Journal of Musculoskeletal and Neuronal Interactions

Original Article

Sex comparisons of non-local muscle fatigue in human elbow flexors and knee extensors

X. Ye[1], T.W. Beck[2], N.P. Wages[2], J.C. Carr[2]

[1]The University of Mississippi, Department of Health, Exercise Science, and Recreation Management, University, MS 38677, USA;
[2]The University of Oklahoma, Department of Health and Exercise Science, Norman, OK 73019, USA

Abstract

Objectives: To examine non-local muscle fatigue (NLMF) in both contralateral homologous and non-related heterogonous muscles for both sexes. **Methods:** Ten men and nine women participated in this study. After the familiarization visit, subjects completed four separate randomly sequenced experimental visits, during which the fatiguing interventions (six sets of 30-second maximal isometric contractions) were performed on either their right elbow flexors or knee extensors. Before (Pre-) and after (Post-) the fatiguing interventions, the isometric strength and the corresponding surface electromyographic (EMG) amplitude were measured for the non-exercised left elbow flexors or knee extensors. **Results:** For the non-exercised elbow flexors, the isometric strength decreased for both sexes (sex combined mean±SE: Pre vs. Post=339.67±18.02 N vs. 314.41±16.37 N; *p*<0.001). For the non-exercised knee extensors, there is a time × sex interaction (*p*=0.025), showing a decreased isometric knee extension strength for men (Pre vs. Post =845.02±66.26 N vs. 817.39±67.64 N; *p*=0.019), but not for women. **Conclusions:** The presence of NMLF can be affected by factors such as sex and muscle being tested. Women are less likely to demonstrate NLMF in lower body muscle groups.

Keywords: Maximal Voluntary Contraction, Isometric Strength, Surface Electromyography, Muscle Activation

Introduction

Non-local muscle fatigue (NLMF), defined as a temporary motor performance deficit in a non-exercised muscle group following a fatiguing protocol on a different muscle group[1], has been gaining attention in the recent decade. This phenomenon not only covers the traditionally studied cross-over muscle fatigue[2,3] in the contralateral homologous muscle group, but includes the potential performance decrements in a non-related muscle group that is located ipsilateral or contralateral, inferior or superior, as well as proximal or distal to the exercised muscle group. Generally speaking, researchers[1-4] believe that the motor performance deficit in the non-exercised muscle or muscle group is likely due to the exercise-induced central fatigue, which can be defined as a reduction of the voluntary drive from the central nervous system (CNS) to the alpha motoneuron pool[5], to fully activate a muscle or a muscle group. However, the magnitude of NLMF varies among studies, mainly due to the fact that most NLMF studies to date have utilized unique experimental designs and measurements, making comparisons between studies difficult[1]. For example, a number of research studies[6-11] focused on examining the motor performance of the unrelated heterogonous muscle groups after fatiguing the unilateral muscle groups (e.g. fatiguing upper limb and examining the motor performance of distal and unrelated lower limb muscles, or vice versa). However, conflicting findings were reported.

While the different fatiguing protocols could potentially have made the results inconsistent, another potential factor is related to which of the non-exercised muscle being examined to demonstrate the NLMF. Based on some previous studies that have investigated cross-over fatigue in homologous contralateral muscle group, the percent decline in maximal strength from the non-exercised upper body muscle groups (e.g., elbow flexors)[12,13] tend to be smaller than that from the lower body muscle groups (e.g.,

The authors have no conflict of interest.

Corresponding author: Xin Ye, Ph.D., CSCS, Assistant Professor of Exercise Science, The University of Mississippi, Department of Health, Exercise Science, and Recreation Management, 236 Turner Center, University, MS 38677, USA
E-mail: xye1@olemiss.edu

Edited by: S. Warden
Accepted 4 August 2017

knee extensors)[3,4]. One possible factor is the size of the muscle being examined: greater descending voluntary drive is generally required to fully activate the larger lower body muscles than the smaller upper body muscles[14]. Thus, a potential exercise-induced central fatigue may result in a greater magnitude of NLMF on the lower body muscles than on the upper body muscles. Another possible explanation is that the neural circuits between legs are stronger than those between arms[3]. Specifically, the inhibition of the H-reflex induced by contralateral leg cycling movement[15] cannot be observed in similar tasks performed in arms[16]. Recently, a systematic review[1] concluded that the NLMF is likely to affect the lower body muscle group more than it does to the upper body muscle. The direct support for this conclusion is the investigation conducted by the same group of researchers[8], where they had their subjects perform isometric unilateral upper limb (elbow flexors) and lower limb (knee extensors) fatiguing interventions, and measured potential NLMF parameters of the homologous contralateral muscle group as well as the heterogonous non-related muscle group under each fatiguing condition. The authors found that only the knee extensors demonstrated the NLMF, but not the elbow flexors, regardless of the muscle being fatigued[8]. However, there are still some investigations that have observed NLMF in the upper body muscles, including the investigation we conducted previously[17,18] by using dynamic elbow flexion exercises as fatiguing interventions.

In addition to the experimental protocol and measurement differences in NLMF research, another important factor that's worth investigating is sex[1], not only because there are very limited number of NLMF studies conducted in female subjects, but women respond to fatigue differently than men do[19]. It is generally accepted that women are less fatigable than men, even though the difference in fatigability become less when higher intensity contractions are performed[20]. Several mechanisms are responsible for this difference. For example, the greater proportional area of type I muscle fiber in women than in men[20] can at least be an important factor responsible for the more fatigue-resistant feature in women than in men[21,22]. Besides, the larger muscle mass and greater absolute force of men is also a factor that can limit blood flow and influence intramuscular pressure more rapidly in men than in women, even at the same relative intensity during an isometric contraction. The greater intramuscular pressure consequently leads to the limited perfusion and oxygen supply, as well as the increased metabolites buildup in men than in women. Furthermore, the accumulation of metabolites in the exercised muscle groups can also activate small afferent fibers such as group III and group IV sensory neurons, thus to impose an inhibitory feedback to the central nervous system (CNS), thereby reducing the voluntary activation from the CNS to the skeletal muscles[23]. Therefore, sex difference in fatigability can at least partially be explained by the differential developments of central fatigue for both sexes, with greater voluntary activation loss in men than in women[3]. This hypothesis is supported by the findings from Martin and Rattey[3], who directly examined the cross-over effects of lower body muscles (knee extensors) for both sexes, and confirmed differential cross-over effects between men and women. However, less is known regarding the cross-over effect between upper body muscles, or between upper and lower body muscles in both sexes. Thus, it would be interesting to compare potential NLMF in other muscle groups (e.g., upper body muscle group elbow flexors) for both sexes, as both factors (sex and muscle being examined) may influence NLMF. We hypothesized that women may respond similarly as men do in upper body muscle (elbow flexors) NLMF, but the magnitude of their lower body muscle (knee extensors) NLMF may be smaller than that in men.

Therefore, using similar experimental design as Halperin et al.[8], the aims of the present study were mainly two folds. The first goal was to examine NLMF in the upper and lower body muscle groups after fatiguing interventions in different unilateral muscle groups (i.e., elbow flexors vs. knee extensors). The second goal was to examine if sex as a factor can influence NLMF. In addition, this study also served as a continuation of the investigation we have conducted previously[17,18] by employing isometric exercise as the fatiguing interventions. Specifically, six sets of 30-s isometric maximal voluntary contractions (MVCs) were used as the fatiguing protocol. We chose to use this protocol rather than longer sustained MVCs (e.g., 100-s) which have been done previously[3,4], mainly due to that most training or sporting activities do not require long sustained maximal effort. Therefore, the findings of the current investigation can potentially be more properly connected to practical applications. In addition to isometric strength, we also chose to use the surface electromyographic (EMG) technique to examine the global muscle activation over the muscles being examined. Specifically, the non-exercised biceps brachii as the prime mover for elbow flexor, and the non-exercised vastus lateralis as one of the prime movers for knee extensors were chosen, due to the fact that these muscles are relative large and well-defined, which ensure clean and less contaminated surface EMG signals.

Materials and methods

This study used a within-subjects crossover design. Five separate visits to the laboratory was required to complete this investigation. Between visits, a minimum of 72 hours of rest was provided. After the familiarization visit, the next four experimental testing visits were conducted in a randomized fashion as follows: the Arm-Arm Visit (fatigue the right elbow flexors-test the contralateral homologous left elbow flexors), the Arm-Leg Visit (fatigue the right elbow flexors-test the non-related heterogonous left knee extensors), the Leg-Leg Visit (fatigue the right knee extensors-test the contralateral homologous left knee extensors), and the Leg-Arm Visit (fatigue the right knee extensors-test the non-related heterogonous left knee extensors). In this study, the fatiguing interventions were always performed at the subjects' right limbs, and the testing was always conducted at the left limbs.

Subjects

Ten men (mean±SD age=26±3 years; height=176.9±6.6 cm; body weight=84.2±12.5 kg) and nine women (mean±SD age=27±2 years; height=164.1±3.5 cm; body weight=59.3±11.4 kg) participated in this investigation. All subjects were healthy and physically active. Prior to any experimental testing, each subject completed an informed consent and a pre-exercise health and exercise status questionnaire, which indicated no current or recent neuromuscular or musculoskeletal disorders. During the consenting process, the subjects were instructed to maintain their normal habits in terms of dietary intake, hydration status, and sleep during the investigation. In addition, they were refrained from performing any upper or lower body resistance exercise at least 72 hours prior to each testing session. All experimental procedures for this investigation were approved by the University Institutional Review Board for the Protection of Human Subjects.

Testing procedures

Familiarization

The purpose of this visit was to familiarize the subjects with both testing and fatiguing protocols. In this investigation, we used custom-built strength testing apparatuses to measure the isometric strength of subjects' elbow flexors and knee extensors. Specifically, each subject was asked to contract against a load cell that was connected between the apparatus and the elbow or ankle (Figure 1). Upon arrival at the laboratory, each subject was first instructed to sit in front of a custom-built table for practicing elbow flexion isometric contraction (Figure 1a). With the left elbow positioned into the U-shaped pad, and the wrist put through a cuff connecting to a load cell (Model SSM-AJ-500; Interface, Scottsdale, AZ, USA), the subject contracted against the load cell. Extra care was taken to ensure that the joint angle between the arm and forearm was 90 degrees. After two to three brief (5 seconds) submaximal isometric contractions with 50% of the subject's perceived maximal effort as a warm-up, the subject was then asked to perform several 5-second maximal voluntary contractions (MVCs) with 30-second rest interval provided. The familiarization for elbow flexion isometric testing was concluded once the subject felt comfortable with this type of exercise. Immediately following this practice, the subject was then familiarized with the knee extension isometric contraction (Figure 1b) by performing the same warm-up and practicing procedures as he/she did during the familiarization for elbow flexion isometric contraction. The last part of this visit was to familiarize the subject with the fatiguing interventions, during which he/she performed one set of 30-second isometric MVCs on the right elbow flexors, followed by the same procedures on the right knee extensors, using the same isometric apparatuses. The familiarization visit was concluded once the subject felt comfortable with both testing procedures and fatiguing interventions.

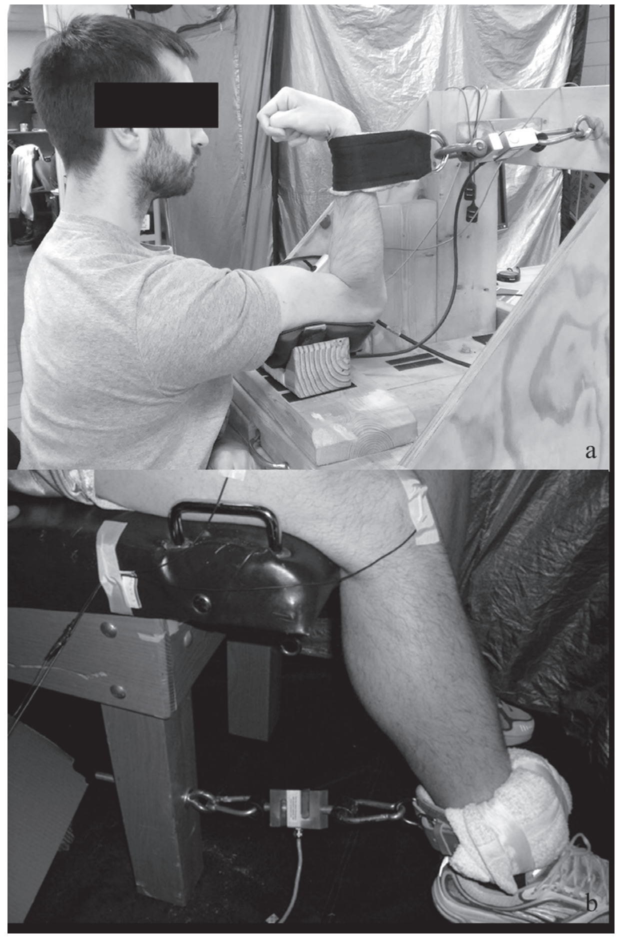

Figure 1. a. Isometric strength testing and apparatus for elbow flexors; b. Isometric strength testing and apparatus for knee extensors.

Experimental testing visits

After a minimum of 72 hours following the familiarization, subjects returned to the laboratory for one of the four experimental testing sessions. During each visit, the session started with the subjects warming up both muscle groups that would be tested and fatigued. Following the warm-up, the subjects performed pre-fatigue isometric strength testing (three 5-s isometric MVCs with 30 seconds rest in between) for the muscle group being tested. After the pre-testing, the subjects were asked to perform 6 sets of 30-second MVCs using the designated fatigue muscle group, with 30-second rest between consecutive sets. Verbal encouragement was provided throughout the entire fatiguing intervention. To prevent compensatory movements or contractions from the non-exercised testing muscles, the research staffs attached surface EMG electrodes on the non-exercised muscles, and visually monitored any muscle activity during the entire fatiguing protocol. If any surface EMG signals were visually detected, the researcher staffs would instruct the subjects to

Table 1. Percent declines (mean±SD) of isometric strength of the exercised muscle groups (right elbow flexors and right knee extensors) after the fatiguing exercise interventions. Percentage Decline of Isometric Strength = (fresh MVC - fatigued MVC) / fresh MVC.

	Right Elbow Flexors		Right Knee Extensors	
Gender	Arm-Arm Visit	Arm-Leg Visit	Leg-Arm Visit	Leg-Leg Visit
Men (n =10)	65.27 ± 10.67%	61.11 ± 10.81%	54.47 ± 18.34%	60.19 ± 19.66%
Women (n = 9)	51.75 ± 12.62%	49.18 ± 12.30%	45.63 ± 24.28%	41.68 ± 20.79%

Arm-Arm Visit: fatigue the right elbow flexors-test the contralateral homologous left elbow flexors; Arm-Leg Visit: fatigue the right elbow flexors-test the non-related heterogonous left knee extensors; Leg-Leg Visit: fatigue the right knee extensors-test the contralateral homologous left knee extensors; Leg-Arm Visit: fatigue the right knee extensors-test the non-related heterogonous left knee extensors

fully relax the non-exercised muscles. Immediately after the fatiguing intervention, the subjects finished the post-fatigue isometric strength testing by performing three 5-s isometric MVCs with 30 seconds rest in between.

Measurements

Isometric strength (non-exercised muscle groups)

During both Pre- and Post-MVCs in all four experimental testing visits, force was detected by the tension applied to the load cell. The force signal was digitized with a 12-bit analog-to-digital converter (National Instruments, Austin, TX) and stored in a personal computer (Dell Optiplex 755, Round Rock, TX) for further analyses. For each force signal, the maximal force output was selected from the highest 1-s portion of the 5-s isometric MVC.

Isometric strength decline (exercised muscle groups)

The decline of isometric strength of the exercised muscle groups during fatiguing interventions was calculated using the following formula:

Percentage Decline of Isometric Strength = (fresh MVC - fatigued MVC) / fresh MVC

The fresh MVC and fatigued MVC values were selected from the first five seconds from the first fatiguing set and the last five seconds from the last (sixth) fatiguing set, respectively.

Surface EMG signal recording and processing

Bipolar surface EMG electrodes (DE 2.1 Single Differential Surface EMG Sensor, Delsys, Inc., Natick, MA; 10 mm interelectrode distance) were placed on the muscle belly of the left biceps brachii during the Arm-Arm Visit and Leg-Arm Visit, and on the left vastus lateralis during the Arm-Leg Visit and Leg-Leg Visit, according to the electrode placement recommendations from the SENIAM project[24]. A reference electrode (5.08 cm diameter Dermatrode HE-R, American Imex, Irvine, CA) was placed over the 7th cervical vertebrae during data collection. Prior to detecting any EMG signals, all skin sites were shaved with a razor and cleansed with rubbing alcohol. In addition, all the surface EMG sensors were firmly secured to the skin with adhesive tape. The bipolar surface EMG sensors recorded EMG signals during all Pre- and Post-testing MVCs, as well as during all the fatiguing interventions.

The analog EMG signals were collected with a modified Bagnoli 16-channel desktop EMG system (Delsys, Inc., Natick, MA). The EMG signals were preamplified (gain=1000) and filtered with high and low pass filters set at 20 Hz and 450 Hz, respectively. The filtered signals were then digitized at a sampling rate of 20000 Hz with a 12-bit analog-to-digital converter (National Instruments, Austin, TX) and stored in a personal computer (Dell Optiplex 755, Round Rock, TX) for subsequent analyses. Specifically, the amplitude (root-mean-square (RMS)) of each recorded EMG signal was calculated, and then normalized as a percentage of the amplitude value obtained during that muscle's Pre-MVC.

Statistical analysis

Separate three-way (sex [male vs. female] × time [Pre vs. Post] × fatiguing condition [Arm-Arm vs. Leg-Arm]) mixed factorial analyses of variance (ANOVAs) were performed to examine potential changes in the isometric strength and the normalized EMG amplitude of the non-exercised elbow flexors before and after the fatiguing interventions. Same three-way mixed factorial ANOVAs (sex [male vs. female] × time [Pre vs. Post] × fatiguing condition [Arm-Leg vs. Leg-Leg]) were also conducted to examine potential changes in the isometric strength and the normalized EMG amplitude of the non-exercised knee extensors before and after the fatiguing interventions. When appropriate, the follow-up test included paired sample t-tests. All statistical tests were conducted using statistical software (IBM SPSS Statistics 19.0, IBM, Armonk, NY) with alpha set at 0.05. Effect sizes were calculated using Cohen's d[25] to examine the magnitude of treatment effects.

Results

Table 1 shows the percent declines of isometric strength of the exercised muscle groups after 6 sets of 30-second maximal isometric fatiguing exercise interventions.

Test-retest reliability

The pre-fatigue maximal isometric strength values for the non-exercised elbow flexors between two experimental

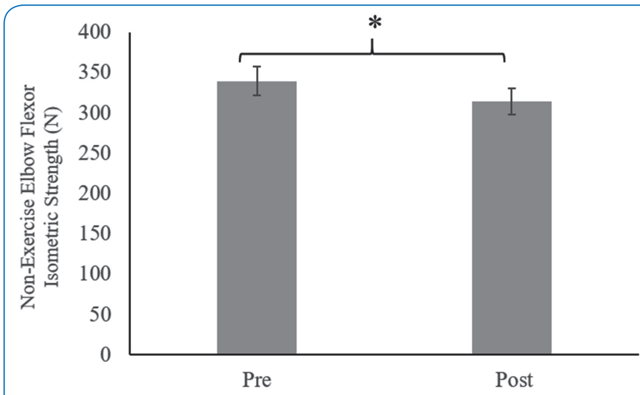

Figure 2. The isometric strength of the non-exercised elbow flexors (collapsed across gender and fatiguing condition) before (Pre) and after (Post) the fatiguing interventions. *Statistically significant difference (p≤0.05).

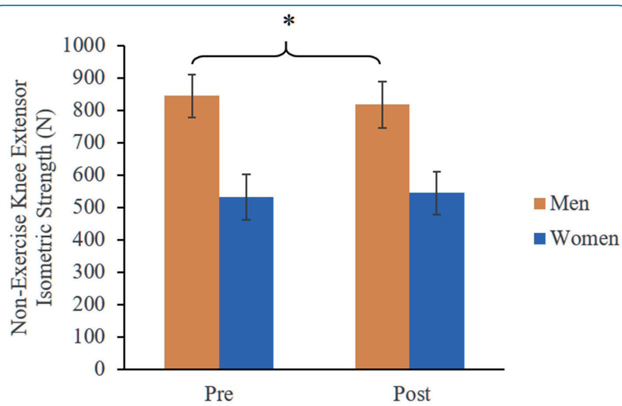

Figure 3. The isometric strength of the non-exercised knee extensors (collapsed across fatiguing condition) before (Pre) and after (Post) the fatiguing interventions. *Statistically significant difference (p≤0.05).

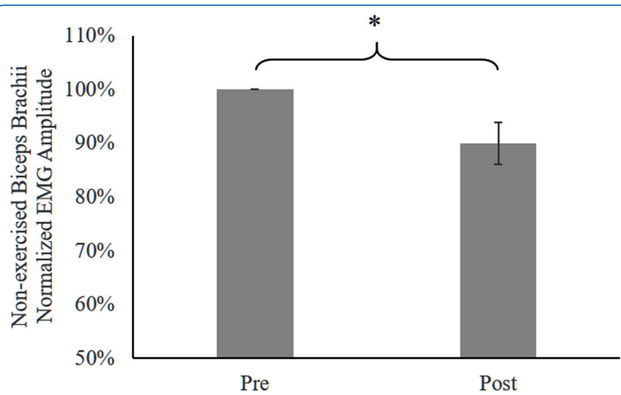

Figure 4. The normalized electromyographic (EMG) of the non-exercised biceps brachii (collapsed across gender and fatiguing condition) before (Pre) and after (Post) the fatiguing interventions. *Statistically significant difference (p≤0.05).

visits (Arm-Arm vs. Leg-Arm) were reliable, with r=0.97 for the intraclass correlation coefficient model (3, 1) ($ICC_{3,1}$) and 17.88 N for the standard error of measurement (SEM)[26]. In addition, the isometric strength values were not significantly different between visits (p=0.331). The pre-fatigue maximal isometric strength values for the non-exercised left knee extensors between two experimental visits (Arm-Leg vs. Leg-Leg) were also reliable, with the $ICC_{3,1}$=0.96, the SEM=25.96 N, and no significant difference between testing days (p=0.203). In addition, our data also showed that the ICCs for the surface EMG amplitudes corresponding to the pre-fatigue MVCs in all non-exercised muscles (biceps brachii and vastus lateralis) are greater than 0.79, with no significant differences between testing days.

Isometric strength (non-exercised limbs)

For the non-exercised elbow flexors, the results from the 3-way mixed factorial ANOVA indicated that there were no significant 3-way or 2-way interactions, but there was a main effect for time (*p*=0.001). When collapsed across sex and fatiguing condition, the follow-up paired sample t-test showed that the isometric strength of the non-exercised elbow flexors significantly decreased 7.43% following the fatiguing interventions (mean±SE: Pre vs. Post=339.66±18.02 N vs. 314.41±16.37 N, *p*=0.001; Cohen's *d*=0.23; Figure 2).

As for the non-exercised knee extensors, the 3-way mixed factorial ANOVA showed that there was no significant 3-way interaction, but there was a significant sex × time 2-way interaction (*p*=0.025). When collapsed across fatiguing condition, the follow-up paired sample t-tests showed that the isometric strength of the non-exercised knee extensors significantly decreased 9.67% for men (mean±SE: Pre vs. Post=845.02±65.96 N vs. 817.39±71.46 N, *p*=0.019; Cohen's *d*=0.13), but not for women (mean±SE: Pre vs. Post=531.31±70.19 N vs. 545.02±66.46 N, *p*=0.15; Cohen's *d*= 0.07) (Figure 3).

Normalized EMG amplitude

Non-exercised biceps brachii

The results from the 3-way mixed factorial ANOVA indicated that there were no significant 3-way or 2-way interactions. However, there was a main effect for time (*p*=0.036). When collapsed across fatiguing condition and sex, the paired sample t-test showed that the fatiguing interventions caused significant decrements in the normalized EMG amplitude for the non-exercised biceps brachii (mean±SE: Pre vs. Post= 100.0±0.0% vs. 90.0±3.9%, *p*=0.024; Cohen's *d*=0.28; Figure 4).

Non-exercised vastus lateralis

The results from the 3-way mixed factorial ANOVA indicated that there were no significant 3-way interaction, 2-way interactions, as well as main effects.

Discussion

The main purpose of this investigation was to examine if NLMF is muscle-specific. In addition, we also aim to examine whether sex factor has any differential effects on NLMF in upper body and lower body muscle groups. The surface EMG amplitude was used as a global measurement of muscle activity to explain or support our results on isometric strength. Based on our results, NLMF was present in the non-exercised upper body muscle groups (percent decline of the isometric strength=7.43%) for both sexes following 6 sets of 30-second unilateral fatiguing protocls; but it was only presented in the lower body muscle groups for men (percent decline of the isometric strength=9.67%), not for women. In addition, whether fatiguing upper body or lower body did not influence the presence of NLMF, which is in agreement with Halperin et al.[8].

NLMF in upper body muscle group

As the primary marker of NLMF, the isometric strength of the non-exercised elbow flexors decreased following the fatiguing interventions. This NLMF observed in upper body, in addition, was not dependent on either sex (male vs. female) or fatiguing condition (fatigue upper body vs. lower body muscles). Accompanied with the decreased isometric strength of the non-exercised elbow flexors is the decreased EMG amplitude of the non-exercised biceps brachii. Although using the surface EMG technique to examine the voluntary drive from the central nervous system to a specific muscle has some limitations[27], the EMG amplitude does provide a useful approximation of the amplitude component of the neural drive to a specific muscle[28]. The results of the normalized EMG amplitude from the current investigation indicated that the subjects were not able to fully activate their biceps brachii muscles following both fatiguing conditions. Thus, the decreased isometric strength of the non-exercised elbow flexors can at least be partially explained by the decreased EMG amplitude following fatiguing interventions.

The presence of NLMF in upper body muscle group belongs to the minority of the literature. Based on a recent systematic review, about 3/4 (23 of 30 measurements) of all performance outcome measurements of the lower limbs observed NLMF, whereas only about 1/3 (9 out of 28 measurements) of all measurements testing the upper body observed evidence for NLMF[1]. In addition, even though we used similar experimental design as used in Halperin et al.[8], the results are different. Specifically, these authors found that only non-exercised knee extensors demonstrated NLMF, but not the non-exercise elbow flexors. The main explanation of greater NLMF observed on lower body is that the knee extensors are bigger muscles which produce greater force, thereby requiring greater amount of neural drive from the central nervous system to be fully activated. Thus, if there was an exercise-induced central fatigue, the deficit of the voluntary drive can have a more influential effect on the activation of bigger muscles. Therefore, with more difficulty to fully activate the quadriceps when comparing to the biceps brachii[14], it is suggested that the quadriceps are more likely susceptible to NLMF. However, the results from the current study, along with our previous investigation using dynamic maximal concentric or eccentric fatiguing protocol[17,18], suggest that even smaller upper body muscles (e.g., elbow flexors) are capable of demonstrating NLMF. It is important to point that though, among all the investigations that have examined NLMF, the different fatiguing protocols being used, the different training status of the participants, as well as the different measurements that being used for testing limbs might have potentially influenced the results. In fact, this variability has been shown from the Tables 1 and 2 listed in Halperin et al.[1]. Using fatiguing protocol as an example, a common fatiguing intervention setup in NLMF investigations is one or two bouts of prolonged MVCs (usually over 60 seconds) on the unilateral limb muscle groups[1-4,8]. During the sustained MVC, blood flow is occluded due to high intramuscular pressure, which minimizes the recovery of muscle fibers and maximizes the fatigue occurring within the muscle throughout the contraction. Thus, prolonged isometric MVC-induced strength loss potentially has a greater peripheral component than intermittent isometric MVCs with resting intervals[29]. Therefore, central fatigue may play a greater role in intermittent MVCs-induced strength loss. In the current investigation, we have used the protocol of 6 sets of 30-s isometric MVCs with 30-s resting interval between sets. It is possible that this protocol might have induced greater central fatigue than the protocol that was used in Halperin et al.[8], even though the total fatiguing exercise durations were similar (2 × 100s = 200s in Halperin et al. vs. 6 × 30s = 180s in the current investigation). If this were the case, even smaller muscle groups such as elbow flexors might have been affected by the greater amount of central fatigue, thereby demonstrating significant level of NLMF. Unfortunately, previous studies and the current investigation were not able to compare the levels of central aspect of muscle fatigue after different fatiguing protocols.

NLMF in lower body muscle group

The NLMF in lower body muscle group (the non-exercised knee extensors) did not show similar trends as the upper body muscle group did. First, the effect sizes of NLMF in lower body muscle group (Men: Cohen's d=0.13; Women: Cohen's d=0.07) are smaller than that in the upper body muscle group (Cohen's d=0.23), indicating that the NLMF in lower body muscles has greater variations than that in the upper body muscles. Second, sex factor does matter: unlike men, women did not demonstrate NLMF in their non-exercised knee extensors. In fact, 5 of 9 women experienced increases in isometric strength for non-exercised knee extensors after the fatiguing exercises. Regarding those who experienced isometric strength increments, our result indeed belongs to the minority of the results from all the similar experiments conducted previously, but it was not the first time to observe this interesting phenomenon. Grabiner and Owings[30] found significant increase in the non-exercised contralateral knee extension moment after their subjects performed 75 unilateral isokinetic maximal eccentric knee extensions. Although the authors did not provide any mechanistic explanations, it does provide an evidence for this possible “potentiation” effect to support our observation in the current investigation.

As one of the very few investigations examined cross-over fatigue in both sexes, Martin and Rattey[3] found that after a 100-s knee extension MVC performed with the dominant leg, men demonstrated a significant reduction of strength in the contralateral non-dominant knee extensors, but this strength reduction was absent in women. This sex difference in cross-over fatigue was accompanied by greater reductions of voluntary activation and muscle activity in the non-dominant knee extensors for men than for women[3]. As the first study investigating potential gender difference in NLMF using different fatiguing conditions (fatigue upper body vs. fatigue lower body), our findings with regards to NLMF in lower body muscle group (non-exercised knee extensors) are generally in agreement with the findings from Martin and Rattey[3]. According to the authors, sex difference in central fatigue may be originated from the supraspinal area of the central nervous system. Specifically, it is possible that interhemispheric connections between fatigued cortex and the motor cortex projecting to the non-exercised limb may be different between sexes. In addition, another potential candidate is the potential difference(s) in neuronal control of upper and lower limbs[31,32], as mentioned in Skarabot et al.[33] regarding the phenomenon of “bilateral deficit”, that the inhibition at the cortical level (interhemispheric inhibition) is absent in lower limbs when compared to upper limbs[33]. Therefore, the combination of these two factors (sex and which muscle being examined) might have resulted in the findings we have observed.

Lastly, there is a small discrepancy between the NLMF observed in the non-exercised knee extensors for men and the unaltered EMG amplitude from the non-exercised vastus lateralis muscle. It is important to mention that, two factors regarding the EMG amplitude might have also contributed to this discrepancy: 1) The nonlinear EMG-force relations in human skeletal muscles[34-36], where the increase/decrease of the EMG amplitude does not always perfectly match the force increment/decrement. 2) The cancellation of EMG amplitude[37] could have also made the discrepancy between force-EMG response possible. Therefore, a small deviation between isometric strength response and EMG amplitude response can still be considered as a normal observation.

Limitations

Our study showed a few novel findings regarding the sex difference in NLMF. However, from the current investigation, we are not able to provide more specific details regarding the exact sites where the NLMF was developed. For example, due to the fact that our experiment did not measure the supraspinal and spinal excitabilities, it is beyond our capability to distinguish the central vs. peripheral component regarding the decreased EMG amplitude. In addition, measuring variable such as rate of relaxation may provide a more mechanistic insight regarding the possibility of peripheral fatigue. Thus, future investigations should include these measurements to explore the exact sites where the NLMF was developed with more mechanistic insights. Another potential limitation that can be overcome in future studies is that, besides isometric strength, more performance-related dependent variables can be used to assess the NLMF, such as force steadiness, endurance, and so on. These variables are more related to functional capacities, which can be specifically useful for older adults and other special populations.

In conclusion, consistent with our previous investigation where the dynamic fatiguing exercises were used[17], isometric fatiguing interventions induced NLMF in the non-exercised upper body muscle group (elbow flexors) for both sexes. We also found that the NLMF was more prominent in the upper body muscle group than in the lower body muscle group (knee extensors). We believe that the less-reported NLMF in upper body might be due to factors such as the different fatiguing protocol used in the current investigation. The presence of NLMF in lower body muscle group (knee extensors) is sex dependent: women seem to be less susceptible to NLMF. This sex difference in lower body NLMF may be due to different neural control of lower body muscles between sexes.

Acknowledgement

The authors would like to thank all the participants who took time out of their schedules to help with this project.

References

1. Halperin I, Chapman DW, Behm DG. Non-local muscle fatigue: effects and possible mechanisms. Eur J Appl Physiol 2015;115:2031-48.
2. Doix AC, Lefevre F, Colson SS. Time course of the cross-over effect of fatigue on the contralateral muscle after unilateral exercise. Plos One 2013;8:e64910.
3. Martin PG, Rattey J. Central fatigue explains sex differences in muscle fatigue and contralateral cross-over effects of maximal contractions. Pflugers Arch 2007;454:957-69.
4. Ratty J, Martin PG, Kay D, Cannon J, Marino FE. Contralateral muscle fatigue in human quadriceps muscle: evidence for a centrally mediated fatigue response and cross-over effect. Pflug Arch Eur J Phy 2006;452:199-207.
5. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. Physiol Rev 2001;81:1725-89.
6. Kennedy DS, Fitzpatrick SC, Gandevia SC, Taylor JL. Fatigue-related firing of muscle nociceptors reduces voluntary activation of ipsilateral but not contralateral lower limb muscles. J Appl Physiol 2015;118:408-18.
7. Kennedy DS, McNeil CJ, Gandevia SC, Taylor JL. Fatigue-related firing of distal muscle nociceptors reduces voluntary activation of proximal muscles of the same

limb. J Appl Physiol 2014;116:385-94.
8. Halperin I, Copithorne D, Behm DG. Unilateral isometric muscle fatigue decreases force production and activation of contralateral knee extensors but not elbow flexors. Appl Physiol Nutr Metab 2014;39:1338-44.
9. Halperin I, Aboodarda SJ, Behm DG. Knee extension fatigue attenuates repeated force production of the elbow flexors. Eur J Sport Sci 2014;14:823-9.
10. Kennedy A, Hug F, Sveistrup H, Guevel A. Fatiguing handgrip exercise alters maximal force-generating capacity of plantar-flexors. Eur J Appl Physiol 2013; 113:559-66.
11. Takahashi K, Maruyama A, Hirakoba K, et al. Fatiguing intermittent lower limb exercise influences corticospinal and corticocortical excitability in the nonexercised upper limb. Brain Stimul 2011;4:90-6.
12. Todd G, Petersen NT, Taylor JL, Gandevia SC. The effect of a contralateral contraction on maximal voluntary activation and central fatigue in elbow flexor muscles. Exp Brain Res 2003;150:308-13.
13. Zijdewind I, Zwarts MJ, Kernell D. Influence of a voluntary fatigue test on the contralateral homologous muscle in humans? Neurosci Lett 1998;253:41-4.
14. Behm DG, Whittle J, Button D, Power K. Intermuscle differences in activation. Muscle Nerve 2002;25:236-43.
15. Brooke JD, Cheng J, Collins DF, McIlroy WE, Misiaszek JE, Staines WR. Sensori-sensory afferent conditioning with leg movement: gain control in spinal reflex and ascending paths. Prog Neurobiol 1997;51:393-421.
16. Zehr EP, Collins DF, Frigon A, Hoogenboom N. Neural control of rhythmic human arm movement: phase dependence and task modulation of hoffmann reflexes in forearm muscles. J Neurophysiol 2003;89:12-21.
17. Ye X, Beck TW, Defreitas JM, Wages NP. An examination of the strength and electromyographic responses after concentric vs. eccentric exercise of the forearm flexors. J Strength Cond Res 2014;28:1072-80.
18. Beck TW, Ye X, Wages NP. Differential Effects of Unilateral Concentric Vs. Eccentric Exercise on the Dominant and Nondominant Forearm Flexors. J Strength Cond Res 2016;30:703-9.
19. Hunter SK. The Relevance of Sex Differences in Performance Fatigability. Med Sci Sports Exerc 2016; 48:2247-56.
20. Hunter SK. Sex differences in human fatigability: mechanisms and insight to physiological responses. Acta Physiol (Oxf) 2014;210:768-89.
21. Wust RC, Morse CI, de Haan A, Jones DA, Degens H. Sex differences in contractile properties and fatigue resistance of human skeletal muscle. Exp Physiol 2008; 93:843-50.
22. Hunter SK, Butler JE, Todd G, Gandevia SC, Taylor JL. Supraspinal fatigue does not explain the sex difference in muscle fatigue of maximal contractions. J Appl Physiol 2006;101:1036-44.
23. Amann M, Dempsey JA. Locomotor muscle fatigue modifies central motor drive in healthy humans and imposes a limitation to exercise performance. J Physiol 2008;586:161-73.
24. Hermens H, Freriks B, Merletti R, et al. SENIAM European recommendations for surface ElectroMyoGraphy: Result of the SENIAM Project. Enschede, The Netherlands: Roessingh Research and Development 1999.
25. Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates 1988.
26. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. J Strength Cond Res 2005;19:231-40.
27. Farina D, Merletti R, Enoka RM. The extraction of neural strategies from the surface EMG: an update. J Appl Physiol 2014;117:1215-30.
28. Enoka RM, Duchateau J. Inappropriate interpretation of surface EMG signals and muscle fiber characteristics impedes understanding of the control of neuromuscular function. J Appl Physiol 2015;119:1516-8.
29. Taylor JL, Allen GM, Butler JE, Gandevia SC. Supraspinal fatigue during intermittent maximal voluntary contractions of the human elbow flexors. J Appl Physiol 2000;89:305-13.
30. Grabiner MD, Owings TM. Effects of eccentrically and concentrically induced unilateral fatigue on the involved and uninvolved limbs. J Electromyogr Kinesiol 1999;9:185-9.
31. Volz LJ, Eickhoff SB, Pool EM, Fink GR, Grefkes C. Differential modulation of motor network connectivity during movements of the upper and lower limbs. Neuroimage 2015;119:44-53.
32. Luft AR, Smith GV, Forrester L, et al. Comparing brain activation associated with isolated upper and lower limb movement across corresponding joints. Hum Brain Mapp 2002;17:131-40.
33. Skarabot J, Cronin N, Strojnik V, Avela J. Bilateral deficit in maximal force production. Eur J Appl Physiol 2016.
34. Woods JJ, Bigland-Ritchie B. Linear and non-linear surface EMG/force relationships in human muscles. An anatomical/functional argument for the existence of both. Am J Phys Med 1983;62:287-99.
35. Bigland-Ritchie B. EMG/force relations and fatigue of human voluntary contractions. Exerc Sport Sci Rev 1981;9:75-117.
36. Milner-Brown HS, Stein RB. The relation between the surface electromyogram and muscular force. J Physiol 1975;246:549-69.
37. Keenan KG, Farina D, Maluf KS, Merletti R, Enoka RM. Influence of amplitude cancellation on the simulated surface electromyogram. J Appl Physiol 2005; 98:120-31.