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Contraction intensity and sex differences in knee-extensor fatigability

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Abstract

Females are less fatigable than males during isometric contractions across various muscles and intensities. However, sex differences in knee-extensor fatigability remain relatively unexplored. **Purpose:** To determine the sex difference in performance fatigability for intermittent, isometric contractions of the knee-extensor muscles. **Methods:** Eighteen participants (10 males, 8 females) performed intermittent, isometric, knee-extensor contractions at 30% of their maximal voluntary force (MVC) for 30 min and in a separate session at 50% MVC until task-failure. During both fatiguing protocols a MVC was performed every 60 s and electromyography (EMG) was recorded during all contractions. **Results:** At task completion males had a larger reduction in MVC force for the 30% MVC task (−32±15% vs. −15±16%, P=0.042) and the 50% MVC task (−34±8% vs. −24±1%, P=0.045). Furthermore, for the 50% MVC task, females had a longer task duration (937±525 s vs. 397±153 s, P=0.007). The rise in EMG activity and force fluctuations were more rapid for the males than females (P<0.05). When participants were matched for strength *post-hoc* (n=10), a sex difference in fatigability for both tasks was still evident. **Conclusions:** Females were less fatigable than males during intermittent, isometric, knee-extensor contractions at moderate relative forces and this difference was independent of strength.

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INTRODUCTION

Fatigue is a disabling symptom characterised by sensations of tiredness and weakness, underpinned by multiple complex mechanisms (Enoka and Duchateau, 2016). The intricacies of fatigue vary depending on circumstances, but during exercise, reductions in physical function [i.e., performance fatigability (Hunter, 2017)] involves impaired force producing capacity of the working muscles. An exercise-induced reduction in force capacity has been termed muscle fatigue (Gandevia, 2001), mechanisms contributing to this reduction in force can occur at various and multiple sites along the motor pathway, between neural activation and the contractile proteins of the working muscles (Enoka and Duchateau, 2016). The contribution of these mechanisms and the magnitude of this fatigability however, are dependent on the demands of the exercise task (Enoka and Stuart, 1992) such as the contraction intensity (Place et al. , 2009). When submaximal tasks are performed at lower intensities for a longer duration, impaired activation of the muscles can contribute substantially to fatigability (Smith et al. , 2007) whereas contractile failure is often dominant for higher intensity–shorter duration tasks with modest deficits in activation (Bigland-Ritchie et al. , 1986).

Performance fatigability is also modulated by the sex of the individual. Males have typically shown to be more fatigable than females in several muscle groups (Hunter, 2014, Hunter, 2016) for both continuous, and intermittent tasks (Hunter and Enoka, 2001, Hunter et al. , 2009, Yoon et al. , 2009). However, the sex difference in fatigability and the contributing mechanisms can be specific to the demands of the task including the contraction intensity and type, and the muscle groups involved. For example, for lower intensity sustained contractions, there were sex differences for the elbow-flexor muscles, but not in the ankle-dorsiflexor muscles (Avin et al. , 2010), and no sex differences for the elbow-extensor muscles (Dearth et al. , 2010). The sex differences in fatigability are also greater at lower intensities during sustained contractions that are held until task-failure for the elbow-flexor muscles, forearm and the knee-extensor tasks (Maughan et al. , 1986, West et al. , 1995, Yoon et al. , 2007), possibly in part due to perfusion-related differences between sexes, as males produce more absolute force for the same relative intensity (Clark et al. , 2005). For intermittent tasks, when perfusion related-differences are minimized, the sex difference is still apparent, even when the sexes are matched for strength in elbow-flexor and forearm muscles (Hunter et al. , 2006, Hunter et al. , 2004). In the *vastus lateralis*, females have been shown to have greater proportion of type-1 oxidative fibres (Staron et al. , 2000) giving rationale for a more fatigue resistant muscle. Lower limb muscles are important for locomotion and often exercise training regimes but there is less information on any sex-related differences across different tasks. While the sex difference in fatigability is primarily attributable to contractile and metabolic processes for the elbow-flexor muscles, for lower limb muscles (ankle-dorsiflexors and knee-extensors), the sex difference has also been attributed to larger reductions in voluntary activation in men during maximal tasks (Martin and Rattey, 2007, Russ and Kent-Braun, 2003). Thus, the mechanisms of sex differences in performance fatigability are specific to the task and muscle groups involved.

A sex difference in fatigability of the knee-extensor muscles was demonstrated for sustained isometric and isotonic contractions (Clark, Collier, 2005, Martin and Rattey, 2007, Maughan, Harmon, 1986, Senefeld et al. , 2013) but it is unknown if the fatigability of male and female knee-extensor muscles also occurs for submaximal intermittent, isometric contractions across different contraction intensities. Whilst Albert et al. (2006) purported to use this contraction style in the knee extensors and found that females were less fatigable, the protocol used 30 s contractions with a 1:1 duty cycle. Therefore, the long duration of contraction likely led to differential degrees of blood flow occlusion between sexes, which might have been the reason for the sex difference reported (Clark et al., 2005). In order to examine whether the sex difference was still apparent without occlusion difference, the present study used a much shorter duration contraction (3 s), with a duty cycle previously reported to negate the influence of occlusion (Hunter et al., 2004). The aim of this study was to determine sex differences in fatigability for two submaximal intermittent contraction intensities performed with the knee-extensors. It was hypothesised that females would exhibit less fatigability than males following intermittent, isometric contractions.

METHODS

Participants

Eighteen recreationally active participants were recruited from University sports teams, 10 males, (age, 21 ± 1 years; stature, 1.78 ± 0.04 m; mass, 78 ± 12 kg) and eight females (age, 21 ± 0 years, stature, 1.64 ± 0.06 m; mass, 61 ± 10 kg) who regularly competed in sport of intermittent nature (hockey, netball, rugby, and soccer) provided written informed consent to volunteer for the study. Participants arrived at the laboratory rested and hydrated, having avoided strenuous exercise in the preceding 48 h, and having refrained from caffeine for 12 h and alcohol for 24 h prior to each experiment. The study received institutional ethical approval and was conducted according to the Declaration of Helsinki.

Experimental Design and Exercise Protocol

Participants visited the laboratory on three separate sessions over a 10-day period that included one familiarisation session (visit 1) followed by two experimental sessions. All sessions were a minimum of 48 and a maximum of 72 hours apart. On visits 2 and 3, participants completed intermittent, isometric, knee-extensor exercise at either 30 or 50% maximal voluntary contraction (MVC) in a randomised, counterbalanced, crossover design. During the familiarisation session participants practiced performing MVCs with their dominant knee-extensors, and two sets of the intermittent contractions (3 s contraction, 2 s rest) at 30% MVC. One set comprised of 12 contractions followed by a MVC (Figure 1).

Each experimental session began with three ~3-5 s MVCs with 30 s of recovery between each trial to attain maximum MVC force. Participants then performed an intermittent fatiguing task either at 30% or 50% MVC with the order of the tasks randomised across the two experimental days. Target forces, based on the MVC achieved on each day, and real-time force were presented on a computer screen placed in view of the participant. For the 30% MVC task, all participants exercised for 30 minutes and for the 50% MVC task, each participant performed the intermittent contractions until task-failure. Task-failure was defined as a failure to meet the target force by 5% three times within one set. A metronome (Gymboss interval timer, Gymboss LLC, St Clair MI, USA) ensured the correct timing for the start and end of each contraction during the fatiguing protocols.

Force and Electromyography

Knee-extensor force (N) was recorded using a calibrated load cell (MuscleLab force sensor 300, Ergotest technology, Norway). The load cell was fixed to a custom-built chair and connected to a non-compliant cuff attached around the participant’s dominant leg, ~1-2 cm superior to the ankle malleoli. Participants were instructed to sit upright in the chair with the hips and knees at 90° of flexion, this position was maintained for the entire trial. The force signal was amplified (×300) with an isolated pre-amplifier (1902, Cambridge Electronic Design, [CED] UK), digitised at 4 kHz (Power 1401, CED, UK) and analysed offline with Spike2 v7.12 (CED, UK).

Electromyographic (EMG) activity was recorded from the *vastus lateralis* using surface electrodes (Kendall, Ag/AgCl H87PG/F, Covidien, MA, USA). After the skin was cleaned and shaved, electrodes were placed 2 cm apart over the muscle belly with a reference over the ipsilateral patella in accordance with SENIAM guidelines (Hermens et al. , 2000). Electrode placement was marked with permanent ink to ensure consistent placement between laboratory visits. From the recorded interference EMG, root mean square EMG (rmsEMG) amplitude was calculated during the submaximal and maximal (rmsMVC) contractions. The EMG signals were amplified (×1000) and band-pass filtered (20-2000 Hz) with an isolated pre-amplifier (1902, CED, UK), digitised (4 kHz; Power 1401, CED, UK), and analysed off line using Spike2 v7.12 (CED, UK).

Data Analysis

Maximal force was determined as the peak force achieved during the greatest of the three MVCs and the rmsMVC was calculated from the corresponding time point centred over a 500 ms window. During the fatiguing task, knee-extensor force, rmsEMG activity, and force fluctuations were measured over a 1.5 s window during each contraction. The rmsEMG during sets of contractions was normalised to the baseline rmsMVC at the beginning of each trial. Force fluctuations were quantified as the coefficient of variation (CV) of force during each submaximal contraction. The same variables were also analysed *post hoc* during the sets of submaximal contractions that were closest in time to the 25, 50 and 75% of task duration. Five males and five females were matched for strength; each pairing had a baseline knee-extensor MVC within ~10% of the matched partner. This was included in the analysis to compare the fatigability of the knee extensors to strength-matched pairs in the elbow flexors (Hunter et al., 2004).

Statistical Analysis

Data are presented as mean ± SD within the text and figures. To detect effects of sex (males, females), time (start and end exercise) and any interactions, the data of the dependent variables were entered into a separate two-way (2 × 2) Analysis of Variance (ANOVA) for each of the fatiguing protocols. Dependent variables included force, rmsEMG, and CV of force. Assumptions of sphericity were explored and controlled for all variables using the Greenhouse-Geisser adjustment, where appropriate. Post-hoc paired sample *t*-tests were used to detect pre- to post-differences within groups (SPSS v21, IBM, Chicago, USA) and effect sizes were calculated for the selected comparisons using Cohen's *d*. Due to the small sample size of strength-matched pairs, ANOVAs and post-hoc tests were not performed, however effect sizes were calculated for the differences between sexes. Statistical significance was assumed at $P \leq 0.05$.

RESULTS

Males were 36% stronger than females (599 ± 139 vs. 384 ± 94 N, $P = 0.005$) consequently, target forces for the men were higher for the 30% MVC task (169 ± 46 vs. 112 ± 29 N, respectively, $P = 0.007$) and 50% MVC task (288 ± 69 vs. 195 ± 37 N, respectively $P = 0.003$). MVC force was not different between the strength-matched males and females (438 ± 69 vs 423 ±82, $P = 0.77$; mean difference: 27 ± 4 N; 5 ± 4%).

30% MVC Fatiguing Task. MVC force declined from pre- to post-exercise (time effect, $F_{1,7} = 28.65$; $P = 0.001$, Figure 2A) and there was a greater reduction for the males compared with females (sex*time interaction, $F_{1,7} = 6.13$, $P = 0.042$, $d = 1.87$). The average reduction in the males was 195 ± 125 N (Δ32 ± 15%; $P < 0.001$) and 57 ± 53 N for the females (Δ15 ± 16%; $P = 0.019$). In strength-matched pairs (Figure 2B), smaller MVC decreases were evident in females compared with males (Δ14 ± 10% vs. Δ23 ± 13% respectively, $d = 0.78$).

The normalised rmsEMG activity (% baseline) increased across time (time effect, $F_{1,7} = 16.99$, $P = 0.004$). There was no difference in rmsEMG (% baseline) between the sexes during the fatiguing exercise (group*time interaction, $F_{1,7} = 0.68$, $P = 0.436$, $d = 0.63$) with the males increasing by 46 ± 39% and the women by 17 ± 17% (Figure 2C). When participants were matched for strength (Figure 2D) the males increased by 24 ± 23% and females by 11 ± 10% ($d = 0.73$).

Force fluctuations did not significantly increase throughout the trial (time effect: $F_{1,7} = 3.47$, $P = 0.105$, $d = 1.41$). There was no difference in force fluctuations between sexes (group*time interaction effect: $F_{1,7} = 0.39$, $P = 0.56$, $d = 0.47$). In strength-matched pairs (Figure 2F), males' CV increased by 37 ± 63% and females by 6 ± 16% ($d = 0.66$).

50% MVC Fatiguing Task. Time to task-failure was longer for females than males (937 ± 525 vs. 397 ± 153 s, $P = 0.007$). Of the participants who were strength-matched, all pairs showed that females exercised for longer (1010 ± 546 s vs. 411 ± 211 s, Figure 3).

MVC force declined over time (time effect, $F_{1,7} = 99.39$, $P < 0.001$, Figure 4A) in both males (Δ203 ± 83 N, Δ34 ± 8%) and females (Δ96 ± 43 N, Δ24 ± 1%). Despite exercising for less time, the decline in MVC force was greater for males (group*time interaction $F_{1,7} = 5.91$, $P = 0.045$, $d = 1.84$) and this was reflected in the greater rate of MVC force loss for males compared with the females (34 ± 18 vs. 10 ±

8 N·min^{-1}, P = 0.003). The difference was also reflected in the strength-matched pairs (Δ23 ± 7% vs. Δ30 ± 8%, *d* = 0.93; Figure 4B).

The rmsEMG activity (% baseline) increased over time ($F_{1,7}$ = 27.33, P = 0.001, Figure 4C), with an increase of 56 ± 40% for males and 20 ± 14% for females. However, these increases were not different between sexes when compared at the same relative time intervals (group*time interaction $F_{1,7}$ = 2.81, P = 0.138, *d* = 1.27). Due to females exercising for longer, the rate of rise in rmsEMG was lower than the males (1.37 ± 1.59 vs. 5.45 ± 4.77%·min^{-1}, P = 0.035). In the strength-matched pairs (Figure 4D), 3 of the 5 females experienced smaller increases in rmsEMG (Δ13 ± 11% vs. Δ45 ± 50%, *d* = 0.88).

Force fluctuations (CV of force) were not different ($F_{1,7}$ = 1.79, P = 0.223) but increased over time (time effect, $F_{1,7}$ = 8.20, P = 0.024, Figure 4E). The increase was not different between the sexes when compared at the same relative time intervals (group*time interaction $F_{1,7}$ = 3.91, P = 0.088, *d* = 1.49). However, due to the shorter time to task-failure for males, the rate of force fluctuation increase was smaller in females (0.17 ± 0.11 vs. 0.39 ± 0.14%·min^{-1}, P = 0.001). In the strength-matched pairs (Figure 4F) 4 of the 5 females experienced smaller increases in CV than the males (Δ52 ± 13 vs. Δ17 ± 32%, *d* = 1.42).

DISCUSSION

The aim of the study was to determine the sex difference in fatigability of the knee-extensors during short duration intermittent, isometric exercise at two submaximal contraction intensities. The data illustrate that males show greater fatigability (reduction in MVC force) than females after intermittent contractions at 30% MVC, and the same pattern was evident for intermittent contractions to volitional exhaustion at 50% MVC. In line with the attenuated fatigue response, females exercised for more than twice as long as the males whilst exhibiting smaller increases in EMG activity and force fluctuations during the 50% task. When females and males were strength-matched (n = 5 pairs), the sex difference in the decline in MVC force, and the time to task-failure, were still evident. Collectively, these data demonstrate that a sex difference in fatigability exists for intermittent, isometric knee-extensor exercise at both low and moderate intensities, and this sex difference is probably not explained by absolute strength.

Our findings add to previous work in other muscle groups demonstrating that males are more fatigable then females during intermittent, isometric contractions (Albert et al., 2006, Hunter et al., 2004, Hunter et al., 2009). Furthermore, similar to when males and females were strength-matched for performance of an intermittent isometric contraction task (Hunter et al., 2004), we showed that females had a much longer time to task-failure (more than two-fold) compared with males for the 50% MVC task (937 vs. 397 s), however these results should be interpreted with caution as the small sample size precluded inferential analysis. Despite the females exercising for longer, MVC reduction was lower when compared with the males in our study, with a ~10% sex difference at task-failure. Thus, the rate of decline for MVC force was over three times greater for males than females (34 vs. 10 $N \cdot min^{-1}$), a finding that was mirrored in the rmsEMG and force fluctuation (CV) data. The data from the present study add to previous literature in other muscle groups showing that a sex difference in performance fatigability following intermittent contractions is present in the knee-extensors. This finding has implications for exercise training given the importance of the knee-extensors to locomotion.

Mechanisms for the sex differences in fatigability during the intermittent tasks (when blood flow is not occluded), include skeletal muscle metabolite accumulation, alterations in the contractile properties and the reductions in voluntary activation (Hunter, 2014, Hunter, 2016). Although surface EMG is not a direct indicator of neural drive (Farina et al. , 2014), we showed that the rate of rise in motor unit recruitment during the 50% task was more gradual for the females than the males, despite no differences at task-failure. During constant load contractions, EMG will typically increase, as we observed in this study. Data in male populations show that increases in EMG activity during strenuous exercise are closely linked with the contribution of anaerobic metabolism (Bundle et al. , 2006). This is primarily caused by an increase in motor unit recruitment and reduced discharge rates (Garland et al. , 1994) in response to compensatory increases in descending drive as the active muscle fibres become progressively fatigued (McNeil et al. , 2011). Data from a similar study in the elbow-flexors (Hunter, Critchlow, 2004) showed that males displayed greater increases in rmsEMG at task-failure following a 50% MVC trial and greater reductions in MVC force. This trend was also seen in the strength-matched pairs suggesting that motor unit activation for males and females were compensating and increased at different rates to sustain the required force.

Similarly, the force fluctuations increased at greater rates for the males during both fatiguing protocols. The magnitude of force fluctuations is primarily modulated by variability in the neural drive of the motor unit discharge rate at low frequencies (1–2 Hz) and explains up to 70% of the force steadiness (Farina and Negro, 2015). The absolute magnitude of force fluctuations (SD of isometric force) increases with contraction intensity. To allow comparisons between contractions between people of different strength, the fluctuations are normalized to the mean force and represented as the CV of force (Enoka et al. , 2003). As we observed, the force fluctuations progressively increase during fatiguing contractions for the knee-extensors during the 50% trial, a response which is observed for other muscles (Hunter, Critchlow, 2004, Hunter and Enoka, 2001). Despite not reaching statistical significance (interaction effect: $P = 0.088$), a trend for greater increases in force fluctuations in males was observed during the 50% trial. As well as this, greater rates of increase (pre-post change divided by time to task-failure, $\%\cdot\mathrm{min}^{-1}$) in force fluctuations were observed for the males in this study. Collectively, force fluctuation and EMG data suggest that motor unit recruitment and discharge rate changed at varying frequencies in response to the muscle fibres fatiguing at different rates between the sexes.

The greater rates of increase in the physiological adjustments reflected in the EMG and force fluctuations likely reflect sex differences originating in the muscle (Hunter, 2014, Hunter, 2016). The primary causes of a sex difference in fatigability during isometric contractions are mostly associated with contractile and metabolic mechanisms. For instance, females typically have a greater proportion of type I fibres (Staron et al., 2000), greater capillarisation of the knee-extensors (Roepstorff et al. , 2006), and greater vasodilation during exercise in the femoral artery (Parker et al. , 2007) than males. Thus, differences in skeletal muscle metabolism and contractile properties result in females exhibiting a more fatigue resistant muscle than males. Even when strength-matched with females, the males were more fatigable and the physiological adjustments reflected in the EMG and force fluctuations followed the same pattern as overall group data.

The sex differences in fatigability were evident at both lower (30%) and higher intensities (50%) of contraction. The time to task-failure of intermittent isometric knee-extensor contractions varies with exercise intensity in a hyperbolic manner describing a force-duration relationship (Burnley et al. , 2012). There is a critical force (intensity threshold) and above such an intensity, the development of fatigue increases rapidly. It is possible that females were exercising lower on the hyperbolic force-duration relationship relative to their critical intensity compared with males. Such that, females fatigued at a slower rate and achieved longer times to task-failure. For dynamic contractions performed with the knee-extensor muscles (cycling), the shape of the hyperbolic relationship does not differ between the sexes (Sundberg et al. , 2017). Whether there are sex differences in the intensity of this critical threshold for intermittent isometric fatiguing contractions is unknown.

There are several practical implications of the findings from this study for training and rehabilitation in males and females. Because males and females fatigue at different rates during relatively short-term exercise, males may need more time to recover than women between exercise training bouts. However, differences in recovery of males and females after fatiguing exercise is relatively unexplored. Furthermore, these results raise the possibility that females may need to train at a higher intensity during training bouts to have similar fatigue effects over a given time and similar neuromuscular adaptions with training. One path forward for future studies is to standardise contraction intensities around a critical intensity, rather than comparing fatigability based on an arbitrary percentage of MVC. This would enable the aetiology of the sex difference in fatigability to be located, and consequently, training and rehabilitation could be optimised for each sex.

One limitation of this study was that menstrual cycle phase or hormonal contraceptives were not controlled for in the group of females tested. While studies have demonstrated that MVC and fatigability varied in the knee-extensors across the phases of the menstrual cycle (Sarwar et al. , 1996, Tenan et al. , 2016), there is conflicting evidence showing no difference (de Jonge et al. , 2001). However, in younger women, the differences in performance and fatigability between males and females appear to be greater in effect size than possible difference across the menstrual cycle (Hunter, 2016).

Conclusion

We showed females to be less fatigable than males during intermittent, isometric knee-extensor exercise at both 30% and 50% of MVC force. The physiological adjustments reflected in the EMG activity and force fluctuations were more rapid for the males than the females. The sex differences in fatigability observed could not be explained by differences in absolute strength between men and women. These findings indicate that exercise performance that involves fatiguing contractions of the knee-extensors muscles may differ for males and females because of fundamental differences in muscle fatigability. Furthermore, understanding the sex differences in fatigability that are necessary for neuromuscular adaptations will promote more targeted and effective strategies during exercise training in males and females.

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Figure Legends

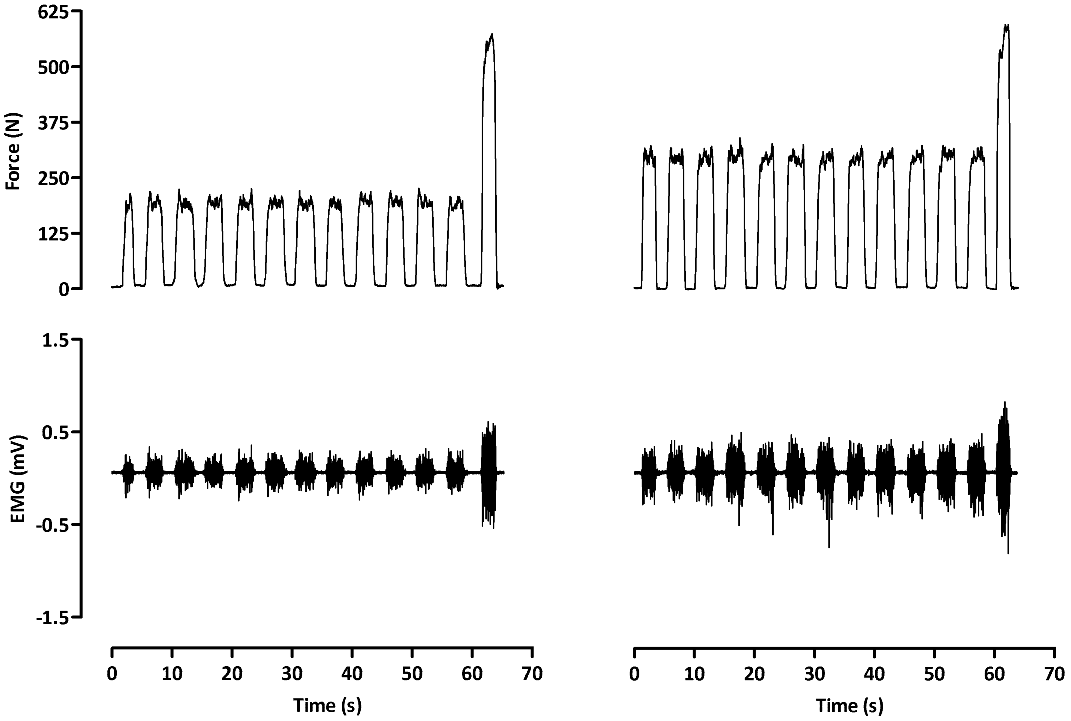

Figure 1. Force and EMG responses during one set of contractions in the 30% MVC (left hand panels) and 50% MVC trials (right hand panels). All data are from the same, representative participant.

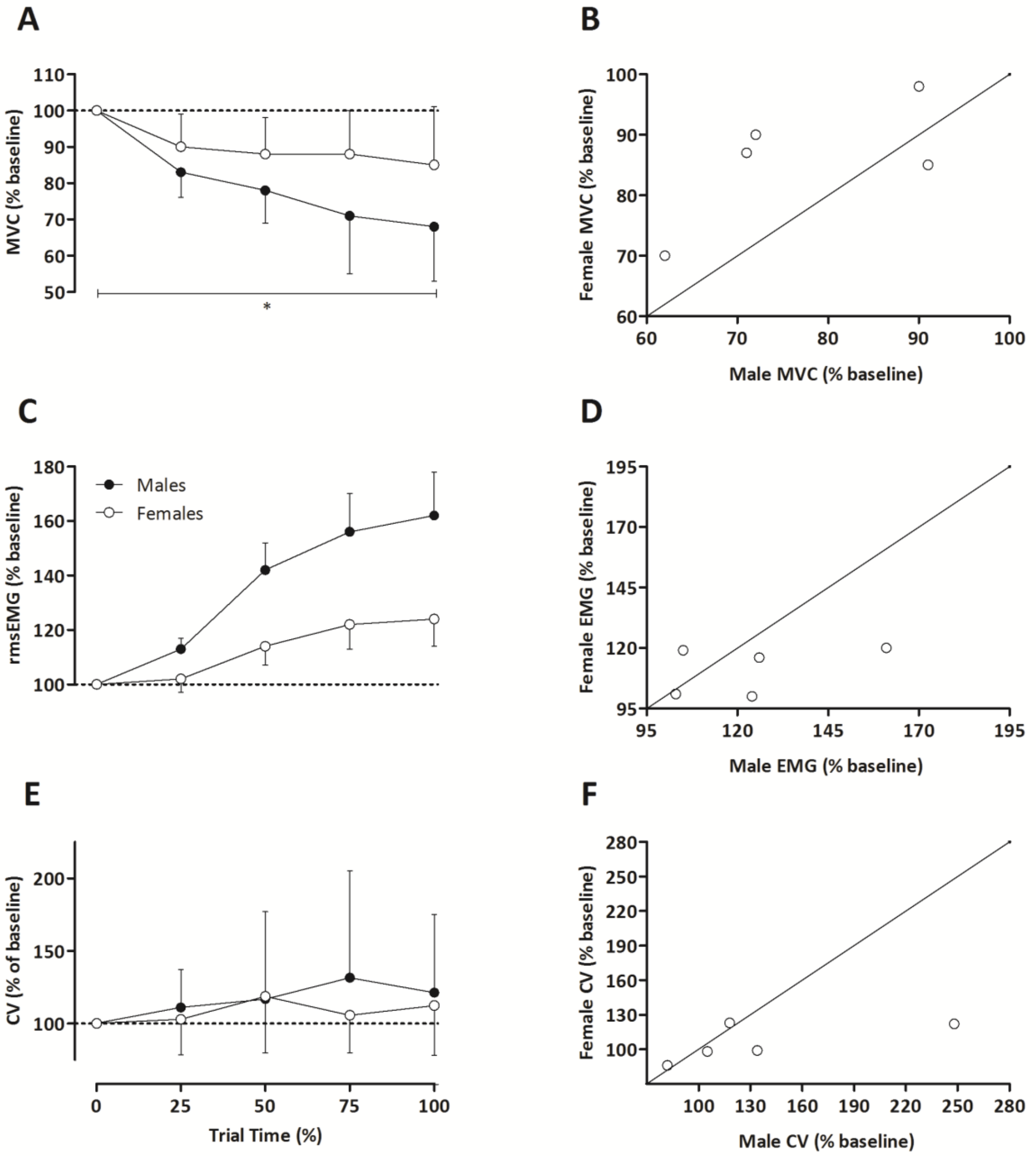

Figure 2. Mean reduction in maximal voluntary contraction force (A), pre-post reductions in maximal voluntary contraction force for the matched pairs (B), change in rmsEMG (C), pre-post change in rmsEMG for the matched pairs (D), change in force fluctuation (CV; E), and pre-post change in force fluctuations for the matched pairs (F) throughout the 30% trial. Black circles: males, unfilled circles: females. In panels B, D, and F the line of equality represents where an equal change for males and females would lie. * = $P < 0.05$ male vs. female for the change in MVC from baseline.

Figure 3. The relationship in time to task-failure in the 50% trial between strength-matched males and females (n = 5 pairs). The line of equality is shown to represent where an equal time in the pairs would lie.

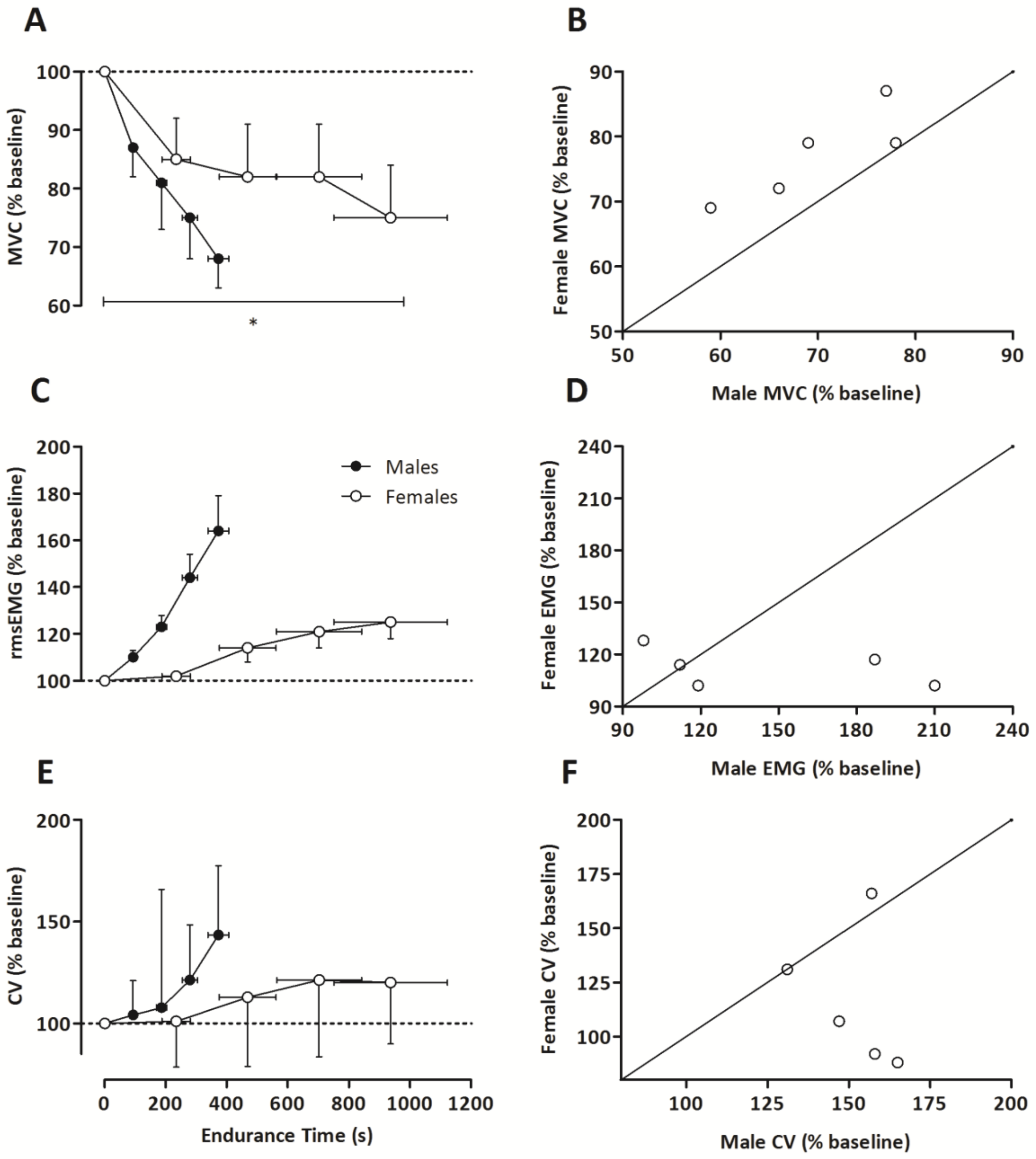

Figure 4. Mean reduction in maximal voluntary contraction force (A), pre-post reductions in maximal voluntary contraction force for the matched pairs (B), change in rmsEMG (C), pre-post change in rmsEMG for the matched pairs (D), change in force fluctuation (CV; E), and pre-post change in force fluctuations for the matched pairs (F) throughout the 50% trial. Black circles: males, unfilled circles: females. In panels B, D, and F the line of equality represents an identical change for males and females. * = P < 0.05 male vs. female for the change in MVC from baseline.