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Sex differences in fatigability and recovery relative to the intensity-duration relationship

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ABSTRACT

Females are less fatigable than males during isometric exercise at intensities relative to maximal voluntary contraction (MVC), however whether a sex difference in fatigability exists when exercise is prescribed relative to a critical intensity is unknown. This study established the intensity-duration relationship, and compared fatigability and recovery between sexes following intermittent isometric contractions normalised to critical intensity. Twenty participants (10 females) completed four intermittent isometric knee extension trials to task failure to determine critical intensity and the curvature constant (W'), followed by fatiguing tasks at +10 and −10% relative to critical intensity. Neuromuscular assessments were completed at baseline and for 45 minutes post-exercise. Non-invasive neurostimulation, near-infrared spectroscopy, and non-invasive haemodynamic monitoring were used to elucidate the physiological mechanisms responsible for sex differences. Females demonstrated a greater critical intensity relative to MVC than males (25±3 vs. 21±2% MVC, P=0.003), with no sex difference for W' (18,206±6,331 vs. 18,756±5,762 $N.s^{-1}$, P=0.850). Time to task-failure was greater for females (62.37±17.25 vs. 30.43±12.75 min, P<0.001) during the +10% trial, and contractile function recovered faster post-exercise (P=0.034). During the −10% trial females experienced less contractile dysfunction (P=0.011). Throughout both tasks, females demonstrated greater increases in oxyhaemoglobin (P≤0.044) and an attenuated exercise pressor reflex. These data show that a sex difference in fatigability exists even when exercise is matched for critical intensity. We propose that greater oxygen availability during exercise permits females to sustain a higher relative intensity than males, and is an explanatory factor for the sex difference in fatigability during intermittent, isometric contractions.

KEY POINTS

- Females demonstrate greater fatigue-resistance than males during contractions at intensities relative to maximum force. However, previous studies haven't accounted for the influence of metabolic thresholds on fatigability.

- This study is the first to test whether sex differences in fatigability exist when exercise intensity is normalised relative to a metabolic threshold: the critical intensity derived from assessment of the intensity-duration relationship during intermittent, isometric knee extensor contractions.

- We show that critical intensity in females occured at a higher percentage of maximum force compared to males. Furthermore, females demonstrated greater fatigue resistance at exercise intensities above and below this metabolic threshold.

- Our data suggests that the sex difference was mediated by a greater capacity for females to maintain oxygenation of the knee-extensors during exercise.

- These data highlight the importance of accounting for metabolic thresholds when comparing fatigability between sexes, whilst emphasising the notion that male data is not generalisable to female populations.

INTRODUCTION

Insight into the metabolic demands of a fatiguing task and the mechanisms responsible for the attainment of task failure can be gained by determining the intensity-duration relationship, which is well described in males (Poole *et al.*, 1988; Dekerle *et al.*, 2003; Jones *et al.*, 2008; Vanhatalo *et al.*, 2010). The duration that exercise can be maintained is progressively reduced as the intensity of the contraction increases, and the relationship becomes hyperbolic once a metabolic threshold, hereafter termed the critical intensity, has been exceeded (Jones *et al.*, 2010; Poole *et al.*, 2016). This phenomenon has been frequently reported during dynamic tasks (e.g. cycling and knee extension, Jones *et al.*, 2008; Vanhatalo *et al.*, 2010), and a similar relationship exists for intermittent, isometric tasks (Burnley, 2009; Burnley *et al.*, 2012). The critical intensity, the asymptote of the hyperbolic curve, represents the maximal sustainable work rate at which energy supply can be provided and sustained from oxidative metabolism (Poole *et al.*, 2016; Burnley & Jones, 2018). Below the critical intensity, substrate-level phosphorylation and the production of intramuscular metabolites are maintained at a steady state (Jones *et al.*, 2008; Black *et al.*, 2016). Exercise performed at intensities above the critical intensity requires ATP to be resynthesized from anaerobic metabolism, leading to a progressive loss of intramuscular homeostasis and a shorter time to task failure (Jones *et al.*, 2008; Vanhatalo *et al.*, 2010; Schäfer *et al.*, 2019). Exercise above the threshold is associated with progressive intramuscular perturbations that can accelerate fatigability 4-5 times faster (Burnley *et al.*, 2012; Thomas *et al.*, 2016). However, this has been described primarily in young males (Burnley, 2009; Burnley *et al.*, 2012). One study included both sexes, but did not conduct a sex comparison of the intensity-duration relationship (Pethick *et al.*, 2016). Whether the critical intensity differs between males and females for tasks where the sex difference in fatigability is commonly reported (e.g. intermittent isometric contractions, Hunter *et al.*, 2004; Ansdell *et al.*, 2018) is unknown, and could provide a physiological mechanism to explain these previous findings.

A range of reported physiological differences between males and females would suggest the critical intensity could differ between sexes for intermittent isometric tasks. Females are reported to be less fatigable than males across a range of exercise tasks and muscle groups, for contractions performed at the same intensity relative to maximal strength (Hunter, 2009, 2016*a*). The sex difference in fatigability is dependent upon the intensity and contraction modality of the task (Yoon *et al.*, 2007; Russ *et al.*, 2008; Hunter, 2016*a*, 2016*b*). During intermittent isometric contractions, females demonstrate greater fatigue-resistance compared to males, even when matched for maximal strength. The magnitude of the sex difference in fatigability might also be magnified at lower contraction intensities (Hunter *et al.*, 2004; Ansdell *et al.*, 2018), but it remains unclear whether the relationship between contraction intensity and task duration (time to task failure, i.e. fatigability)

differs between males and females, and whether the underlying mechanisms of fatigue differ. A crucial determinant of the intensity-duration relationship is oxygen delivery to the skeletal muscle, with positive correlations between critical intensity and the fraction of inspired oxygen (Vanhatalo *et al.*, 2010; Dekerle *et al.*, 2012). Critical power (during cycling exercise), for example, is positively correlated with type I fibre proportion and muscle capillarity of the knee extensor muscles (Vanhatalo *et al.*, 2016; Mitchell *et al.*, 2018). Typically, females have a greater proportion of type I muscle fibres (Simoneau & Bouchard, 1989; Staron *et al.*, 2000; Roepstorff *et al.*, 2006), which are less fatigable than type 2 fibres (Schiaffino & Reggiani, 2011). Females also exhibit greater capillarisation per unit of *vastus lateralis* muscle (Roepstorff *et al.*, 2006), and an augmented vasodilatory response of the femoral artery during exercise (Parker *et al.*, 2007). Furthermore, females exhibit greater skeletal muscle oxygenation and less deoxygenation during upper and lower limb exercise than males when assessed with near infrared spectroscopy; NIRS (Mantooth *et al.*, 2018; Marshall *et al.*, 2019). Whether these physiological sex differences could influence the critical intensity of the intensity –duration relationship for intermittent isometric contraction task is unknown.

Finally, recovery of exercise is also influenced by the aforementioned properties of skeletal muscle and could therefore differ between males and females; however, the extent of possible sex differences and the involved mechanisms of neuromuscular revcovery are not understood. Limited evidence exists examining the sex difference of recovery for short durations after exercise (10-20 minutes), showing that force producing capacity of female knee extensors recovers more rapidly than males (Senefeld *et al.*, 2018). Greater capillary density of the exercising muscle(s) can increase the rate of recovery from fatigue (Tesch & Wright, 1983; Casey *et al.*, 1996), possibly due to an increased rate of metabolite clearance and ATP/phosphocreatine re-synthesis post-exercise (Casey *et al.*, 1996; McDonough *et al.*, 2004), or a reversal in disruptions to calcium handling (Fitts & Balog, 1996). The latter has been shown to differ between sexes during exercise (Harmer *et al.*, 2014). There is a paucity of data relating to sex differences in recovery, and of the neural and contractile mechanisms involved following fatiguing exercise.

The present study had three primary aims: 1) to compare the relative torque (% MVC) at which critical intensity is achieved within the intensity-duration relationship for intermittent, isometric tasks in males and females; 2) determine the mechanisms that contribute to fatigability during intermittent isometric tasks at intensities of torque above and below the critical intensity in males and females; and 3) compare the rate of recovery following fatiguing exercise and the underpinning neuromuscular mechanisms. We *hypothesised* that: 1) due to greater oxygen availability within the muscle, females would demonstrate a higher critical intensity than men when expressed relative to MVC. 2) There

would be no sex difference in the time to task failure when the tasks were compared at the same metabolic intensity of contraction, relative to critical intensity. 3) Recovery from fatiguing exercise would be more rapid in females than males due to the properties of contractile elements of the muscle. To understand the mechanisms of fatigability and recovery both above and below the critical intensity in males and females, we used motor nerve and cortical stimulation to delineate the contractile and neural responses to exercise, as well as NIRS to determine the oxygenation of the muscles.

METHODS

Ethical Approval

The study received institutional ethical approval from the Northumbria University Health and Life Sciences Research Ethics Committee (submission reference: 2434) and was conducted according to all aspects of the Declaration of Helsinki, apart from registration in a database. Participants provided written, informed consent to volunteer for the study.

Participants

Using the effect size for the sex difference in exercise tolerance at 50% MVC from Ansdell *et al.* (2017), a power calculation (alpha = 0.05, power 0.80) determined that a sample size of 16 participants was required. Therefore, to maximise statistical power, ten males (mean ± SD age: 26 ± 5 years, height: 178 ± 8 cm, mass: 83.4 ± 14.4 kg) and ten females (age: 24 ± 2 years, height: 168 ± 9 cm, mass 68.5 ± 7.7 kg) were recruited to take part in the study. The females that volunteered were all using monophasic oral contraceptive pills (>6 months), and were tested in the 21-day consumption period of the pill cycle in order to negate the effects of endogenous hormones on neuromuscular function and fatigability (Ansdell *et al.*, 2019). Participants arrived at the laboratory rested and hydrated, with strenuous physical activity avoided for 48 hours, and caffeine and alcohol prohibited for 24 hours.

Experimental Design

All participants visited the laboratory seven times, completing a familiarisation visit, four constant load trials to estimate critical intensity, then trials 10% above and below critical torque (see *Experimental Protocol*). Testing took place over a three to five week period, with a minimum of 48 h between visits to permit full recovery of fatigue (Carroll *et al.*, 2016). The time of day for each testing session was replicated (± 1 h) to account for diurnal variations in maximal force generating capacity and corticospinal excitability (Tamm *et al.*, 2009).

Experimental Protocol

Visit 1: Familiarisation. Participants were sat in the isometric dynamometer with hip and knee angles at 90˚. This set up was replicated for all visits. Electrical nerve stimulation threshold was determined, followed by TMS hotspot, active motor threshold (aMT) and voluntary activation (VA) stimulator intensity determination (described below). Following this, a baseline neuromuscular function assessment was performed. After five minutes of passive rest, participants performed the fatiguing task at 60% MVC. An MVC and electrical stimulation was performed, each minute throughout the fatiguing task. Immediately following the fatiguing task, participants performed a 'post-exercise' neuromuscular assessment.

Visits 2-5: Critical Intensity Estimation Trials. To establish critical intensity, participants performed four trials to task failure. These involved intermittent isometric knee-extensor contractions at submaximal intensities between 40-80% MVC. The first trial was set at 60% MVC, based on the pre-exercise MVC in the first trial. The following three estimation trials were set at intensities that elicit task failure between 2 and 15 minutes in a randomised order (Burnley, 2009; Burnley *et al.*, 2012). Participants were instructed to match a target force displayed using a visual guideline on a computer screen ~1 m in front of them, and were blinded to the time elapsed in each trial. The contraction regime for all trials involved 3 s contractions interspersed with 2 s rest, with an MVC and electrical stimulation performed at the end of each minute. This contraction duty cycle has previously displayed sex differences independent of strength, and therefore occlusion differences between males and females (Ansdell et al., 2017; Hunter et al., 2006). Task failure was deemed as a failure to meet the target force three consecutive times despite strong verbal encouragement. Participants were informed each time they failed to reach the target force. Before the submaximal task, participants performed five 3 s MVCs separated by 30 s, with electrical stimulation during and 2 s after the final three contractions. Immediately following task failure this was repeated with three MVCs and superimposed electrical stimulations.

Visits 6 and 7: Critical Intensity Trials. The supra (+10%) and sub (−10%) critical intensity trials began with electrical nerve stimulation and TMS thresholds being determined. Baseline near infrared spectroscopy (NIRS) values were recorded once participants were sat in the dynamometer in the same position as the fatiguing task. NIRS data was captured for the entirety of the trials, and was used to measure changes in muscle oxygenation during the fatiguing task. Cardiac output ($\dot{Q}$) , heart rate (HR), and mean arterial pressure (MAP) were measured throughout the trial via a fingertip arterial pressure cuff (Finometer Midi, Finapres Medical System, Arnhem, The Netherlands). Participants completed a

standardised isometric warm up (Gruet et al., 2014), before a baseline neuromuscular function assessment. After five minutes of passive rest participants completed an intermittent isometric fatiguing task to failure at an intensity relative to their critical intensity (+10 or −10%). An MVC with electrical stimulation during and ~2 s following was performed and delivered at the end of each minute of the task to assess neuromuscular function (see below). The −10% trial was terminated after 45 minutes, as this intensity contraction could theoretically be maintained indefinitely without task failure (Burnley et al., 2012). Therefore, male and female fatigability was compared after an identical 'dose' of exercise. The intensity for the first critical intensity trial was randomised and counterbalanced. Upon task failure or termination, a post-test neuromuscular function assessment (see below) was immediately performed, then repeated at 15, 30 and 45 minutes post-exercise.

Intensity-Duration Relationship

Critical intensity and curvature constant (W') were estimated from the force-impulse relationship of the four submaximal trials. A linear regression between force impulse at task failure from the four submaximal trials against time to task failure was plotted to determine the characteristics of the relationship. The slope of the regression determined critical intensity, and the y-intercept determined W' (Burnley et al., 2009, 2012). Critical intensity was expressed in Newtons, and as %MVC to account for sex differences in absolute force production.

Measurements

Neuromuscular Function

Participants completed five isometric knee-extensor MVCs separated by 30 s, with electrical nerve stimulation delivered during and after the final three contractions to quantify voluntary activation (VA_{MNS}) and quadriceps potentiated twitch force ($Q_{tw.pot}$). In the final two visits (critical intensity trials) voluntary activation was also assessed with TMS (VA_{TMS}) using two sets of five contractions (100, 87.5, 75, 62.5, and 50% MVC, Dekerle *et al.*, 2019); single pulse TMS was delivered during each contraction. Finally, short interval cortical inhibition (SICI) and corticospinal excitability (MEP/M_{max}) were assessed during a 10% MVC contraction.

Force and EMG

Participants were seated on a custom-built chair, with force (N) measured using a calibrated load cell (MuscleLab force sensor 300, Ergotest technology, Norway). The load cell was attached to the

participant's dominant right leg, superior to the ankle malleoli, using a cuff. The load cell height was adjusted to ensure a direct line with the applied force for each participant. Participants were sat upright with knee and hip angles kept at 90˚ flexion. Electromyography (EMG) of the knee extensors was recorded from the *rectus femoris* (RF), with antagonist knee flexor activity recorded from the long head of the *biceps femoris* (BF). Skin was shaved and cleaned, surface electrodes (Ag/AgCl; Kendall H87PG/F, Covidien, Mansfield, MA, USA) were then placed 2 cm apart over the muscle belly, according to SENIAM guidelines (Hermens *et al.*, 2000), with a reference electrode placed over the patella. EMG electrodes recorded signals during maximal and submaximal contractions and were quantified as root-mean-square amplitude (rmsEMG). Compound muscle action potentials (maximal M-wave) following motor nerve stimulation, and MEPs elicited by TMS were also recorded. Surface electrode signals were amplified (×1,000; 1902, Cambridge Electronic Design, Cambridge), band-pass filtered (20-2,000 Hz), digitized (4 kHz, micro 1401, Cambridge Electronic Design) and acquired for off-line analysis (Spike2 version 7.01, Cambridge Electronic Design).

Transcranial Magnetic Stimulation

Single and paired pulse magnetic stimuli of 1 ms duration were delivered over the contralateral motor cortex (postero-anterior intracranial current flow) with a concave double cone coil (110 mm diameter, maximum output 1.4 Tesla) powered by a BiStim unit and two Magstim 200^2 stimulators (The Magstim Company, Whitland, UK). Optimal stimulation location was located by stimulating at ~50% maximum stimulator output during a 10% MVC contraction. The position eliciting the greatest MEP amplitude in the RF, and a concurrent small MEP in the antagonist BF muscle, was marked with indelible ink to ensure consistent placement within trials. Stimulator output for aMT was defined as the lowest stimulus intensity required to elicit a MEP of at least 0.2 mV in three out five stimulation in the RF during a 10% MVC contraction. Mean aMT was not different between males and females (39 ± 7 vs. 43 ± 10%, P = 0.379), or between visits (41 ± 9 vs. 41 ± 9%, P = 0.423). The conditioning pulses were delivered at 70% aMT, 2 ms prior to a test stimulus at 120% aMT during a 10% MVC contraction (Brownstein *et al.*, 2018). Ten unconditioned and ten conditioned stimuli were delivered and the resultant motor evoked potential (MEP) amplitudes were averaged and presented as a normalised value ((conditioned MEP/unconditioned MEP)×100) as an index of SICI. The average amplitude of the unconditioned pulse normalised to maximal M-wave was used as an index of corticospinal excitability. Stimulator output for VA_{TMS} was determined as the greatest mean SIT elicited by two pulses delivered during a ~6 s contraction at 50% MVC, as TMS intensity was increased in a step-wise (i.e. 5% increments) fashion from 50% maximal stimulator output (Thomas *et al.*, 2016; Brownstein *et al.*, 2017). Each contraction was separated by 30 s rest. Mean stimulator intensity was not different

between males and females (63 ± 6% vs. 66 ± 11%, P = 0.462) or between visits (66 ± 10% vs. 63 ± 7%, P = 0.218). The intensities used activated a large proportion of the motoneuron pool for the RF that was not different between trials at baseline (53 ± 13% M_{MAX} vs. 53 ± 16% M_{MAX}, P = 0.920). The TMS pulse also avoided substantial activation of the antagonist (*biceps femoris*) with small incidental MEPs recorded at baseline (0.68 ± 0.52 mV vs. 0.70 ± 0.1 mV, P = 0.902).

Motor Nerve Stimulation

Single electrical stimuli (200 μs duration) were delivered to the femoral nerve via 32 mm-diameter surface electrodes (CF3200; Nidd Valley Medical, North Yorkshire, UK) using a constant-current stimulator (DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK). The cathode was placed high in the femoral triangle over the nerve, and the anode positioned midway between the greater trochanter and iliac crest. The cathode was repositioned until the largest knee extensor twitch amplitude (Q_{tw}) and maximal RF M-wave (M_{MAX}) was elicited at rest. Stimulations began at 20 mA, and increased by 20 mA until a plateau in Q_{tw} and M-wave amplitude occurred. This value was then be increased by 30% to ensure supramaximal stimulations during the protocol. Mean stimulus intensity was not different between sexes (276 ± 142 vs. 190 ± 75 mA, P = 0.057) or between visits (241 ± 104 vs. 229 ± 107 mA, P = 0.492).

Near Infrared Spectroscopy

A multi-distance, continuous-wave, single channel NIRS (NIRO-200NX, Hamamatsu, Hamamatsu City, Japan) evaluated changes in *vastus lateralis* muscle oxy- (HbO_2), and deoxy- (HHb) haemoglobin concentrations [μM], as well as tissue oxygenation index (TOI = $HbO_2 \div [HbO_2 + HHb] \times 100$), sampled at a rate of 1 Hz. The light-emitting probe comprised of diodes operating at three wavelengths (735, 810, and 850 nm). The probe was placed on the *vastus lateralis*, 20 cm above the fibular head lateral side of the patella (Keane *et al.*, 2018). Optodes were held in place by an elasticised, tensor bandage and covered by an opaque, dark material to avoid motion and ambient light influences. Pre-exercise, participants remained seated and avoided muscle contraction for five minutes to establish baseline muscle oxygenation, with the final 30 s used as the pre-exercise value. During the fatiguing tasks, the 30 s window around 25, 50, 75% of the task, as well as the final 30 s of the task (100%), were expressed as changes from baseline (Δ%).

Haemodynamic Monitoring

Mean arterial blood pressure and heart rate were measured continuously throughout the final two testing visits using finger arterial pressure pulse wave analysis (Finometer Midi, Finapres Medical

System, Arnhem, The Netherlands). This system was also used to estimate $\dot{Q}$ using the Modelfow equation (Wesseling *et al.*, 1993). An appropriately sized cuff was placed between the distal proximal inter-phalangeal joint of the middle finger. To minimise the effect of arm and hand movement during the trials, arm position was maintained stationary throughout the trial. To account for hydrostatic pressure differences between the level of the hand and heart, a height correction unit was used. The Finapres was activated prior to the exercise tasks to allow calibration via the Physiocal function within the BeatScope software. This technique has previously been validated and shown to be reliable at rest and in exercise conditions (Parati *et al.*, 1989; Waldron *et al.*, 2017). Signals were linearly interpolated and resampled at 1 Hz (Faisal *et al.*, 2009), then a 5 s rolling average was used to smooth the data (Beltrame *et al.*, 2017), before 30 s time intervals were taken pre-exercise, 25, 50, 75 and 100% of time to task failure. Pre-exercise, participants remained seated for five minutes to establish baseline values, with the final 30 s used as pre-exercise values.

Data Analysis

Voluntary activation using motor nerve stimulation was determined using the twitch interpolation method (Merton 1954) by comparing the amplitude of the superimposed twitch (SIT) with the amplitude of the potentiated resting twitch ($Q_{tw.pot}$) using the following formula: VA_{MNS} (%) = (1 – [SIT ÷ $Q_{tw.pot}$]) × 100]. Voluntary activation using TMS was assessed during two sets of contractions at 100, 87.5, 75, 62.5 and 50% MVC (Dekerle *et al.* 2019). Single pulse TMS was delivered during each contraction, and the linear regression between SIT amplitude and contraction intensity was extrapolated to the *y* intercept to obtain an estimated resting twitch (ERT; Todd *et al.* 2003). In order to achieve significant linearity ($P < 0.05$), a total of five out of 850 SITs across all trials were excluded (0.6%), which led to five regressions containing 9 data points rather than 10 (1 pre-exercise, 4 post-exercise). As a result, mean r^2 values for ERTs were linear throughout the study (0.93 ± 0.06). The SIT during 100% MVC was compared with the ERT using the following formula: VA_{TMS} (%) = (1 – [SIT ÷ ERT]) × 100. Short interval intracortical inhibition was quantified as the percentage ratio between the amplitude of conditioned MEPs to the amplitude of unconditioned MEPs. Corticospinal excitability was determined by expressing the mean MEP amplitude during the 10% MVC as a percentage of M_{MAX}. The root-mean-square of EMG activity (rmsEMG) was recorded during the preceding 100 ms before each stimulation, and the middle 500 ms epoch of each 3 s contraction during the fatiguing task. rmsEMG was then expressed as a percentage of M_{max}. The NIRS (O_2Hb, HHb, TOI, and cHb) and Finapres (HR, $\dot{Q}$, MAP) data were expressed as a percentage of baseline, and the 30 s epochs throughout exercise are presented as Δ%.

Despite a linear relationship between TTF and work done in the estimation trials (r^2 = 0.98), and a physiologically normal value for the critical intensity (22.7% MVC), one female participant demonstrated no signs of fatigability during the supra-critical intensity trial (i.e. MVC did not decrease), thus the trial was terminated after 90 minutes, and the participant was excluded from further analyses. Similarly, one male was excluded due to the intensity-duration relationship residing >3 SDs from the mean value for males (critical intensity = 31.3% MVC, W' = 2005 $N.s^{-1}$), likely caused by premature task failure in the higher intensity estimation trial(s).

Statistical Analysis

Data are presented as mean ± SD within the text and figures. Normal Gaussian distribution of data was confirmed using the Kolmogorov–Smirnov test. If a violation was detected, the data was logarithmically transformed. This occurred for rmsEMG/M_{max} during the fatiguing tasks, therefore, statistical tests were run on the transformed data, but in text and figures the non-transformed data is presented. The alpha for all statistical tests was set at $P < 0.05$.

For variables assessed pre-, during, and post- exercise (MVC, VA_{MNS}, $Q_{tw.pot}$, rmsEMG, O_2Hb, HHb, TOI, HR, CO, and MAP) a two-way (2×5) repeated measures ANOVA was used to assess differences between sex (male vs. female) and over time (Pre, 25, 50, 75% TTF, and Post). For variables that were assessed pre and post-exercise (ERT, VA_{TMS}, M_{MAX}, MEP/M_{max}, SICI) a two-way 2×2 repeated measures ANOVA was used to assess differences between sex (male vs. female) and over time (Pre vs. Post). For variables that were assessed during the recovery period (MVC, VA_{MNS}, $Q_{tw.pot}$, ERT, VA_{TMS}, M_{MAX}, MEP/M, SICI) a two way (2×4) repeated measures ANOVA was used to assess difference between sex (male vs. female) and over time (Post, and 15, 30 and 45 min post-exercise). If significant main or interaction effects were observed, these were followed up by *post-hoc* Bonferroni-corrected pairwise comparisons.

RESULTS

Intensity-Duration Relationship

The trials to estimate the intensity-duration relationship ranged from 1.6 – 16.0 minutes in duration (Table 1). In order to match the TTFs between sexes, the trial intensities were required to be greater in females than the males (mean difference of 10-11% MVC for the four trials, all $P < 0.001$). Furthermore, the relationship between TTF and impulse across the four trials was linear (r^2 range: 0.89 – 1.00) for all participants (Figure 1A).

Figure 1 here

Maximal voluntary contraction was greater in males compared to females (708 ± 119 N vs. 458 ± 59 N, $P < 0.001$); however, absolute critical intensity was not significantly different (143 ± 26 N vs. 123 ± 26 N, $P = 0.109$). When normalised to MVC, females had a greater critical intensity compared to males (24.7 ± 2.5 vs. 20.8 ± 2.3% MVC, $P = 0.003$, Figure 1B), however, there was no difference in W' (18,206 ± 6,331 vs. 18,765 ± 5,762 $N.s^{-1}$, $P = 0.850$, Figure 1C).

Males and females demonstrated a consistent decline in MVC, $Q_{tw.pot}$, and VA_{MNS} across the four estimation trials (Figure 2, Trial × Time interactions $P \geq 0.144$), confirming that all trials took place in the same exercise intensity domain.

Figure 2 here

Supra (+10%) Critical Intensity Trials

Fatigability

Compared to males, females had a greater time to task failure for the intermittent isometric contraction tasks performed at 110% of critical intensity (3,742 ± 1,035 vs. 1,826 ± 765 s, $P < 0.001$, Figure 3).

Figure 3 here

Throughout the +10% task and at task failure MVC, $Q_{tw.pot}$, VA_{MNS}, VA_{TMS}, and MEP/M_{max} all decreased (all time effects $P < 0.001$, Figures 4 and 5), whilst $rmsEMG/M_{max}$ increased ($P < 0.001$, Table 2). However, SICI ($P = 0.232$) and M_{max} ($P = 0.109$) did not change. When comparing the changes between sexes, MVC ($F_{2.2,34.5} = 4.36$, $P = 0.017$, $\eta_p^2 = 0.214$), and $Q_{tw.pot}$ ($F_{4,64} = 2.52$, $P = 0.049$, $\eta_p^2 = 0.136$)

decreased more in males compared with the females (Figure 4, panel A & B), whilst the rmsEMG/M_{max} increased more in the males than the females ($F_{2.2,34.5} = 7.33$, $P = 0.002$, $\eta_p^2 = 0.314$). However, VA_{MNS}, VA_{TMS}, MEP/M_{max}, and SICI were not different between the sexes ($P \geq 0.062$).

Figure 4 here

Recovery

In the 45 minute recovery period, MVC, $Q_{tw.pot}$, VA_{MNS}, VA_{TMS}, and MEP/M_{max} all demonstrated a return towards baseline (recovery effects all $P < 0.001$, Figures 4 and 5). Females however, demonstrated a faster recovery for $Q_{tw.pot}$ ($F_{3,48} = 3.13$, $P = 0.034$, $\eta_p^2 = 0.164$), and VA_{TMS} ($F_{1.8,25.4} = 3.63$, $P = 0.045$, $\eta_p^2 = 0.206$), with no difference in recovery for MVC, VA_{MNS}, or MEP/M ($P \geq 0.096$).

Figure 5 here

Oxygenation and Haemodynamics

Muscle oxygenation was altered during the +10% fatiguing task (Figure 6), with O_2Hb ($F_{1.4,22.5} = 7.00$, $P = 0.009$, $\eta_p^2 = 0.304$), HHb ($F_{1.4,22.5} = 11.53$, $P = 0.003$, $\eta_p^2 = 0.419$), and TOI ($F_{1.1,18.3} = 7.12$, $P = 0.004$, $\eta_p^2 = 0.393$) all demonstrating changes from baseline. Females demonstrated a lesser increase in HHb ($F_{1.4,22.5} = 8.96$, $P = 0.007$, $\eta_p^2 = 0.359$), and decrease in TOI ($F_{1.2,18.3} = 7.12$, $P = 0.013$, $\eta_p^2 = 0.308$) than males (Figure 6B and C). For O_2Hb, females demonstrated an increase from baseline, whilst males decreased ($F_{1.4,22.5} = 8.05$, $P = 0.005$, $\eta_p^2 = 0.335$, Figure 6A).

Figure 6 here

The +10% fatiguing task induced changes in cardiovascular function (Table 2) with HR ($F_{4,64} = 47.39$, $P < 0.001$, $\eta_p^2 = 0.748$), $\dot{Q}$ ($F_{4,64} = 19.70$, $P < 0.001$, $\eta_p^2 = 0.552$), and MAP ($F_{4,64} = 12.24$, $P < 0.001$, $\eta_p^2 = 0.433$) all increasesing. Females demonstrated a lesser increase in HR ($F_{4,64} = 8.99$, $P < 0.001$, $\eta_p^2 = 0.360$) and $\dot{Q}$ ($F_{4,64} = 4.02$, $P = 0.006$, $\eta_p^2 = 0.201$), but not MAP ($P = 0.175$).

Sub (−10%) Critical Intensity Trials

Fatigability

All participants successfully completed the 45 minutes of exercise below critical intensity and did not reach task failure. MVC, $Q_{tw.pot}$, M_{max}, VA_{MNS}, and VA_{TMS} all decreased (time effects: $P \leq 0.016$) throughout the intermittent isometric task, whereas rmsEMG/M_{max} ($P = 0.020$), and MEP/M ($P =$

0.017) increased. Short interval intracortical inhibition did not change (P = 0.061). Of these variables, a sex × time interaction was demonstrated for $Q_{tw.pot}$ ($F_{1.97,31.49}$ = 5.31, P = 0.011, η_p^2 = 0.249) indicating a lesser decrease over the course of the intermittent isometric task. Post-hoc differences are displayed in Figure 7 and Table 2.

Recovery

In the 45 minute recovery period the MVC, $Q_{tw.pot}$, VA_{MNS}, and VA_{TMS} increased (recovery effects: $P \leq$ 0.032). Conversely, M_{max} (P = 0.267), MEP/M (P = 0.080), and SICI (P = 0.085) demonstrated no recovery effects. Of the variables demonstrating recovery effects, VA_{TMS} demonstrated a sex × time interaction ($F_{1.45,20.26}$ = 4.57, P = 0.033, η_p^2 = 0.246), indicating a faster recovery in females compared with males. No other variables (MVC, $Q_{tw.pot}$, and VA_{MNS}) demonstrated this sex by time interaction ($P \geq$ 0.069).

Figure 7 here

Oxygenation and Haemodynamics

Muscle oxygenation was altered during the intermittent isometric task (Figure 8). Whilst O_2Hb ($F_{1.6,26.5}$ = 10.27, P = 0.001, η_p^2 = 0.391) increased, HHb did not change (P = 0.945), and TOI decreased ($F_{1.36,21.71}$ = 4.98, P = 0.027, η_p^2 = 0.237). Of these variables, O_2Hb demonstrated a sex × time interaction ($F_{1.64,26.25}$ = 3.77, P = 0.044, η_p^2 = 0.191), indicating a greater increase in females compared with males.

Figure 8 here

Heart rate ($F_{2.6,41.5}$ = 18.42, P < 0.001, η_p^2 = 0.535), $\dot{Q}$ ($F_{2.83,45.23}$ = 4.06, P = 0.014, η_p^2 = 0.380) and MAP ($F_{1.96,31.37}$ = 6.72, P = 0.004, η_p^2 = 0.296) all increased throughout the intermittent isometric task (Table 2), with a sex × time interaction for HR ($F_{2.59,41.49}$ = 5.59, P = 0.004, η_p^2 = 0.259), indicating a greater increase in HR in males than females.

DISCUSSION

The present study aimed to compare the intensity-duration relationship between males and females during intermittent, isometric knee extensor exercise, and assess whether a sex difference in fatigability and recovery existed when exercise was normalised to the critical intensity. We found that females demonstrated a greater relative critical intensity during intermittent isometric knee extensor exercise compared with males. Contrary to our hypothesis however, females lasted approximately twice as long than males for an open-ended exercise 10% above this threshold. Following exercise normalised to 110% and 90% of critical intensity, females demonstrated a lower degree of contractile impairment, and a faster rate of recovery following the 110% trial. Furthermore, females were able to better maintain muscle oxygenation during exercise, which provides a plausible explanation for the observed sex differences in exercise tolerance and fatigability. These data are the first to demonstrate that when normalised to a maximum, critical intensity is greater for females during intermittent isometric contractions. This was likely underpinned by a greater ability to maintain muscle oxygenation, observed via NIRS, and led to a more fatigue-resistant muscle in females.

Intensity-Duration Relationship

Of the two parameters of the intensity-duration relationship, a sex difference was observed for critical intensity, but not W'. Females had a critical threshold ~4% MVC greater than males, due to a steeper slope in the TTF-impulse relationship (Figure 1A) and smaller absolute MVC. Critical intensity notes the maximal sustainable metabolic rate during exercise, at which oxidative energy provision is sufficient and reaches a steady state (Poole *et al.*, 2016). Increasing the fraction of inspired oxygen (FiO_2) during exercise increases critical intensity (Vanhatalo *et al.*, 2010), whereas decreasing FiO_2 reduces the maximal sustainable intensity (Dekerle *et al.*, 2012). Similarly, complete blood flow occlusion reduces critical power to less than zero (Broxterman *et al.*, 2015*a*). Differences in skeletal muscle properties between males and females could explain the difference in critical intensity. It is well established that in the *vastus lateralis*, females possess a greater relative proportion of type I muscle fibres (Simoneau & Bouchard, 1989; Staron *et al.*, 2000; Roepstorff *et al.*, 2006) and greater capillary density (Roepstorff *et al.*, 2006) than males. When combined with a greater vasodilatory response of the femoral artery to exercise in females (Parker *et al.*, 2007), it is likely that these factors permit greater delivery of oxygenated blood to the muscle tissues of the knee-extensors, contributing to an ability to sustain greater rates of oxidative metabolism (i.e. critical intensity) than males. These observations could explain why females were able to attain a higher relative critical intensity than males in the present study. Indeed, recent evidence suggests that type I fibre % and muscle capillarisation are positively correlated with critical power during cycling exercise (Vanhatalo *et al.*,

2016; Mitchell *et al.*, 2018). Mitchell *et al.* (2018) suggested that greater capillary supply likely leads to greater oxygen supply and extraction during exercise. To support this, during both +10% and −10% trials in the present study, a sex difference was observed for O_2Hb, with females demonstrating greater increases from resting values (Figures 5 and 7). Therefore, the present data suggest that females are able to maintain elevated delivery of oxygen to the knee-extensors, leading to a greater relative rate of maximal sustainable oxidative metabolism.

The curvature constant of the intensity-duration relationship (W'), was not different between sexes. Whilst less is known about the origins and determinants of W' (Poole *et al.*, 2016), evidence suggests that there is no relationship between it and skeletal muscle properties (Vanhatalo *et al.*, 2016; Mitchell *et al.*, 2018). More likely, W' is related to the depletion of intramuscular energy stores (e.g. phosphocreatine, PCr) and accumulation of metabolites (e.g. Pi, H+, ADP; Vanhatalo *et al.*, 2010). This notion has been suggested to oversimplify such a concept, with the possibility of a different source in W' between whole-body and single-muscle exercise (Poole *et al.*, 2016). However, in single-muscle exercise, Broxterman *et al.* (2015*b*) suggested that W' might be related to the maximum tolerable degree of neuromuscular dysfunction. Considering there was no difference in the Δ% in MVC, $Q_{tw.pot}$, and VA_{MNS} between males and females at task-failure in the +10% trial (Figure 3A), this notion could explain why W' was not different between sexes in the intermittent, isometric model used in the present study.

Fatigability and Recovery above Critical Intensity

Despite normalising exercise to the intensity-duration relationship, which is a key step when modelling fatigability (Burnley & Jones, 2018), females outlasted males during the open-ended isometric intermittent contraction task (Figure 3). A similar W' in males and females would suggest that task failure should occur in a similar time, as evidence previously suggested task failure occurs once this work capacity is completely utilised and a 'critical metabolic milleu' is attained (Vanhatalo *et al.*, 2010). One potential explaination could be the absolute force produced by females was ~40% lower than males in the present study. This meant for a male and female with identical critical intensity (%MVC) and W', the impulse ($N \cdot s^{-1}$) per contraction was lower in absolute terms during the +10% fatiguing task for contractions at similar %MVC. This led to a slower rate of W' utilisation and decrease in indices of neuromuscular function during the fatiguing task (e.g. MVC, $Q_{tw.pot}$, VA_{MNS}), until a constant degree of post-exercise dysfunction was reached at task failure (Figure 4). In the present dataset it was not possible to *post hoc* match individual male and female participants for critical intensity, W' and MVC within <10% of each other, thus, it is not possible to discount the potential effect of absolute force.

The sex difference in critical intensity and fatigability above critical intensity can therefore explain previous studies that have normalised to an arbitrary % of MVC and shown a sex difference in fatigability (e.g. 50% MVC, Hunter *et al.*, 2004; Ansdell *et al.*, 2018). For example, at 50% MVC, males would be exercising at a greater relative intensity above their threshold, therefore would experience a faster rate of fatigue (Burnley *et al.*, 2012), but also as a consequence of greater absolute force production, deplete W' faster.

Following the +10% trial, females demonstrated a faster rate of recovery for $Q_{tw.pot}$ (Figure 3B), which supports the conclusions of (Senefeld *et al.*, 2018) who demonstrated a similar pattern following a fixed-duration dynamic fatiguing task. Recovery of contractile function following long-duration isometric exercise is related predominantly to restoration of intracellular calcium handling/sensitivity, rather than metabolite clearance (Carroll *et al.*, 2016). Female skeletal muscle demonstrates a 24% lower maximal rate of Ca^{2+}ATPase activity (Harmer *et al.*, 2014), which has previously been suggested to lead to lower calcium-related impairments during exercise, and create a more fatigue-resistant muscle compared to males (Hunter, 2014). Thus, it could be the case that differences in calcium handling in female skeletal muscle translated to better post-exercise recovery kinetics. Although somewhat speculative, calcium handling has been studied *in vitro* to support the sex difference in fatigability (Harmer *et al.*, 2014), but no similar data in cell models exists to compare recovery of calcium handling between males and females after exercise. Therefore, calcium-related properties of skeletal muscle could help to explain why female contractile function recovered quicker in the present study, but further research to support this proposition is warranted.

Fatigability and Recovery below Critical intensity

For the same duration of exercise below critical intensity, both sexes experienced an initial decrease in MVC and $Q_{tw.pot}$, then no further impairment throughout the fatiguing task (Figure 6). Whilst females experienced a lesser decrease from baseline, the attainment of a constant degree of contractile dysfunction is consistent with the notion that exercise below the critical intensity reaches a 'steady-state' of metabolic adjustment (Burnley & Jones, 2018). A similar study in males (Burnley *et al.,* 2012) speculated that the origins of contractile dysfunction below threshold might be related to the effects glycogen depletion had on calcium transients in skeletal muscle (Ørtenblad *et al.*, 2013). During whole-body exercise, females oxidise relatively more fat than carbohydrate compared to males (Roepstorff *et al.*, 2002, 2006); when combined with the more fatigue-resistant calcium properties in female muscles (Harmer *et al.*, 2014), this could explain why the post-exercise Δ% in $Q_{tw.pot}$ was less in females (Figure 7C). Similar to the +10% trial, females were better able to maintain oxygen availability within

the working muscles (Figure 7A), however, this is not thought to be a limiting factor to exercise performance below critical intensity (Poole *et al.*, 2016), as oxidative metabolism is not at maximal rates. Post-exercise, MVC, $Q_{tw.pot}$ and VA all demonstrated returns towards baseline, however, male $Q_{tw.pot}$ was still reduced 45 minutes post-exercise. If muscle glycogen-related factors are the cause of this contractile impairment below threshold, the continued impairment at 45 minutes would be expected, as complete re-synthesis can take >2 hours following single-limb exercise (Pascoe *et al.*, 1993).

Further Considerations

The responses to corticospinal stimulation (MEP/M_{max}) showed divergent effects when comparing pre-post exercise changes above and below critical intensity. Following the +10% trial, a depression was observed (Figure 4E), whereas following the −10% trial, a facilitatory effect occurred (Figure 6E). During whole-body exercise, fatigue induced at high-intensities is suggested to activate group III/IV afferent neurons, causing inhibition of spinal motoneurons (Weavil *et al.*, 2016) and increasing GABAergic inhibition within the motor cortex (Sidhu *et al.*, 2018). These adjustments are suggested to reduce the capacity of the central nervous system to activate the working muscles during exercise (Sidhu *et al.*, 2017); this could explain why the reduction in corticospinal excitability was only observed above critical intensity, when decreases in measures of VA were also demonstrated. The present study assessed the activity of group III/IV neurons indirectly through the monitoring of the metaboreflex, and demonstrated an augmented response above threshold (Table 2). Interestingly, females had a lesser increase in HR and $\dot{Q}$ during the +10% trial, which could explain the slower rate of central nervous system dysfunction (Figure 4C). On the contrary, moderate intensity exercise increases corticospinal excitability (Lulic *et al.*, 2017). This effect occurs at lower intensities without the development of fatigue or the attainment of task failure; such an effect was observed in the present study, where facilitatory effects were only evident during exercise below critical intensity, alongside minor decrements in VA. The critical intensity might therefore provide an integrative neuromuscular threshold at which facilitatory neuroplasticity is attainable after exercise beneath. Future research should investigate the effects of exercise intensity on both MEPs and spinal evoked potentials in the lower limbs (e.g. Škarabot *et al.*, 2019) to discern the aetiology of exercise-induced neuroplasticity.

The present study utilised an intermittent, isometric model of exercise (Burnley, 2009; Burnley *et al.*, 2012) to compare the intensity-duration relationship between sexes. Whilst the principles of the model remain the same across different exercise modalities (Jones *et al.*, 2010), it is well established that the determinants of exercise tolerance differ between single-limb and whole-body exercise

(Hureau *et al.*, 2018; Thomas *et al.*, 2018). Indeed Poole *et al.* (2016) suggested that in single-limb exercise, W' likely constitutes of substrate depletion and metabolite accumulation, whereas during whole-body exercise, W' is likely influenced by cardiopulmonary limiting factors to exercise. Indeed, despite a sex difference present for the cardiovascular response to isometric exercise (HR and $\dot{Q}$, Table 2), the present study showed submaximal end-exercise values for these parameters, implying that oxygen delivery was not the limiting factor to exercise, but rather oxygen extraction determined exercise tolerance. Therefore, whether the conclusions of the present study apply to whole-body exercise remains to be determined.

To further support the notion that females possess more fatigue-resistant knee extensors, the rise in rmsEMG/M_{max} was smaller compared to males during the +10% task (Table 2). Despite the known limitations (Farina *et al.*, 2014; Enoka & Duchateau, 2015) associated with surface EMG, increases are suggested to reflect additional neural drive and recruitment of further motor units, as the contractile apparatus become fatigued (Gandevia, 2001). Therefore the smaller increase in rmsEMG/M_{max} could suggest that female musculature was able to sustain the required intensity with a reduced need for additional neural drive and motor unit activation. This could also explain the smallerr decrease in $Q_{tw.pot}$ experienced during the tasks, further supporting the notion that the sex differences in skeletal muscle properties influence fatigability during intermittent isometric exercise. Further research could employ the use of high density EMG, which is capable of discerning motor unit properties (Merletti *et al.*, 2008), without the limitations associated with bipolar surface EMG (Farina *et al.*, 2014; Enoka & Duchateau, 2015).

Conclusions

The present study is the first to demonstrate that females can sustain a greater relative work intensity compared with males during single limb exercise, as shown by the greater critical intensity. Importantly, when exercise intensity was normalised to this threshold, females out-performed males during the open-ended task (+10%), and showed reduced fatigability during a fixed workload task (−10%). These sex differences in the intensity-duration relationship and fatigue resistance are likely related to a greater ability to preserve oxygen availability within the knee-extensors during exercise, as demonstrated by the NIRS data. Following exercise, a faster rate of recovery was observed for contractile function in females, suggesting that, in addition to possessing more fatigue-resistant skeletal muscle, females are able to resolve exercise-induced dysfunction at a faster rate. These data explain previous findings related to sex differences in fatigability tasks, whilst providing the first sex-comparison of fatigability during work normalised to a metabolic threshold. Furthermore, the

difference between sexes highlights the importance of individualising exercise and recovery prescription to males and females, rather than generalising from previously generated male-only data within the literature.

Conflicts of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Author Contributions

PA, GH, KT, and SG conceived and designed the experiments; PA, CB, and JS performed the experiments; PA analysed the data; PA, KMH, KT, GH, SKH, and SG interpreted the results of the experiments; PA drafted the manuscript; PA, CB, JS, KMH, GH, KT, SKH, and SG edited the manuscript; all authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Table 1: Intensity, times to task failure and impulse for the critical intensity estimation trials. Values are mean ± SD

	Males			Females		
Trial	**% MVC**	**TTF (s)**	**Impulse ($N \cdot s^{-1}$)**	**% MVC**	**TTF (s)**	**Impulse ($N \cdot s^{-1}$)**
1	61 ± 2	217 ± 38	50,188 ± 10,600	71 ± 3*	216 ± 139	52,353 ± 22,164
2	56 ± 2	335 ± 102	74,185 ± 27,746	66 ± 3*	355 ± 158	70,105 ± 23,355
3	51 ± 2	427 ± 117	82,614 ± 22,044	61 ± 3*	486 ± 163	94,263 ± 33,207
4	46 ± 2	647 ± 186	120,318 ± 33,089	57 ± 4*	760 ± 148	141,504 ± 4,7839
r^2		0.98 ± 0.03			0.99 ± 0.01	

MVC: maximal voluntary contraction, TTF: time to task failure; * = greater than males ($P < 0.001$)

824 **Table 2: Neuromuscular and cardiovascular function throughout the fatigue and recovery periods in both +10% and -10% trials.**

		110% Critical Intensity					90% Critical Intensity				
		Neuromuscular Function									
		Pre	***Post***	***Post 15***	***Post 30***	***Post 45***	***Pre***	***Post***	***Post15***	***Post30***	***Post 45***
ERT (N)	Males	167 ± 66	130 ± 67*	135 ± 60#	133 ± 66	132 ± 63	167 ± 63	124 ± 52*	122 ± 47	120 ± 44	110 ± 39
	Females	151 ± 43	101 ± 23*	134 ± 27#	127 ± 23	129 ± 45	149 ± 33	131 ± 37*	123 ± 37	135 ± 39	132 ± 30
M_{MAX} (mV)	Males	6.55 ± 2.57	5.89 ± 2.54	5.86 ± 2.28	5.95 ± 2.51	6.41 ± 2.56	6.33 ± 2.44	5.52 ± 2.58*	5.61 ± 2.39	5.75 ± 2.48	5.19 ± 2.32
	Females	5.18 ± 2.95	4.75 ± 2.28	4.36 ± 2.32	4.47 ± 2.07	4.59 ± 2.80	4.98 ± 2.40	4.39 ± 1.66	4.43 ± 1.57	4.27 ± 1.63	4.2 ± 1.52
Pre-Stimulus rmsEMG (% M_{MAX})	Males	0.62 ± 0.27	0.65 ± 0.28	0.67 ± 0.28	0.70 ± 0.29	0.66 ± 0.30	0.64 ± 0.23	0.84 ± 0.34	0.80 ± 0.33	0.81 ± 0.32	0.90 ± 0.36
	Females	0.75 ± 0.34	0.8 ± 0.77	0.82 ± 0.56	0.87 ± 0.49	0.87 ± 0.64	0.73 ± 0.39	0.85 ± 0.53	0.79 ± 0.54	0.79 ± 0.46	0.77 ± 0.46
		1st Set	***25% TTF***	***50% TTF***	***75% TTF***	***100% TTF***	***1st Set***	***25% TTF***	***50% TTF***	***75% TTF***	***100% TTF***
rmsEMG during task (% M_{MAX})	Males	16 ± 8	22 ± 13*	24 ± 12*	25 ± 10*$	27 ± 11*$	8 ± 3	8 ± 3	8 ± 3	8 ± 4	8 ± 3
	Females	16 ± 5	19 ± 8	17 ± 5	17 ± 4	17± 4	8 ± 4	9 ± 3	9 ± 4	8 ± 4	9 ± 4
		Cardiovascular Function									
		Pre	***25% TTF***	***50% TTF***	***75% TTF***	***100% TTF***	***Pre***	***25% TTF***	***50% TTF***	***75% TTF***	***100% TTF***
Heart Rate (bpm)	Males	78 ± 5	95 ± 12*	99 ± 10*	108 ± 16*	116 ± 16*$	71 ± 11*	88 ± 20*	92 ± 18*	91 ± 19*	91 ± 17*
	Females	80 ± 13	91 ± 18*	94 ± 21*	94 ± 21*	96 ± 19*	81 ± 14	86 ± 13	87 ± 13	87 ± 12	87 ± 12
Cardiac Output ($L \cdot min^{-1}$)	Males	8.1 ± 2.2*$	10.0 ± 2.3*$	10.3 ± 2.0*$	10.6 ± 2.2*$	10.4 ± 2.2*$	6.8 ± 1.6	7.4 ± 1.8	7.5 ± 1.7*	7.6 ± 1.8*	7.6 ± 1.7*
	Females	6.0 ± 1.8	7.2 ± 1.9*	7.0 ± 1.6*	6.9 ± 1.6	6.8 ± 1.5	6.0 ± 1.3	6.2 ± 1.3	6.3 ± 1.4	6.3 ± 1.4	6.3 ± 1.2
Mean Arterial Pressure (mmHg)	Males	90 ± 13	98± 13	100 ± 15	104 ± 18*	107 ± 15*	94 ± 8	94 ± 10	95 ± 13	97 ± 10	101 ± 13
	Females	93 ± 11	104 ± 12*	104 ± 12	101 ± 12	105 ± 11*	93 ± 14	98 ± 15	99 ± 13	100 ± 13	100 ± 15

* = significantly different from Pre ($P < 0.05$), # = significantly different from Post ($P < 0.05$), $ = significantly greater than Females. ERT: estimated resting twitch; M_{max}: maximal compound action potential; rmsEMG: root mean squared EMG; TTF: time to task failure.

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Figure Captions:

Figure 1: Characteristics of the intensity duration relationship for males and females. Panel A: The linear relationships between impulse and time to task failure across the four estimation trials. Panel B: Critical intensities expressed as a percentage of MVC. Panel C: W' in both sexes.

Figure 2: Pre-post changes in neuromuscular function across the four estimation trials. A: maximum voluntary contraction (MVC); B: voluntary activation (assessed with motor nerve stimulation, VA_{MNS}); C: potentiated quadriceps twitch force ($Q_{tw.pot}$). TTF: time to task failure.

Figure 3: Time to task failure during intermittent, isometric knee extensor exercise at 110% of critical intensity. Individual participants are represented as the dots, and group mean and standard deviations are illustrated by the horizontal bars.

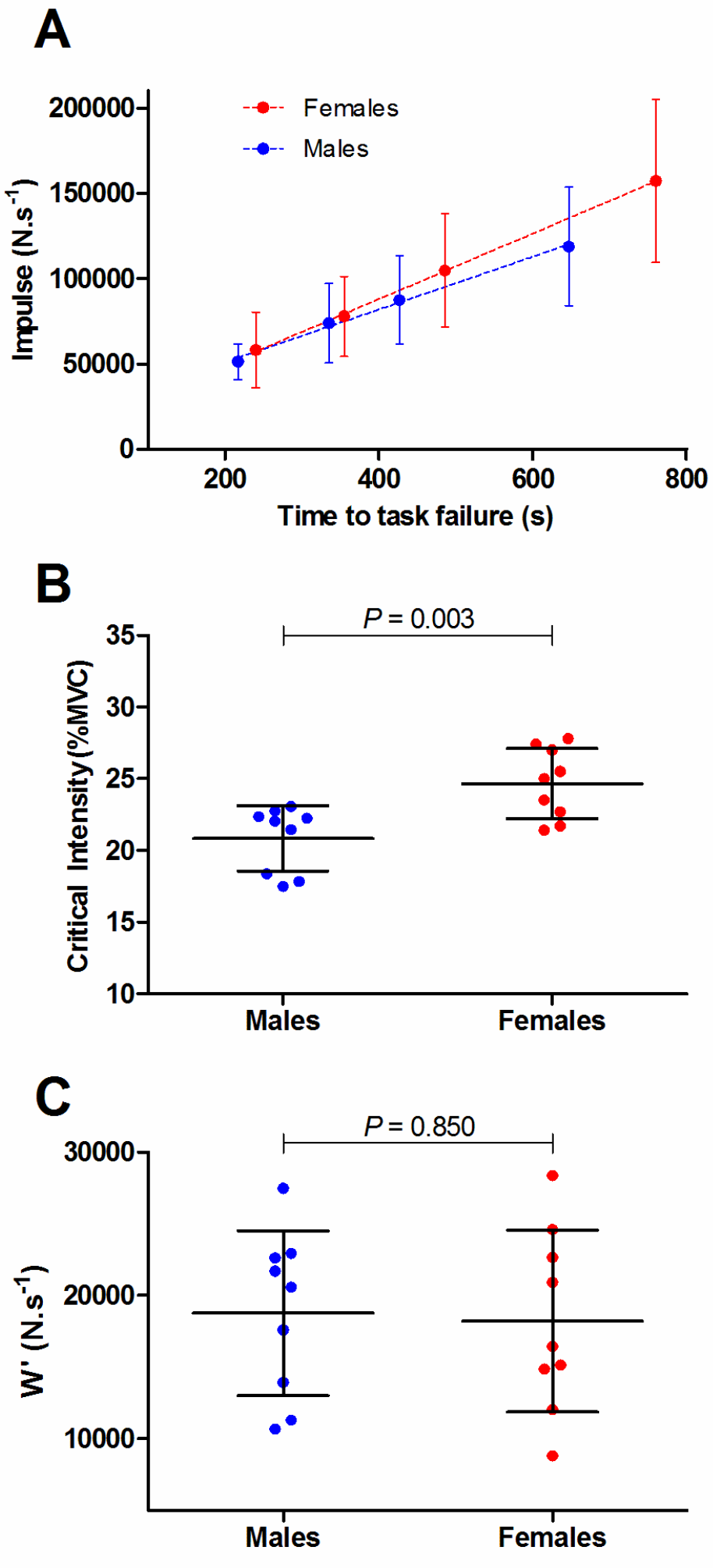
Figure 4: Changes in neuromuscular parameters assessed during the +10% exercise task and recovery period. Panel A: maximum voluntary contraction (MVC); Panel B: potentiated quadriceps twitch force ($Q_{tw.pot}$); Panel C: voluntary activation assessed with motor nerve stimulation (VA_{MNS}). Filled lines and circles represent the group mean values, and the dashed lines represent individual participants. * = different from Pre ($P < 0.05$), $ = significantly different from Post ($P < 0.05$), # = different between males and females ($P < 0.05$).

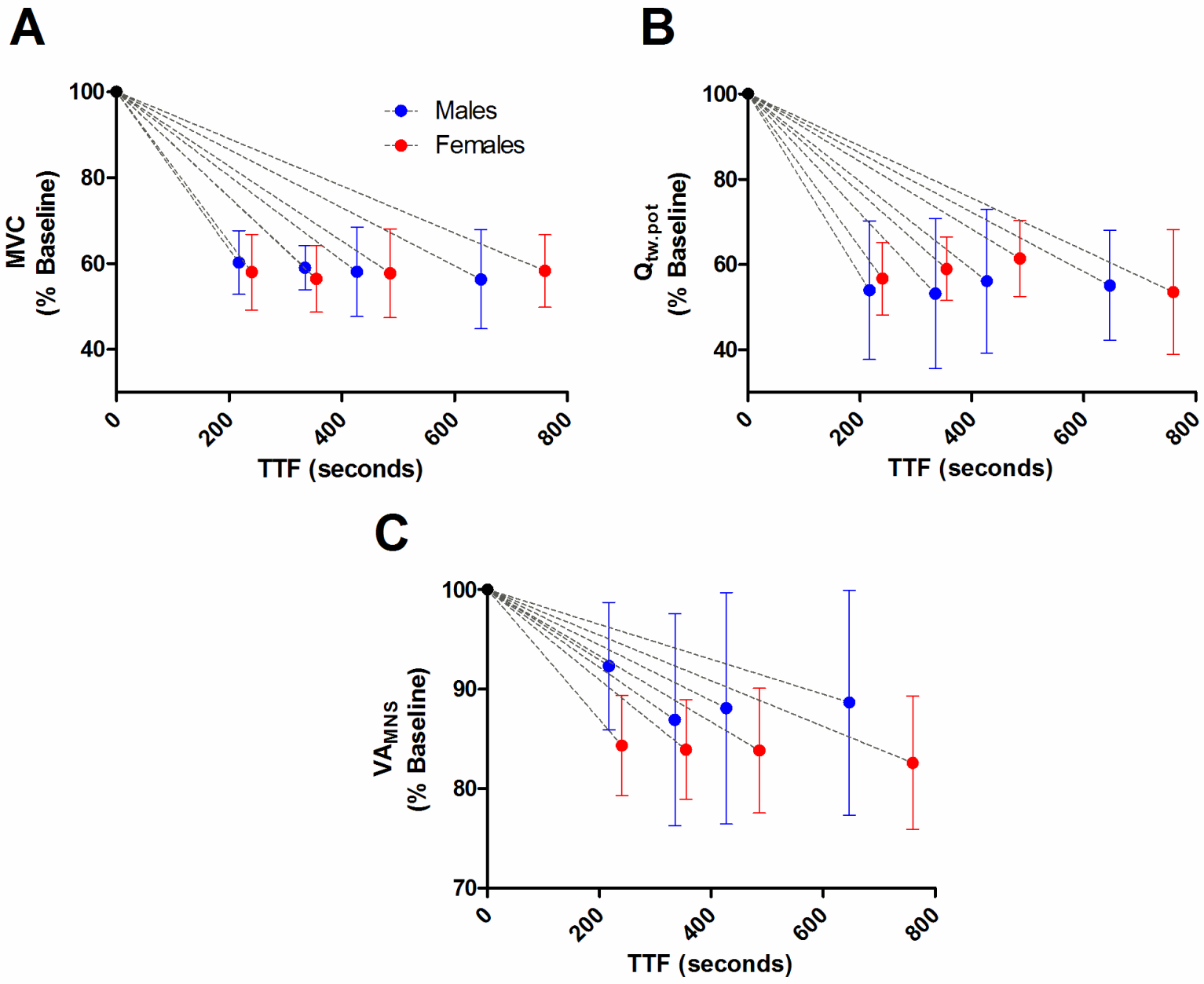
Figure 5: Neuromuscular changes across the fatiguing task (+10%) and the recovery period. A: voluntary activation (transcranial magnetic stimulation, VATMS); B: motor evoked potentials (normalised to M_{max}, MEP/M_{max}), C: short interval intracortical inhibition (SICI). * = different from Pre ($P < 0.05$), $ = significantly different from Post ($P < 0.05$), # = different between males and females ($P < 0.05$).

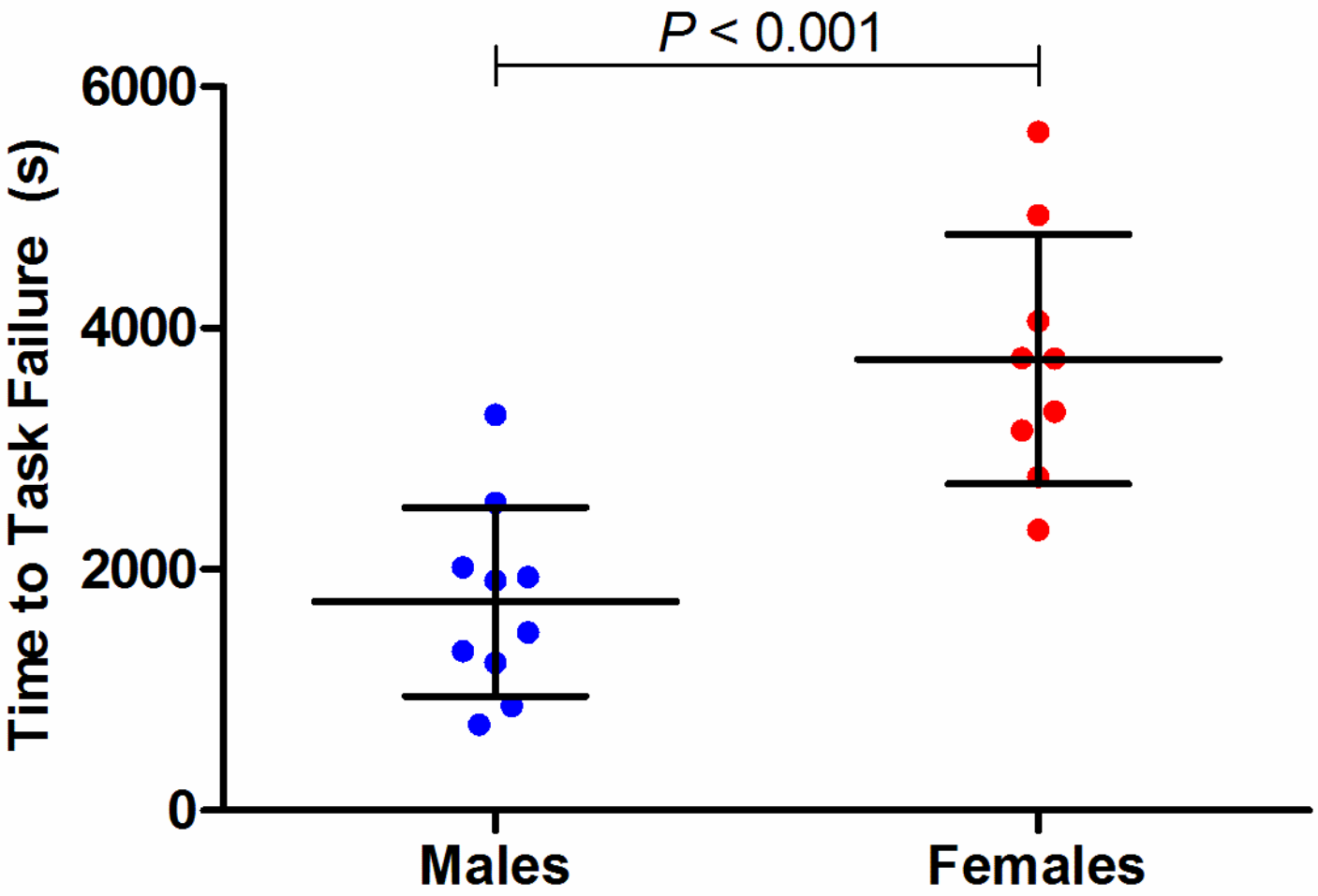
Figure 6: Near Infrared Spectroscopy variables throughout the fatiguing task (+10%). A: Oxyhaemoglobin (O_2Hb), B: Deoxyhaemoglobin (HHb), C: Tissue oxygenation index (TOI). # = significantly different between males and females ($P < 0.05$), * = significantly different from Pre ($P < 0.05$).

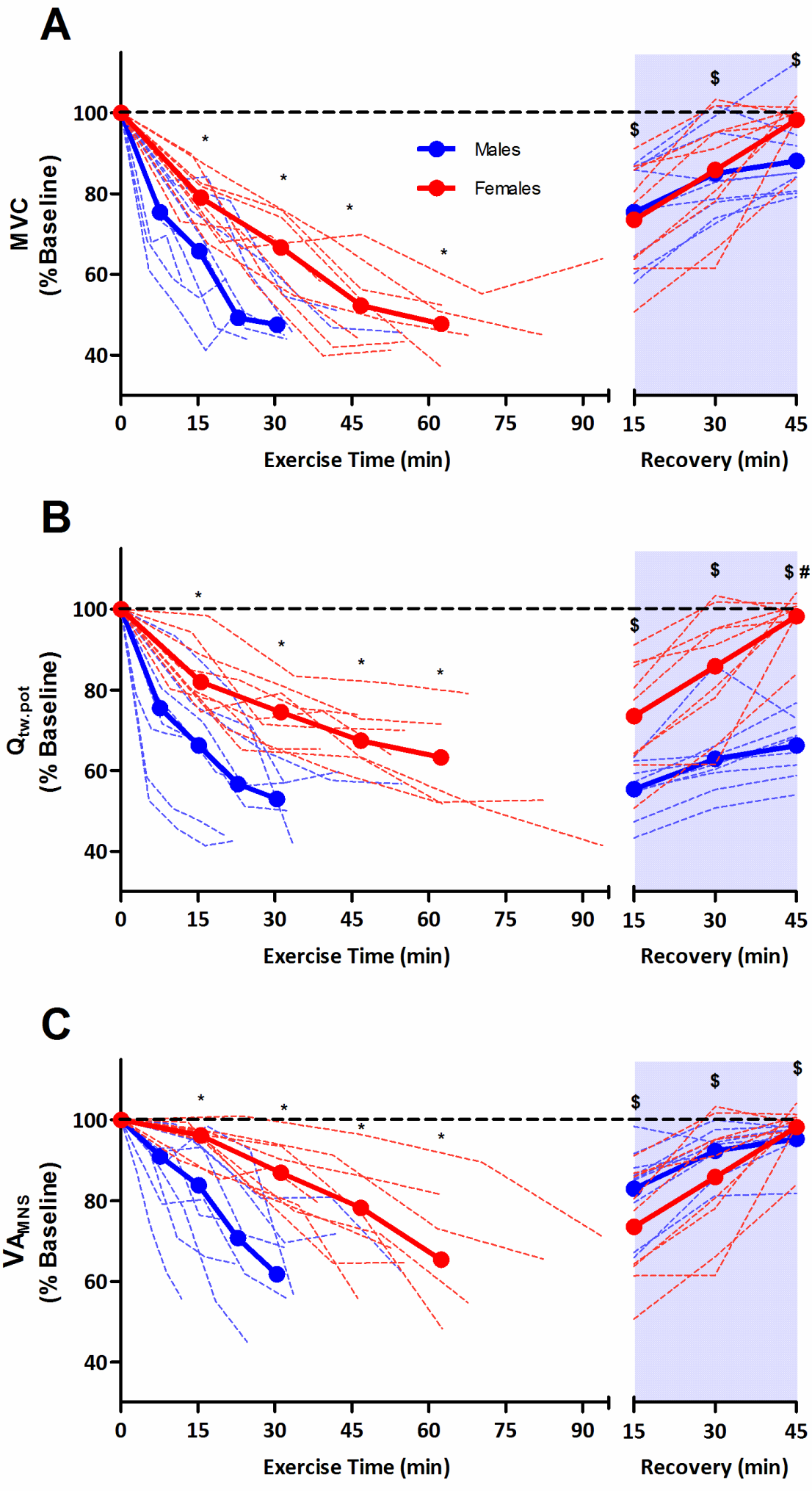
Figure 7: Neuromuscular changes across the fatiguing task (-10%) and the recovery period. A: maximal voluntary contraction, B: voluntary activation (transcranial magnetic stimulation), C: potentiated twitch force, D: motor evoked potential amplitude normalised to M_{MAX}, E: voluntary activation (motor nerve stimulation), F: short interval intracortical inhibition. * = significantly different from Pre ($P < 0.05$), $ = significantly different from Post ($P < 0.05$).

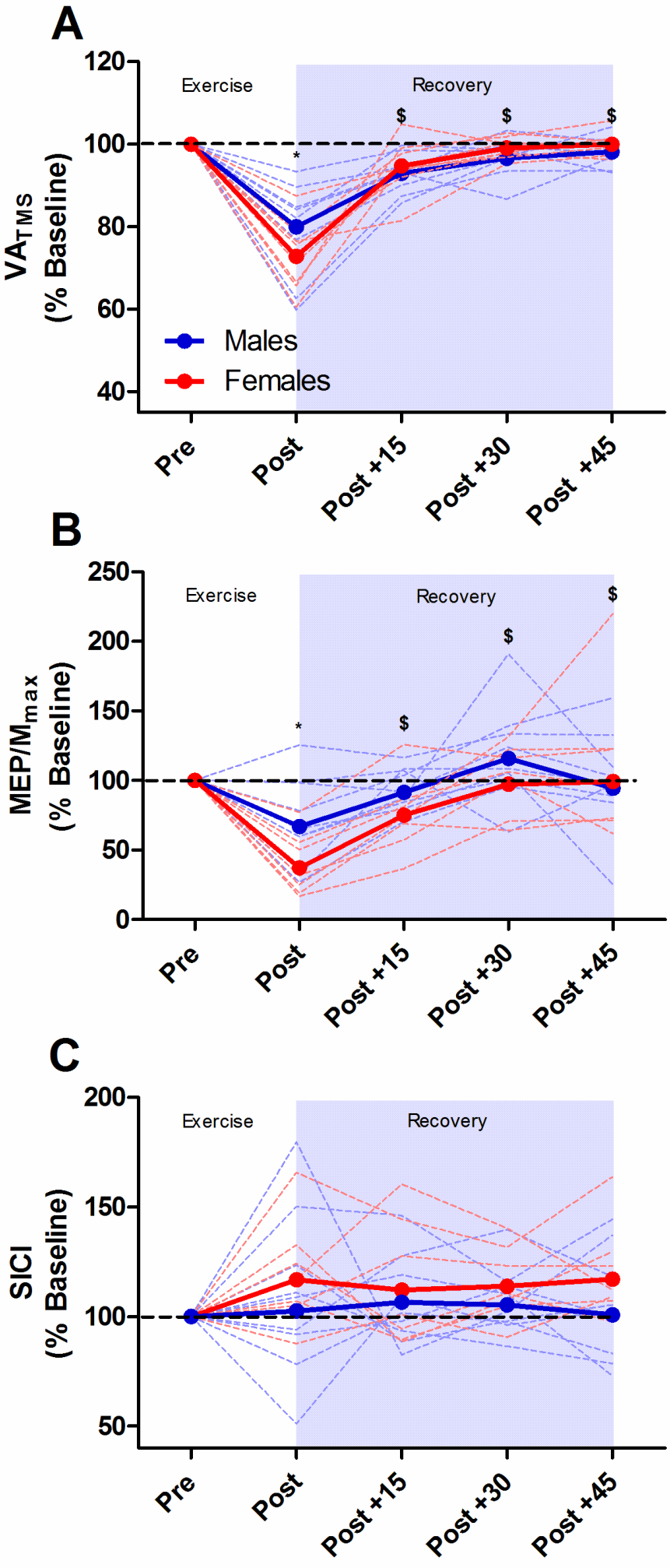
Figure 8: Near Infrared Spectroscopy variables throughout the fatiguing task (-10%). A: Oxyhaemoglobin, B: Deoxyhaemoglobin, C: Tissue oxygenation index. # = significantly different between males and females ($P < 0.05$).

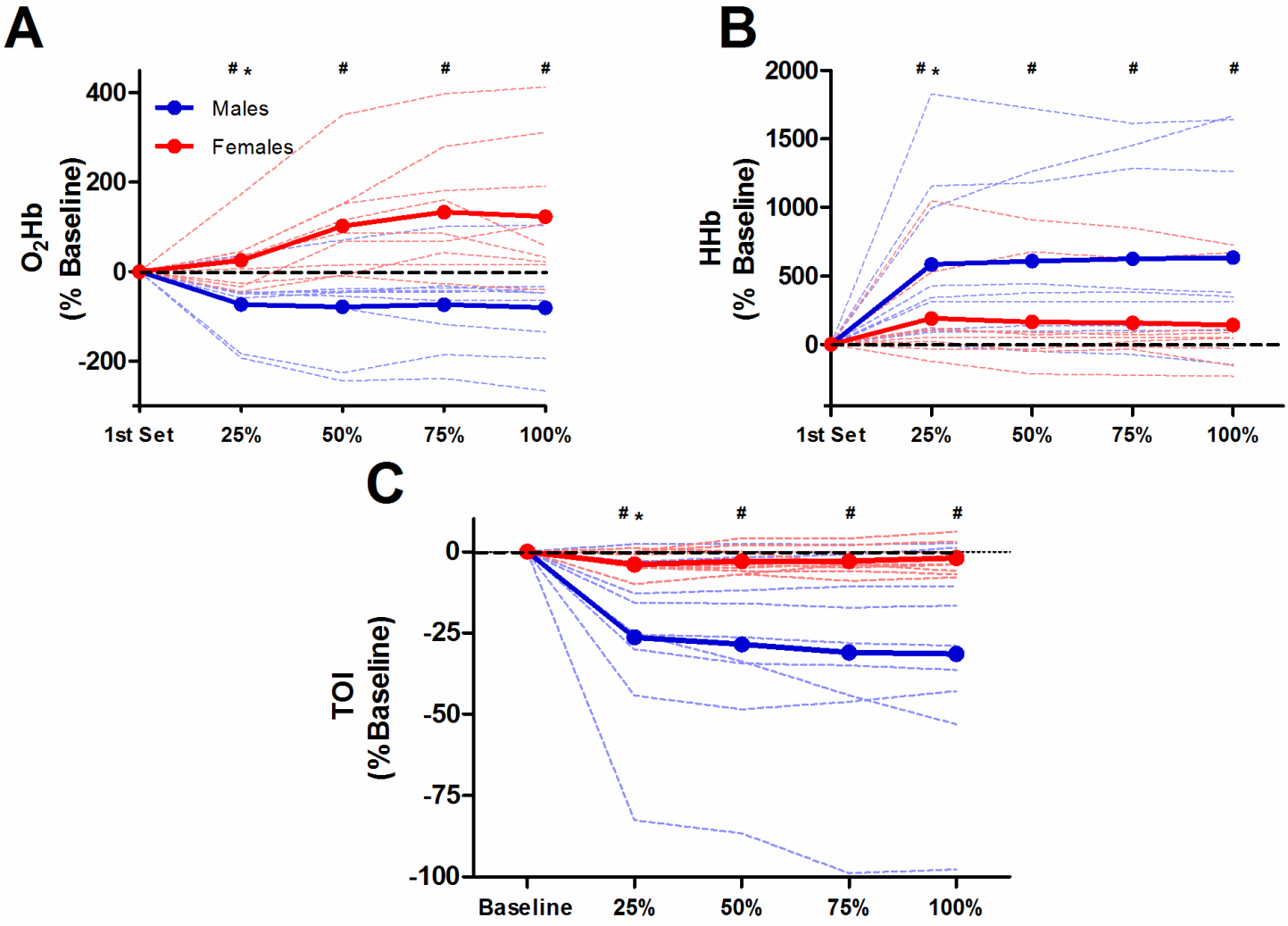

A
Females
Males
Impulse (N.s-1)
200000
150000
100000
50000
0
200
400
600
800
Time to task failure (s)
B
P = 0.003
Critical Intensity (%MVC)
35
30
25
20
15
10
Males
Females
C
P = 0.850
W' (N.s-1)
30000
20000
10000
Males
Females

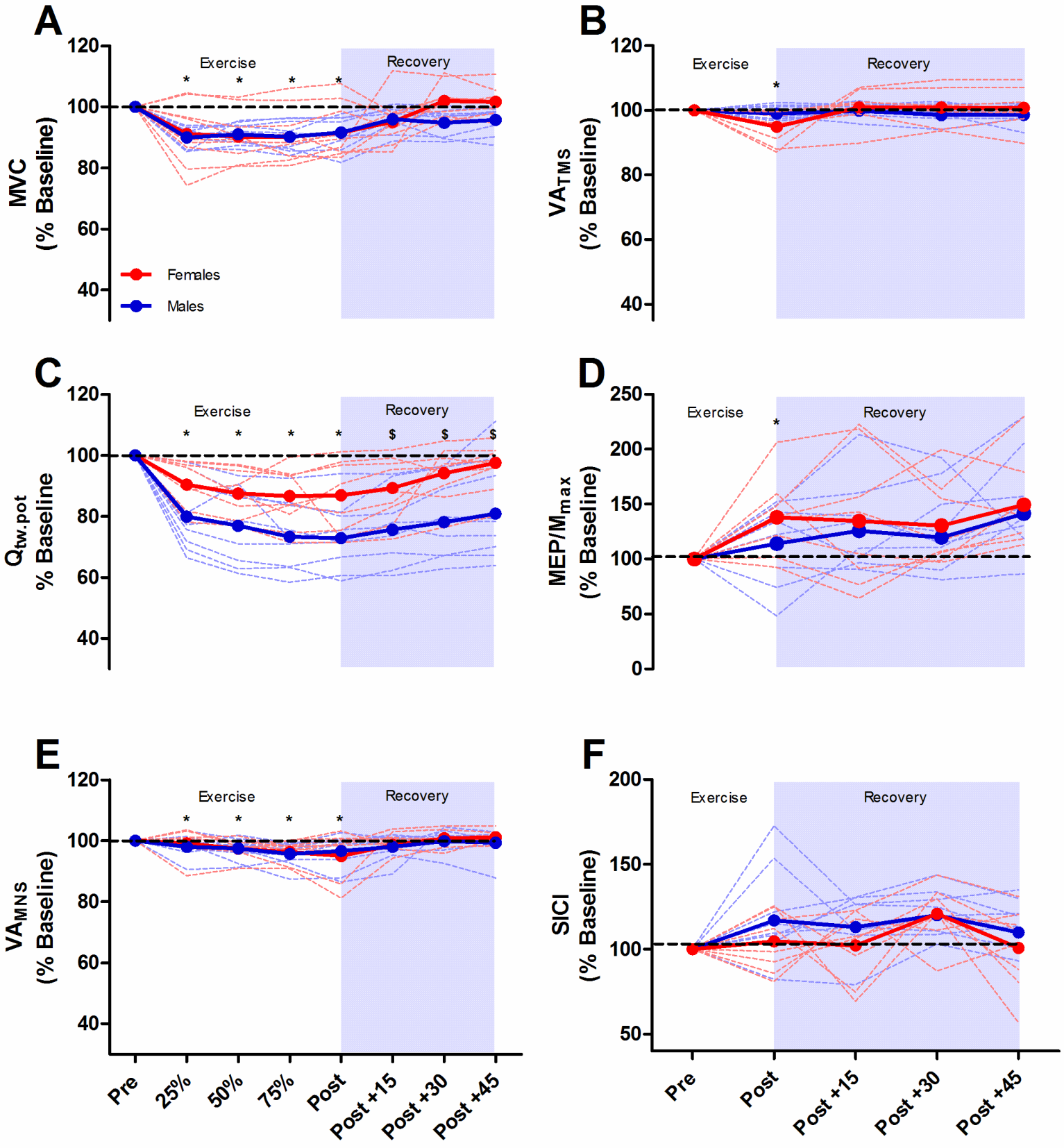

A
100
80
60
40
MVC
(% Baseline)
Males
Females
0
200
400
600
800
TTF (seconds)
B
100
80
60
40
$Q_{tw.pot}$
(% Baseline)
0
200
400
600
800
TTF (seconds)
C
100
90
80
70
VA_{MNS}
(% Baseline)
0
200
400
600
800
TTF (seconds)

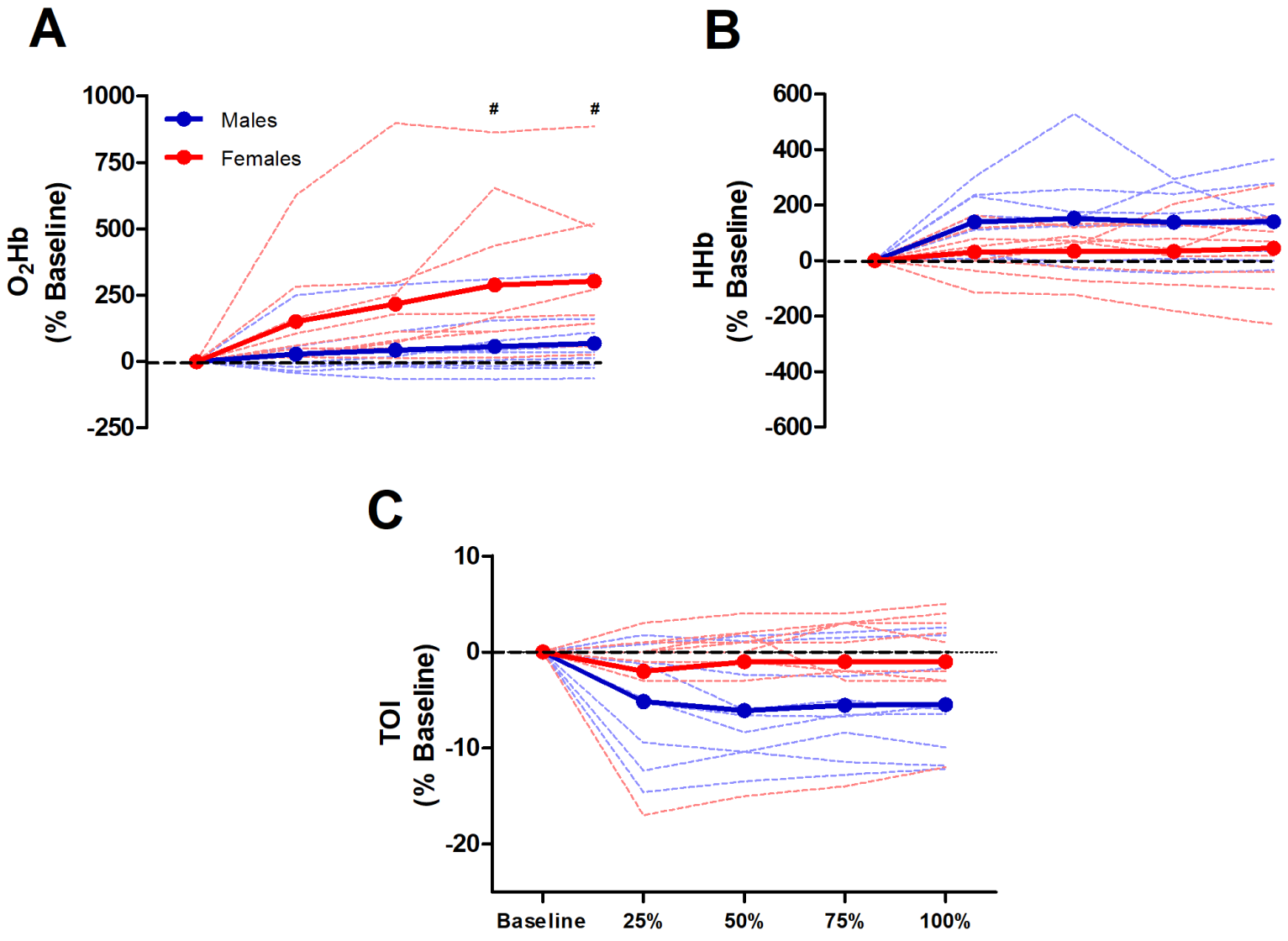

P < 0.001
6000
4000
2000
0
Time to Task Failure (s)
Males
Females


A
MVC (% Baseline)
100
80
60
40
Males
Females
*
$
0
15
30
45
60
75
90
Exercise Time (min)
Recovery (min)
B
$ #
C


A
120
100
80
60
40
VA$_{TMS}$ (% Baseline)
Exercise
Recovery
$
$
$
*
Males
Females
Pre
Post
Post +15
Post +30
Post +45
B
250
200
150
100
50
0
MEP/M$_{max}$ (% Baseline)
Exercise
Recovery
$
$
$
*
Pre
Post
Post +15
Post +30
Post +45
C
200
150
100
50
SICI (% Baseline)
Exercise
Recovery
Pre
Post
Post +15
Post +30
Post +45


A
B
C
Males
Females
O_2Hb (% Baseline)
HHb (% Baseline)
TOI (% Baseline)
1st Set
25%
50%
75%
100%
Baseline
*
#


A
MVC
(% Baseline)
120
100
80
60
40
Exercise
Recovery
*
*
*
*
Females
Males
B
VA$_{TMS}$
(% Baseline)
120
100
80
60
40
Exercise
Recovery
*
C
Q$_{tw.pot}$
% Baseline
120
100
80
60
40
Exercise
Recovery
*
*
*
*
$
$
$
D
MEP/M$_{max}$
(% Baseline)
250
200
150
100
50
0
Exercise
Recovery
*
E
VA$_{MNS}$
(% Baseline)
120
100
80
60
40
Exercise
Recovery
*
*
*
*
Pre
25%
50%
75%
Post
Post +15
Post +30
Post +45
F
SICI
(% Baseline)
200
150
100
50
Exercise
Recovery
Pre
Post
Post +15
Post +30
Post +45


A
B
C
Males
Females
#
#
O_2Hb (% Baseline)
HHb (% Baseline)
TOI (% Baseline)
1000
750
500
250
0
-250
600
400
200
0
-200
-400
-600
10
0
-10
-20
Baseline
25%
50%
75%
100%