URTEP (G80) increased the muscle strength of the transfer arm by 18%.

The increase in muscle strength in the low-load URTEP was accompanied by an increase in sEMG amplitude (table 1 and figure 3). As it has been shown that bilateral increases in corticospinal excitability during unilateral exercise may not occur in lower-load URT (Green and Gabriel 2018; Hendy et al. 2017; Muellbacher et al. 2000), another training stimulus may have been responsible for the cross-education in lower-load URTEP (Frazer et al. 2018; Ruddy and Carson 2013). The inclusion of externally paced movements, controlling the velocity of contraction (fast concentric and slow eccentric contractions), may have contributed to these cross-education adaptations because these training stimuli lead to greater increases in the

excitability of ipsilateral primary motor cortex and reductions in short-interval intracortical inhibition after unilateral resistance training (Colomer-Poveda et al. 2019; Howatson et al. 2011; Leung et al. 2015, 2018; Uematsu et al. 2010). It is possible that the inclusion of controlled velocity of contraction generated greater neural resources needed to program and plan eccentric contractions (Fang et al. 2001). In addition, the synchronized contractions to an external auditory signal used in the current study may have contributed to both reduced intracortical inhibition (Leung et al. 2015, 2018; Stinear and Byblow 2003) and increased corticospinal excitability (Ackerley et al. 2007; Jantzen et al. 2009; Leung et al. 2015, 2018).

Some studies have observed a significant increase in isometric strength of the untrained muscle from 2 weeks (Barss et al. 2018; Carr et al. 2019; Hortobagyi et al. 2011). However, studies using dynamic unilateral resistance training have not assessed dynamic muscle strength before three weeks of intervention (Coombs et al. 2016; Goodwill and Kidgell 2012; Mason et al. 2018). To better translate resistance training in rehabilitation settings, it is necessary to determine the time course of cross-education of muscle strength. In the current study, while low-load URTEP promoted cross-education of muscle strength after four weeks, high-load URTEP promoted cross-education of muscle strength after one week. This is important because it is possible to adapt the resistance training protocol depending on the immobilization time of limb. That is, even in short periods of immobilization (i.e., one week), URTEP (i.e., high-load) can be effective in promoting cross-education and preventing loss of muscle strength.

Cross-activation during unilateral resistance training may lead to neuroplastic adaptations in both cortices that increases the output produced by the motor command (Green and Gabriel 2018; Hortobagyi et al. 2011; Ruddy and Carson 2013). Thus, an approach that may offer insight regarding the cross-education is related to training-related motor unit adaptations in the untrained homologous muscle. In this sense, we observed that high-load URTEP increased maximal sEMG amplitude of biceps during the 1RM test from baseline to

week 1. Besides, we did not observe any change in the sEMG amplitude of the antagonist muscles during the 1 RM test. This finding is consistent with that of Del Balso and Cafarelli who showed neural changes and ability to produce muscular strength in trained limb after three sessions (one week) of resistance training (Del Balso and Cafarelli 2007). Indeed, bilateral increases in corticospinal excitability during unilateral exercise are observed in higher-load resistance training (Green and Gabriel 2018; Hendy et al. 2017; Muellbacher et al. 2000). Our results corroborate with previous studies that suggest that intensity of load may be an important training stimulus in cross-activation of the corticomotor pathway (Green and Gabriel 2018; Hendy et al. 2017; Hortobagyi et al. 2011; Muellbacher et al. 2000; Ruddy and Carson 2013). Consequently, this may lead to neuroplastic adaptation that increases the output produced by the motor command, potentially explaining the enhancement of cross-education of muscle strength (Green and Gabriel 2018; Hortobagyi et al. 2011; Ruddy and Carson 2013) in the early and later phase of URTEP. Although caution is necessary when attempting to deduce the neural drive to muscle from interference EMG recordings (Enoka and Duchateau 2015), some studies have shown greater efferent neural drive (i.e., V-wave) (Green and Gabriel 2018) and voluntary activation (Lee et al. 2009) for the untrained limb following unilateral training.

Isometric strength (MVIC)

In our study, there was not enough evidence to support that URTEP increases isometric muscle strength. Although there was an increase in isometric strength in the transfer arm only after four weeks of dynamic URTEP (Table 1), the magnitude of increase of MVIC in the G80 was not superior to the TEM (2.23 kg.f and CI95%: 1.62 – 2.84 kg.f). Moreover, at week one, the changes in isometric and dynamic strength consequent to the unilateral dynamic resistance training were unrelated (only 11% of common variance, $P = 0.052$). At week four, although the dynamic strength gain was significantly associated with the isometric strength gain in the

transfer arm (0.43% and $P < 0.001$), this association did not validate the concept of “generality” of cross-education of muscle strength because for this it would be necessary to have a correlation of $R^2 = 0.50$ or greater (Baker et al. 1994).

It is known that there are physiological and biomechanical differences between isometric and dynamic movements. In dynamic movements, there is a greater connection of cross-bridges (Fenwick et al. 2017; Kruger et al. 2019) and a higher discharge rate for motor units (Kallio et al. 2013; Maffiuletti et al. 2016) compared to isometric movements. Also, in dynamic movement, there is an activation of antagonists (Aagaard et al. 2000) while in isometric movement, the agonist is recruited predominantly and the antagonist plays a very small role (Bampouras et al. 2017). This suggests that the mechanisms that contribute to enhanced cross-education of dynamic strength seem unrelated to the mechanisms that contribute to enhanced cross-education of isometric strength in the early phase of URT (Ruddy and Carson 2013). However, further work is required to establish the viability of our speculations.

Effect of sex on cross-education

Although the effect of sex on cross-education has not been observed by other studies (Green and Gabriel 2018), surprisingly, in the sub-analysis of the data, we observed an effect of sex on cross-education of dynamic strength. Therefore, a possible effect of sex is uncertain and we can only speculate on such mechanisms. Neuroactive steroids, such as estradiol and progesterone modulate the function of multiple neurotransmitter systems. While estradiol enhances N-methyl-D-aspartate receptor activity (enhancing neuronal excitability), progesterone enhances gamma-aminobutyric acid ($GABA_A$, an inhibitory neurotransmitter) activity (Amin et al. 2006; Guennoun et al. 2015). Particularly, GABA has been proposed as one element contributing to local cortical changes during fast motor learning (Floyer-Lea et al.

2006). In this sense, Inghilleri et al reported that motor evoked potential increased on day 14 of the menstrual cycle, but not on day 1 (when estradiol and progesterone level are low), after repetitive transcranial magnetic stimulation over cortex motor (Inghilleri et al. 2004). In addition to neural adaptations and also related to them, changes in exercise performance and muscle function of the woman is also reduced in the initial follicular phase, compared to when estrogen is highest in the ovulatory period (McNulty et al. 2020; Romero-Moraleda et al. 2019; Sung and Kim 2019). However, not all studies have observed the effect of sex on exercise-induced neuroplasticity (El-Sayes et al. 2019). Thus, further studies are still needed to establish the role of sex on cross-education.

This study has limitations. First, this study was not blinded. The examiner who performed the anamnesis and evaluations also supervised the training. However, we use controls that may have reduced the bias. For instance, test and retest, supervision and monitoring of evaluations by other researchers blinded to the participants, TEM, and limitation of the maximum elbow amplitude by a piece of string in the 1 RM tests and during the training, allowing the same angle for all individuals and all tests. Also, measurement of angles by a goniometer, timed time for isometry and rest time in MVIC, and standardized verbal command. Second, we did not control the volunteers' diet, but we made sure that none of them were on a diet to impair muscle performance. Third, labor activity was not controlled in detail; however, we take care that individuals had similar activities, with function office activities. Moreover, all volunteers were instructed to avoid possible heavy manual labor for the duration of the research. Fourth, sEMG of synergist and postural muscles and cortical sites were not measured. Moreover, the interpretation of sEMG has limitations (Enoka and Duchateau 2015). Therefore, the results of sEMG data should be interpreted with caution. Fifth, we did not check the phase of the menstrual cycle of the women.

In short, the finding of our study suggests that in the early phase of URTEP (i.e., one week), cross-education of dynamic strength may be promoted particularly by high-load URTEP (80% of 1RM). In the later phase (four weeks), cross-education of dynamic strength may be achieved in both loads (40% or 80% of 1RM). However, high-load URTEP seems to enhance the cross-education effect when compared to low-load URTEP in four weeks. Moreover, the generality of cross-education of isometric strength needs to be considered with caution. URTEP does not seem to be the best option to promote cross-education of isometric strength. Finally, the effect of sex observed in the present study suggests a lower magnitude of cross-education of muscle strength in women. However, these findings were obtained from sub-analyses and therefore need to be interpreted with caution. This is an important issue for future research.

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CONFLICTS OF INTEREST

None of the authors have conflicts of interest.

AUTHOR CONTRIBUTIONS

DP and FO conceived, designed and conducted the study. FO performed randomization. DP enrolled participants, and assigned participants to interventions. DP and FO analyzed the data and wrote the manuscript. All authors approved the manuscript.

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Tables

Table 1. 1RM, MVIC, and peak of sEMG amplitude of transfer arm at baseline, week 1 and week 4.

		GC	G40	G80	P group)	P (time)	P (group x time)
1RM (kg)	Baseline	14.1±2.9	12.8±3.0	12.9±2.8			
	Week 1	13.9±2.9	13.6±2.9*	14.3±2.8*	0.778	0.568	<0.001
	Week 4	13.9±2.8	14.00±2.9*	15.2±2.8*†			
sEMG amplitude (MVIC %)	Baseline	100±27	77±27	66±26			
	Week 1	88±33	89±32	95±32*	0.864	0.395	0.002
	Week 4	80±35*	98±35*	96±34*			
MVIC (kg.f)	Baseline	30.0±6.7	27.8±6.6	27.3±6.5			
	Week 1	28.6±5.8	28.4±5.8	28.5±5.7	0.900	0.221	0.003
	Week 4	29.1±6.8	28.5±6.7	30.2±6.6*†			
sEMG amplitude (µV)	Baseline	943±552	911±548	726±540			
	Week 1	965±593	945±588	672±577	0.278	0.383	0.128
	Week 4	803±482	1108±476	799±470			

These values are presented as mean ± SD or CI95%. 1RM: one-repetition maximum test; sEMG: surface electromyography; MVIC: maximal voluntary isometric contraction. * indicates significant difference from baseline; † indicates significant difference from week 1. The values were adjusted to the confoundment factor (age, trained arm side, and sex).

FIGURE LEGENDS

Figure. 1. Schematic overview of study design.

** = both arms, * = untrained arm (transfer arm) and transfer control arm, # = randomization of participants and † = randomization of arms (training or strength transfer)

Figure 2. Apparatus used to perform the 1RM (A) and MVIC (B) tests. a = elbow flexion range of motion from 30 to 120 degrees, and b = "Piece of String" to show maximum elbow extension, c = rulers (millimeter) were positioned at both sides of the Scott bench, d = load cell was attached to a support on the wall; e = cable passed through a pulley; f = 50 degrees of shoulder flexion and g = face protection apparatus and h = Fixed at 90 ° elbow flexion.

Figure 3. Effect of intensity of load on change (deltas) of 1RM (A) and sEMG amplitude (B) of transfer arm after one and four weeks of URT. Means and IC95%. * indicates significant difference from the GC; ** indicates significant difference from the G40.

Figure 4. Effect of sex at different intensities of load on change (deltas) of 1RM (A) and sEMG amplitude (B) of transfer arm after one and four weeks of URT. Means and IC95%.

* indicates significant difference from the women.

Figure 1

891
892 A

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894 B

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896 Figure 2a-b

Figure 3a-b

Figure4a-b