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ORIGINAL ARTICLE

Sex differences in central and peripheral mechanisms of fatigue in cyclists

Beth W. Glace · Ian J. Kremenic · Malachy P. McHugh

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Abstract We examined peripheral versus central contributions to fatigue in men and women during prolonged cycling using a peripheral nerve magnetic stimulation-based technique. 11 men (41 ± 3 years) and 9 women (38 ± 2 years) cycled for 2 h at ventilatory threshold with 5, 1-min sprints interspersed, followed by a 3-km time trial. Quadriceps strength testing was performed isometrically in a semi-reclined position pre- and post-cycling: (1) MVC; (2) MVC with superimposed 3-s magnetic stimulation to measure central activation ratio (CAR), a measure of central fatigue; (3) peripheral magnetic stimulation (PMS) alone of the femoral nerve in a 4-s pulse train, a measure of peripheral fatigue. Data were analyzed with mixed model ANOVA. When adjusted for body mass, men and women had similar strength ($p = 0.876$), and changes in MVC with time were similar between sexes, declining 22 % in men and 16 % in women ($p = 0.360$). CAR was similar between sexes and decreased 15 % (effect of time, $p < 0.001$). Changes in PMS-elicited force were different between sexes: only men lost stimulated strength (6.30 to 5.21 vs. 5.48 to 5.53 N kg^{-1}, interaction $p = 0.036$). Results clearly demonstrate that quadriceps fatigue after >2 h of cycling was of both central and peripheral origin in men but solely due to central mechanisms in women.

Keywords Exercise · Gender · Endurance · Neuromuscular stimulation

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B. W. Glace (✉) · I. J. Kremenic · M. P. McHugh
Nicholas Institute of Sports Medicine and Athletic Trauma, Lenox Hill Hospital, 100 East 77th Street, 2 Uris, New York, NY 10075, USA
e-mail: lb@nismat.org

Abbreviations

AUG	Voluntary contraction augmented with superimposed magnetic stimulation
CAR	Central activation ratio
MVC	Maximal voluntary contraction
PMS	Peripheral magnetic stimulation
RQ	Respiratory quotient
RPE	Rating of perceived exertion
VO_2	Oxygen consumption
VOL	Voluntary contraction
VT	Ventilatory threshold

Introduction

Neuromuscular fatigue can be defined as any transient exercise-induced lessening of work capacity. Both central and peripheral mechanisms play a role in fatigue (Davis 1995). Central fatigue represents the failure of mechanisms proximal to the motor neurons, which result in a decreased ability to send a signal to the neuromuscular junction. Peripheral fatigue can be described as fatigue due to mechanisms originating in the muscle fibers themselves. Both magnetic stimulation and electrical stimulation have been used to assess fatigue (Lepers et al. 2002; Todd et al. 2003). The practicality and validity of using peripheral magnetic stimulation (PMS) of the femoral nerve to elicit quadriceps contractions has been established (Kremenic et al. 2004, 2009; Verges et al. 2009) and PMS is being used as a viable alternative to transcranial magnetic stimulation. We have used PMS pulse trains to induce contractions in the quadriceps which produce force similar to maximal voluntary contraction (Kremenic et al. 2004, 2009) whereas transcranial stimulation is limited to single pulses or doublets to produce muscle twitches as there is a risk of seizures using pulse trains (Pascual-Leone et al. 1993). Verges et al. (2009) elegantly demonstrated that PMS of the quadriceps provides similar force responses to electrical stimulation in both fatigued and unfatigued states.

Nearly all of the studies which have evaluated the role of central mechanisms in fatigue have used men. However, similar relative work intensity has been shown to result in greater fatigue in men when compared to women (Glace et al. 1998; Hunter et al. 2006; Yoon et al. 2007). We have previously found that 2 h of running produced profound sex-specific losses in knee strength (Glace et al. 1998), wherein men but not women lost strength. Most other studies comparing fatigue in men and women used isometric contractions (Hunter et al. 2006; Yoon et al. 2007). Some of these studies suggest a similar central component but greater peripheral fatigue in men while others have found central fatigue to be greater in men (Martin and Rattey 2007; Russ et al. 2005). The mechanism for the differences in fatigue between men and women is unknown but may be due to metabolic factors or to mechanical differences such as muscle occlusion, muscle mass, fiber type, or fiber recruitment (Hunter and Enoka 2001; Kent-Braun et al. 2002; Larivière et al. 2006; Miller et al. 1993; Yoon et al. 2007).

Most work examining the central versus peripheral components of fatigue use protocols employing relatively high-intensity or isometric contractions at constant workloads (Hunter and Enoka 2001; Lepers et al. 2000; Nybo 2003; Yoon et al. 2007). Data collected during this kind of exercise may be limited in its applicability to the type of fatigue experienced by endurance athletes in racing situations such as cyclists, distance runners, and triathletes whose muscles contract at relatively low intensity, over the course of many hours and who are likely to deplete glycogen stores (Jeukendrup 2011). In addition, this dynamic type of exercise is not associated with the occlusion of blood flow seen in isometric exercise. There is a dearth of studies that examine fatigue, i.e., central versus peripheral, during prolonged endurance exercise. Verges et al. (2009) examined fatigue after a 30 min downhill run, and Cureton et al. (2007) used a protocol which was meant to more closely mimic the fatigue developed in "real world" racing situations, in which multiple sprints were interspersed with sustained, steady-state cycling, and where a maximal effort was exerted over the final stages of the ride.

Two-plus hours of cycling induces both peripheral and central fatigue in men (Kremenic et al. 2009), and 2 h of running results in significant losses of knee extensor and flexor strength in men but not women (Glace et al. 1998). The purpose of this study was to compare mechanisms of fatigue in both men and women cyclists and triathletes during prolonged exercise, similar to that described by Cureton et al. (2007), using magnetic stimulation. Elucidating the source of fatigue during exercise may allow development of nutritional interventions meant to delay fatigue that are sex-specific. We hypothesized that there would be a significant central component to fatigue in both men and women following prolonged sub-maximal cycling but that men would exhibit more peripheral fatigue.

Methods

Eleven healthy men and 9 women cyclists or triathletes from the New York metropolitan area reported to the physiology laboratory on 2 separate days, no less than 7 days apart and no more than 3 weeks apart. Subjects had to be experienced cyclists, currently training at least 100 miles weekly, and were excluded if they: had ever worked in a metal shop, had a pacemaker or cardiac defibrillator, aneurysm clip, carotid artery vascular clamp, an implanted neurostimulator or drug infusion pump, a bone growth stimulator, a cochlear ear implant, or a sensory impairment. In addition, women were excluded if they were post-menopausal. Prior to testing, subjects gave written informed consent to participate in the protocol, which had been approved by the Institutional Review Board of Lenox Hill Hospital. Subjects were instructed to eat prior to the testing as they normally do prior to racing. On the first day, subjects underwent a maximal exercise test to volitional exhaustion on a cycle ergometer. Electrocardiograms and oxygen consumption were measured throughout the test using the Sensor Medics Vmax system (Sensor Medics, Yorba Linda, CA). Data were collected using the breath-by-breath mode, and values reported as means per minute. Before each test, the flowmeter was calibrated using a 3-l volumetric syringe, and the gas analyzer was calibrated using standardized gases. The protocol was performed on a Monark 834 Ergomedic cycle ergometer (Monark Exercise AB, Vansbro, Sweden), using an incremental protocol. Pedal frequency was maintained at 80–90 rpm, and work was increased by 20–30 watts each minute according to the athlete's fitness. Maximal oxygen consumption and ventilatory threshold were determined from the data.

The ventilatory threshold (VT) was determined through visual inspection of the graphs of the ventilatory equivalents for oxygen and for carbon dioxide according to the method of Caiozzo, et al. (1982). Respiratory gas measures are plotted graphically, and the VT is determined by identifying the interval before the increase in the ventilatory equivalent for oxygen (ventilation/VO_2), without an increase in the ventilatory equivalent for carbon dioxide (ventilation/CO_2).

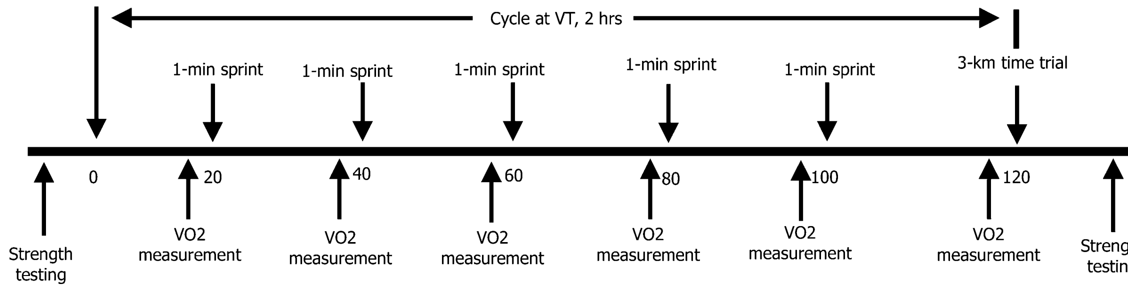

Fig. 1 Experimental protocol timeline

Prior to the second day of testing cyclists were instructed to exercise minimally for 2 days and eat as they normally do prior to racing, but to abstain from caffeine on the morning of the test. Upon arrival at the lab, the subjects' body mass was determined after voiding. A time line of the test protocol is shown in Fig. 1. Subjects' isometric quadriceps strength was assessed while seated in a chair in a slightly reclined position (to facilitate magnetic stimulation), with the knee flexed 60°. Subjects were secured to the chair using cross-over shoulder straps, as well as a belt across the abdomen. The ankle was attached to a chain which was attached to a force transducer (Kistler, Inc., Amherst, NY). Subjects then performed two 5-s maximal voluntary contractions to determine quadriceps strength. Following this, the femoral nerve was stimulated using magnetic stimulation at a frequency of 40 Hz, using a MagStim Rapid Stimulator (MagStim Corp, Wales, UK) with 8 booster units and a double-circular 90 mm coil. Intensity of the stimulus was set at 100 % of the output of the unit. Prior to administration of the pulse trains, optimal location for the stimulating coil over the femoral nerve was determined by identifying the position giving the greatest twitch response to stimulation with single pulses. Two contractions were performed with stimulation superimposed upon 5-s maximal voluntary contractions followed by two with stimulation alone. This allowed measurement of central activation ratio (CAR) to differentiate central from peripheral sources of fatigue. CAR was defined as the ratio of maximal voluntary force produced to that produced by maximum volitional effort with PMS superimposed, see Fig. 2. For the superimposed stimuli, a 3-s stimulus at 100 % of the power output of the stimulator was superimposed on a 5-s voluntary MVC, approximately 2-s into the contraction. For PMS alone, the magnetic stimulator ramped in intensity from 50 to 100 % over the course of 1-s followed by 3-s of 100 % intensity stimulation. All contractions were separated by 30 s of rest. Force was recorded continuously at 1,000 Hz into a computer using AcqKnowledge 3.2 (Biopac, Santa Barbara, CA).

Subjects then cycled for 2 h at the workload eliciting their previously-determined VT (approximately 65–70 % of maximal oxygen consumption). They pedaled on their own bicycles, which were set up on a cycle trainer (Kurt Kinetic Road Machine, Kurt Kinetic, Jordan, MN). Bicycles' rear wheels were mounted with a meter to determine distance, speed, and power (Kurt Kinetic Power Computer, Jordan MN). Respiratory gas measurements were made periodically for 5 min, every 20 min of cycling. Workload was adjusted to maintain oxygen consumption at VT. The Borg Scale was used to assess ratings of perceived exertion (RPE) at each measurement period (Borg 1982). Immediately following each gas measurement the cyclists sprinted for 1 min; a total of 5 1-min sprints were performed at a self-selected intensity. Heart rate was determined using a Polar Heart Rate Monitor (Polar CIC, Port Washington, NY) and water was provided at a rate of 1 % of body weight each hour. This rate of water ingestion was based upon the most recent ACSM Position Stand for fluid replacement (Sawka et al. 2007) and minimized the risk of hyponatremia in the women (Twerenbold et al. 2003). Immediately after cycling for 2 h, they performed a 3 km time trial. Cyclists were encouraged to work as hard as possible during the time trial as they would during a final surge to the finish of a race. Strength testing with magnetic stimulation was repeated, as described above, within 5 min of dismounting the bike, after the fatiguing bout of cycling. Subjects were then instructed to void, and their body mass was measured.

Study design and statistical analysis

Differences between sexes in anthropometric variables, and percent changes in strength measures pre- to post-exercise were compared using unpaired *t* tests. Changes in metabolic parameters and changes in strength measures over time and between sexes were analyzed using mixed model analysis of variance with Greenhouse–Geiser corrections applied where violations of sphericity were found. The strength measures examined were voluntary (VOL) and stimulated (PMS) strength, augmentation from superimposed magnetic stimulation (AUG) and CAR. Mean values from the two contractions were used for analysis, and all

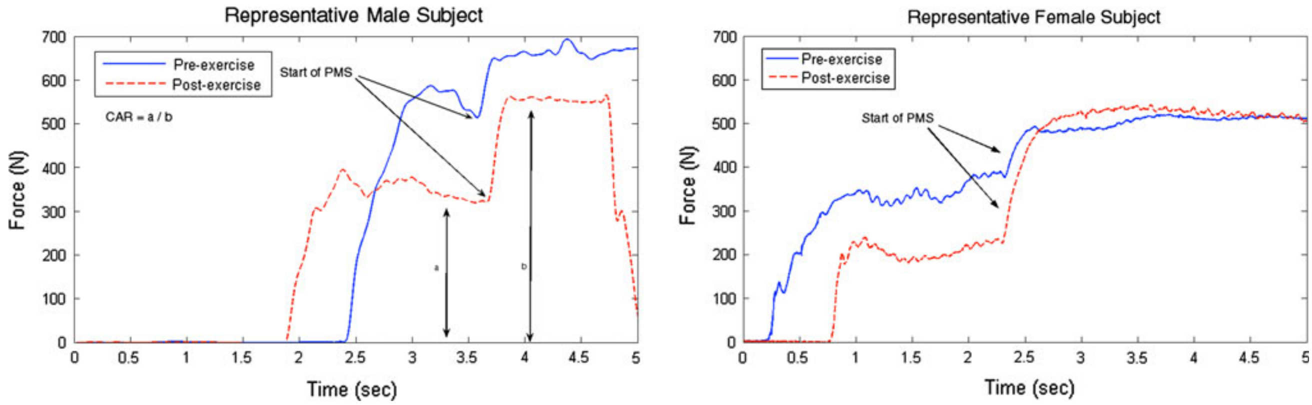

Fig. 2 Representative strength data for male (*left plot*) and female (*right plot*) subjects. *Solid line* maximal isometric force prior to fatiguing exercise. *Dashed line* maximal isometric force following fatiguing exercise. *Arrows* indicate start of PMS imposed upon voluntary contraction. CAR computed from ratio of voluntary contraction force (**a**) to force from contraction augmented with PMS (**b**)

strength measurements were normalized to body mass to facilitate comparisons between men and women. Previous testing in our lab has shown that we can detect a force decrement of 24 % with 80 % power using 10 subjects with magnetic stimulation of the femoral nerve. Fatigue has been shown to produce force decrements of 23.5 % using similar techniques to those described above with endurance athletes (Millet et al. 2003).

Results

Subject demographics

Subject descriptives are listed in Table 1. The subjects ranged from recreational triathletes to Category 1 competitive cyclists. Men and women were of similar age ($p = 0.30$), and the median age for the group was 36 years. The mean peak oxygen consumption (VO_{2peak}) of 55.9 mls kg^{-1} min^{-1} for men and 48.1 mls kg^{-1} min^{-1} for women was typical of recreational athletes. The VT occurred at similar relative intensities, approximately 66 % of their VO_{2peaks}, for men and women, respectively.

There was a significant effect of time on body weight with body mass declining slightly in both sexes ($p = 0.002$): the men's mass decreased from 75.96 ± 2.25 to 75.29 ± 2.37 kg, and the women's decreased from 63.85 ± 4.64 to 63.75 ± 4.76 kg. The amount of dehydration represented less than 1 % of initial mass. Exercise intensity was verified via oxygen consumption at 6 time points during the 2 h of cycling. Men maintained oxygen consumption at 36 ± 1 ml kg^{-1} min^{-1} and women at 30 ± 2 ml kg^{-1} min^{-1}. Oxygen consumption did not change during the prolonged cycling bout (effect of time $p = 0.34$), nor was there an interaction of time × sex ($p = 0.16$). Over the 2-h period, the respiratory quotients (RQ) were similar between men and women, declining from 0.94 ± 0.01 to 0.85 ± 0.01 (Fig. 3; effect of time, $p < 0.001$, no sex × time interaction); mean RQ was 0.88 ± 0.02 for men, and was 0.89 ± 0.01 for women with no effect of sex. RPE while pedaling at their own VT increased similarly for men and women during the 2-h period (effect of sex, $p = 0.94$), from a mean of 12 at 20 min, to 13 at 2 h ($p = 0.01$). Likewise, heart rate increased over time, from a mean of 132 ± 3 beats per minute at 20 min to 139 ± 3 beats at 2 h (Fig. 4; effect of time, $p = 0.01$) but was not different between men and women (effect of sex, $p = 0.40$, sex × time, $p = 0.30$).

Heart rate during the 5, 1-min sprints did not change with repeated sprinting (effect of time, $p = 0.37$), nor was there a difference between sexes ($p = 0.93$; time × gender, $p = 0.41$). The heart rate ranged in men from 165 ± 6 to 168 ± 5, and in women from 163 ± 6 to 168 ± 6 beats per minute. During the time trial similar heart rates were held by the men and women, 162 ± 4 versus 164 ± 5, respectively ($p = 0.90$). Men reported higher RPEs, 18

Table 1 Subject descriptives

	Body mass (kg)	Height (cm)	Age (years)	VO_{2peak} (ml kg^{-1} min^{-1})	VT (% VO_{2peak})
Men	76.0 ± 2.3	180.7 ± 2.1	40.7 ± 3.1	55.9 ± 1.6	66.1 ± 0.7
Women	62.3 ± 4.4	164 ± 3.2	38.4 ± 2.9	49.3 ± 2.2	66.6 ± 1.0

Results reported as mean ± standard error

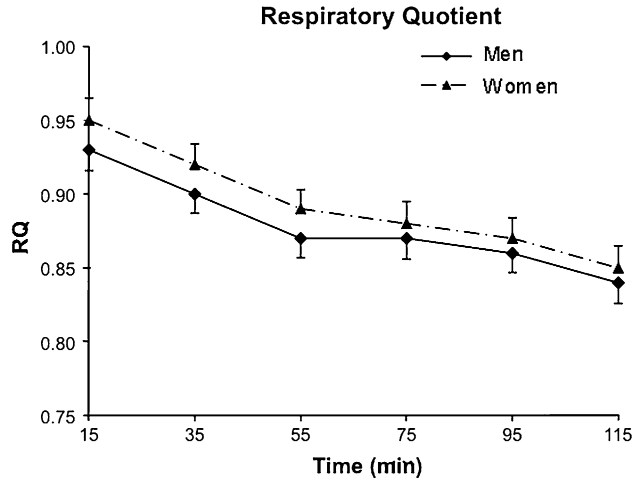

Fig. 3 Respiratory quotient (VCO_2/VO_2). Effect of time, $p < 0.001$; no effect of gender nor interaction of gender × time. Data are mean ± standard error

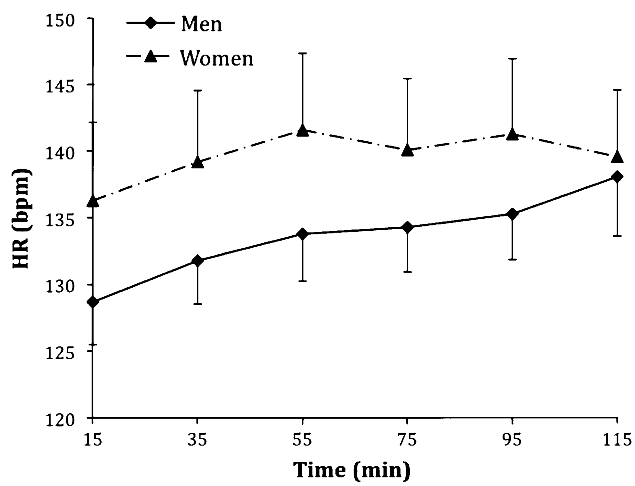

Fig. 4 Heart rate. Effect of time, $p = 0.01$; no effect of gender nor interaction of gender × time. Data are mean ± standard error

versus 16 ($p = 0.001$) and men tended to finish the time trial faster than the women ($p = 0.10$: men, 4.67 ± 0.17 vs. women, 5.98 ± 0.69 min). There were correlations between time to complete time trial and RPE ($r = -0.69$, $p = 0.004$) and between RPE and VO_{2peak} ($r = 0.58$, $p = 0.010$).

As expected, men cycled at a higher work rate than women while pedaling at their VT ($p = 0.022$), and during their sprints ($p = 0.009$). There was neither an effect of time nor an interaction between time and gender. Likewise, mean work during the time trial was 81 % greater in the men than the women: 355 ± 42 watts in men versus 196 ± 38 in women ($p = 0.022$). During the time trial women were able to maintain 168 % of the workload which elicited their VT (196 vs. 117 watts) while men averaged 209 % of their work at VT (355 vs. 171 watts).

Table 2 Results of pre- and post-cycling strength testing in men and women. Force data are normalized to body mass and reported as N/kg

	Pre-cycling	Post-cycling
VOL (N/kg)*		
Men	7.10 ± 0.45	5.53 ± 0.45
Women	6.78 ± 0.50	5.65 ± 0.50
PMS (N/kg)†		
Men	6.30 ± 0.83	5.21 ± 0.71
Women	5.48 ± 0.92	5.53 ± 0.78
AUG (N/kg)*		
Men	1.55 ± 0.37	2.37 ± 0.56
Women	1.13 ± 0.41	1.85 ± 0.62
CAR*		
Men	0.83 ± 0.04	0.71 ± 0.05
Women	0.87 ± 0.04	0.78 ± 0.06

Results reported as mean ± standard error

* Effect of time

† Interaction of time × sex

Strength data normalized to body mass (VOL, PMS, AUG, CAR) are shown in Table 2 and representative data for one man and one woman are shown in Fig. 2. Peripheral magnetic stimulation-induced force was >80 % MVC in both sexes confirming our ability to substantially activate the muscle. Both men and women fatigued after cycling as demonstrated by their similar loss in voluntary strength pre- to post-exercise (effect of time, $p < 0.001$). There was a significant sex × time interaction in stimulated strength changes ($p = 0.008$) indicating that men but not women lost strength when stimulated by PMS. Post hoc testing demonstrated that the change in stimulated strength in men was significant ($p = 0.001$) but non-significant in women ($p = 0.920$). Force augmentation with PMS (AUG) was significantly increased with fatigue in both sexes ($p = 0.003$). Our measure of central activation, CAR, decreased following the cycling protocol in both men and women (effect of time $p < 0.001$), with no sex effect or time × sex interaction. Relative changes in strength are shown in Table 3. There was no difference in their relative loss of strength: men lost 22 % in voluntary strength and

Table 3 Relative changes in strength pre- to post-exercise

	Men $n = 11$ (%)	Women $n = 9$ (%)
Voluntary strength	−22.4 ± 5.2	−15.8 ± 4.6
Stimulated strength*	−15.1 ± 5.0	7.3 ± 7.0
CAR	−14.8 ± 4.7	−15.2 ± 3.2

Results reported as mean ± standard error

* Men differed from women, $p = 0.016$

women lost 16 % ($p = 0.360$). However, elicited force, our measure of peripheral fatigue, was significantly different between sexes, decreasing by 15 % in men but remaining the same (a non-significant 7 % increase) in women after cycling ($p = 0.016$).

Discussion

The objective of this study was to compare neuromuscular fatigue between men and women after a prolonged cycling bout which mimicked racing demands in a cohort of recreational triathletes and cyclists. The age of most cyclists and triathletes is between 25 and 49 years (Virnig and Mcleod 1996). However, almost all studies which have evaluated fatigue mechanisms have studied young, college-age subjects, or subjects over 60 years of age (Hunter 2009). While these comparisons are useful, the populations described do not represent the typical population of recreational and competitive endurance cyclist or triathletes.

Much of the previous work which investigated peripheral versus central mechanisms of fatigue has used protocols employing relatively high-intensity or isometric contractions (Hunter and Enoka 2001; Lepers et al. 2000; Nybo 2003; Yoon et al. 2007). However in endurance exercise, thousands of contractions are performed at low intensities, and the mechanisms leading to fatigue may be quite different from those mechanisms which contribute to fatigue during exercise requiring orders of magnitude fewer shortening cycles (Clark et al. 2003). A protocol similar to that of Cureton et al. (2007) may be more appropriate to study fatigue commonly experienced by endurance athletes. We found that our cycling protocol induced fatigue (decreases in VOL), and that this fatigue had both peripheral and central components in men. While women were similarly fatigued, i.e., they had similar losses in strength compared to men, all of these fatigues appeared to be due to central mechanisms (15 % loss of CAR, but no change in stimulated strength). Representative data illustrating these changes for 2 subjects are shown in Fig. 2. This is the first study, to our knowledge, that used PMS with pulse trains to examine fatigue in both men and women after prolonged endurance activity.

We did not anticipate that this cohort of women would become equally fatigued to men (similar losses in voluntary strength), and suspect that this can be attributed to the protocol used. Compared to a study we conducted previously which found no loss in quadriceps strength in women after 2 h of sub-maximal running (Glace et al. 1998), this study added a time trial component where cyclists pedaled in an all-out maximal effort. Other research (Albert et al. 2006; Clark et al. 2003; Hunter 2009; Russ et al. 2005; Yoon et al. 2007) has used relatively high-intensity, short-duration isometric contractions whereas we used a more aerobically-based protocol which lasted for slightly over 2 h.

Metabolic parameters

We controlled work during the 2-h period to maintain energy expenditure at the VT. RPE increased for both sexes as cycling progressed, which would be expected with fatigue. Several studies have demonstrated that men may be more susceptible to fatigue than women after performing isometric contractions (Albert et al. 2006; Clark et al. 2003; Russ and Kent-Braun 2003), perhaps due to ischemia-related mechanisms associated with the greater muscle mass of men (Russ and Kent-Braun 2003) or to gender-specific differences in substrate utilization.

Men and women did not differ in substrate usage as determined by RERs, making it unlikely that substrate limitations caused the peripheral fatigue observed in the men. Although respiratory exchange ratios are typically about 5 % lower in women than men, indicating a greater reliance on lipids at exercise intensities of 65 % of VO_{2peak} or less (Tarnopolsky 1998), our relative intensity of exercise was slightly above 65 % of VO_{2peak}.

The revised central fatigue hypothesis suggests that the neurotransmitter serotonin and importantly, the ratio of serotonin to dopamine, may play a role in the development of fatigue (Davis et al. 2000). Serotonin affects arousal, lethargy, sleepiness, and mood (Newsholme and Blomstrand 2006). Increased amounts of serotonin in the brain might, therefore, lead to central fatigue during prolonged exercise. Increases in plasma fatty acids, as are seen in endurance exercise, displace tryptophan from its binding site on albumin, creating an increase in freely-circulating tryptophan. Free tryptophan is transported across the blood–brain barrier, where it serves as a precursor to serotonin (Davis et al. 2000). While we have no blood substrate measures, the RQ values which we observed in men and women suggest that fatty acid oxidation was similar. Similar substrate usage would be expected to result in similar central fatigue, according to the revised central fatigue hypothesis, as we observed.

Peripheral and central fatigue

The difference between sexes in our measure of peripheral fatigue is striking. Although both sexes experienced similar declines in voluntary strength following prolonged exercise, we were unable to demonstrate peripheral fatigue in women. Force elicited by PMS alone is an indicator of peripheral fatigue, as stimulation bypasses the central drive from the motor cortex. Men demonstrated a significant decrease in stimulated force, whereas women were unchanged pre- to post-exercise. While a decrease in this measurement may be reflective of changes in the motor threshold of the femoral nerve (Vagg et al. 1998), the difference between men and women (i.e., the lack of change in women) would indicate a sex difference in peripheral fatigue (see Table 3). The similar decrease in CAR is largely indicative of central fatigue in both men and women.

We can only speculate as to why men alone exhibited peripheral fatigue. Men were able to maintain both a higher absolute workload during their time trials, and also a higher workload relative to the work performed at their ventilatory threshold. Such high intensities might produce more ischemic conditions within the muscle (Russ and Kent-Braun 2003), greater anaerobic contribution to metabolism and concomitantly greater lactate production. Under such conditions men may be more compromised peripherally than women.

Women's RPE was less than that of the men during their time trials despite having maintained similar relative workloads for the previous 2 h. Both men and women were strongly verbally encouraged to complete the 3 km as quickly as possible. Mean time to complete the trial time was 28 % greater for the women compared to the men, and that likely affected the relative intensity of effort they could maintain as they paced themselves through the distance. Loss of voluntary strength was our primary measure of fatigue. As loss of voluntary strength did not differ between the sexes, men and women exhibited similar fatigue, despite the lower RPEs of the women.

Limitations and future work

This PMS-based technique lends itself to exploration of many different facets of fatigue, such as sex differences in the sites of fatigue, as we have done here. Magnetic stimulation may also be used to explore the mechanism of known ergogenic aids such as caffeine and carbohydrates. PMS, however, is not without limitations. Its use requires access to superficial nerves, and thus, body fatness may limit its use in obese subjects. The cost of the equipment is also substantially greater than the traditionally-used electrical stimulation units.

Nybo (2003) has demonstrated that hypoglycemia, produced by cycling for 3 h without supplemented carbohydrate, attenuated central nervous system activation compared to a euglycemic condition. Our protocol was limited in that we did not measure blood glucose levels. While hypoglycemia could have contributed to the fatigue our subjects experienced, none reported any symptoms associated with low blood sugar (e.g., shakiness, dizziness, confusion, or difficulty speaking). Further, not only did the mean RERs differ between men and women, but also at no time did any individual's RER drop below 0.75, indicating that some carbohydrate was always being used as substrate in all participants. We plan to investigate the effect of carbohydrate supplementation in future studies. It is well-known that exogenous carbohydrates permit the exerciser to maintain a given exercise intensity for a longer period of time (Vandenbogaerde and Hopkins 2011). It has generally been accepted that carbohydrates serve as substrate for the peripheral muscle, providing an exogenous source of energy and sparing limited glycogen reserves (Campbell et al. 2008). Carbohydrates may also affect fatigue by altering central mechanisms by serving as substrate for the neurons of the central nervous system, thereby extending their ability to work (Matsui et al. 2011). If carbohydrate has a role in preventing both peripheral and central fatigue, men may be more likely to see performance benefits from its use.

Menstrual phase might affect endurance exercise performance. Although one study showed an effect of menstrual phase on performance, when exercising in hot conditions (Tenaglia et al. 1999), most studies fail to demonstrate an effect of menstrual phase on time to exhaustion during sub-maximal, steady-state exercise (de Jonge 2003). We would not expect an effect of menstrual cycle in our protocol, where the room temperature was maintained at 21 °C. However, we may have introduced more variability to our comparisons by not controlling for menstrual phase. Despite the potential for increased variability, profound differences in peripheral fatigue were demonstrated between men and women. It is unknown if this fatiguability is more apparent in a particular phase of the cycle.

Conclusions

These results clearly demonstrate that trained male and female cyclists experience significant central fatigue during prolonged cycling. However, only men experienced peripheral fatigue. This may have implications for sex-specific interventions to delay or attenuate fatigue. Further work in this area is needed to elucidate the metabolic factors underlying this sex difference.

Ethical standards The experiments performed comply with the current laws of the United States and were approved by the Institutional review Board of Lenox Hill Hospital.

Conflict of interest The authors declare that they have no conflict of interest.

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