Journal of Science and Medicine in Sport xxx (xxxx)

Contents lists available at ScienceDirect

Journal of Science and Medicine in Sport

journal homepage: www.elsevier.com/locate/jsams

Original research

Sex differences in quadriceps and inspiratory muscle fatigability following high-intensity cycling

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ARTICLE INFO

Article history:
Received 2 October 2022
Received in revised form 8 February 2023
Accepted 10 February 2023
Available online xxxx

Keywords:
Quadriceps fatigue
Metaboreflex
Cycling performance
Neuromuscular
Exhaustion

ABSTRACT

Objectives: As females have been hypothesized to have more fatigue resistant inspiratory muscles, this study aimed to compare the development of inspiratory and leg muscle fatigue between males and females following high-intensity cycling.
Design: Cross-sectional comparison.
Methods: 17 healthy young males (27 ± 6 years, $\dot{V}O_{2peak}$ 55 ± 10 $ml \cdot min^{-1} \cdot kg^{-1}$) and females (25 ± 4 years, $\dot{V}O_{2peak}$ 45 ± 7 $ml \cdot min^{-1} \cdot kg^{-1}$) cycled until exhaustion at 90% of the peak power output achieved during an incremental test. Changes in quadriceps and inspiratory muscle function were assessed via maximal voluntary contractions (MVC) and assessments of contractility via electrical stimulation of the femoral nerve and cervical magnetic stimulation of the phrenic nerves.
Results: Time to exhaustion was similar between sexes ($p = 0.270$, 95% CI −2.4 – 0.7 min). MVC of the quadriceps was lower after cycling for males (83.9 ± 11.5% vs. 94.0 ± 12.0% of baseline for females, $p = 0.018$). Reductions in twitch forces were not different between sexes for the quadriceps ($p = 0.314$, 95% CI −5.5 – 16.6 percent-points) or inspiratory muscles ($p = 0.312$, 95% CI −4.0 – 2.3 percent-points). Changes in inspiratory muscle twitches were unrelated to the different measures of quadriceps fatigue.
Conclusion: Females incur similar peripheral fatigue in the quadriceps and inspiratory muscles compared with men following high-intensity cycling, despite smaller reduction in voluntary force. This small difference alone does not seem sufficient to warrant different training strategies to be recommended for women.

Practical implications

- When matched for training status, the endurance capacity of males and females is similar during high-intensity cycling
- Females do not seem to reach exhaustion during high-intensity cycling with a different level of peripheral fatigue in the quadriceps or inspiratory muscles compared to males
- These similarities in endurance capacity and fatigue levels at exhaustion do not warrant different training strategies for female athletes.

1. Introduction

Males and females possess anatomical and physiological differences that are important for exercise performance and possibly training prescription. While males are significantly stronger and have greater aerobic capacity than females of similar training level,[1] females show similar or increased endurance capacity and resistance to muscle fatigue, depending on the task performed.[2] Sex differences at the anatomical and physiological level are also present in the respiratory system, which may further differentiate the exercise capacity of males and females. Females have smaller lungs than males of similar height and smaller airway diameter when matched for lung size[3] – and therefore a smaller surface area for O_2 diffusion and a higher propensity for developing expiratory flow limitation. While the latter does not limit pulmonary ventilation per se, it forces changes in breathing towards hyperinflated volumes, where the diaphragm contracts from shorter and weaker lengths – eventually incurring a higher metabolic cost for pulmonary ventilation at higher ventilation levels,[4] with a higher fraction of whole-body $\dot{V}O_2$ to be directed the respiratory muscles.[5] On

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Abbreviations: CLT, Constant load test; PPO, Peak power output; HR, Heart rate; VTh, Ventilatory threshold; EMG, Electromyography; STERNO, Sternocleidomastoid; INTER, Intercostals; VAST, Vastus lateralis; RMS, Root mean square; HHb, Deoxyhemoglobin; Q_{TW}, Twitch force from an electric stimulus delivered to the quadriceps; MVC, Maximal voluntary contraction; $P_{m,TW}$, Twitch force at the mouth from a magnetic stimulation to the phrenic nerves.

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https://doi.org/10.1016/j.jsams.2023.02.006

Please cite this article as: F.G. Beltrami, C.E. Schaer and C.M. Spengler, Sex differences in quadriceps and inspiratory muscle fatigability following high-intensity cycling, Journal of Science and Medicine in Sport, https://doi.org/10.1016/j.jsams.2023.02.006

the other hand, females have a more fatigue resistant diaphragm and better respiratory muscle endurance compared to males,[6,7] arguably decreasing the potential for the so-called respiratory muscle metaboreflex, whereby fatigue of the inspiratory muscles – apparent when exercise above 80% of maximal VO_2 is performed[8] – triggers an increase in sympathetic outflow that ultimately restricts blood flow to the exercising limbs and exacerbates contractile muscle fatigue.[6,9]

Yet, despite these differences, males and females seem to have similar times to exhaustion when exercising at 80–90% of their respective peak power outputs, even though women show attenuated diaphragmatic peripheral fatigue at exhaustion.[10–12] To date, however, it has never been demonstrated how fatigue of the respiratory and lower limbs muscles interact during high-intensity exercise performed at similar relative intensities by males and females, which could have important implications for training given the potentially different contributors to exhaustion. Therefore, the aim of this study was to test whether the level of quadriceps and inspiratory muscle fatigue would be similar between the sexes following high-intensity cycling performed until exhaustion. We hypothesized that females would display a similar time to exhaustion compared to males while showing a lower degree of inspiratory muscle fatigue, but comparable levels of lower limb fatigue, without an association between inspiratory and lower limb fatigue after whole-body exercise.

2. Methods

Thirty-four healthy, moderately trained female (age 25 ± 4 years, weight 59 ± 5 kg, height 166 ± 5 cm, VO_{2peak} 45 ± 7 $ml \cdot kg^{-1} \cdot min^{-1}$) and male (age 27 ± 6 years, weight 73 ± 9 kg, height 178 ± 6 cm, VO_{2peak} 55 ± 10 $ml \cdot kg^{-1} \cdot min^{-1}$) participants took part in this study (Supplemental Table 1). All visit days were separated by at least 48 h. Participants gave written informed consent when enrolling in the study, which was approved by the local ethics committee (2014-N-02) and was performed according to the Declaration of Helsinki 2008. Participants reported to the laboratory on three occasions. On the 1st visit, lung function (including 12-s maximal voluntary ventilation, MVV) and respiratory muscle strength were assessed according to current guidelines.[13] Participants then performed an incremental cycling test until volitional exhaustion and, following adequate rest, were familiarized with the femoral nerve stimulation and cervical magnetic stimulation protocols. On the 2nd visit, participants performed a constant load test (CLT) at 90% of the peak power output (PPO) achieved during the incremental test until volitional exhaustion, which was performed to ensure familiarization with the exercise task. The 3rd visit contained the same exercise test as the 2nd with the addition of measures of quadriceps and respiratory muscle contractility before and after the CLT (see below). Femoral nerve stimulation was performed 2 min after exhaustion and cervical magnetic stimulation 10 min after exhaustion.

The incremental cycling test (Ergoline 900, Ergoline, Blitz, Germany) began at 100 W for men and at 70 W for females. Subsequently, the load was increased by 30 W every 2 min until exhaustion. Participants kept cadence between 70 and 100 rpm and the test was finished when the subject stopped or when the cadence dropped below 70 rpm. Ventilation and gas exchange were measured breath-by-breath by the metabolic cart (Oxycon Pro; Jaeger, Höchberg, Germany). VO_{2peak} was defined as the highest 30 s average of the cycling test. The ventilatory threshold (VTh) was determined as the last point (30-s moving average, 5-s epochs) at which RER was ≤1.00 during the incremental test and was expressed as a function of the PPO of the test.[14]

The CLT test started at 40% PPO for 2 min and 2 min at 60% PPO, after which the workload was increased to 90% PPO. Participants were instructed to cycle for as long as they could while maintaining the cadence. The test was terminated when cadence fell below 70 rpm despite strong verbal encouragement (for two female participants termination frequency was adapted to 60 rpm). Muscle activity was measured using electromyographic activity (EMG). Bipolar surface electrodes were placed on the skin above the muscle belly of the right sternocleidomastoid (STERNO), intercostals (INTER) and vastus lateralis (VAST) of the dominant leg (self-reported preference for kicking a ball) according to SENIAM recommendations.[15] In order to measure changes in deoxygenated hemoglobin (HHb) and oxygenated (O_2Hb) of the STERNO, INTER and the VAST, near-infrared spectroscopy optodes (NIRS, OxyMon MK III; Artinis Medical Systems B.V., Zetten, Netherlands) were used. Methodological details are provided in the supplementary information. During rest, every 2 min during the test and at exhaustion, participants were asked to rate their perceptions of breathlessness, leg and respiratory effort, followed by the collection of 20 μl of capillary blood taken from an earlobe for determination of blood lactate concentration [La^-]. Perception of breathlessness, respiratory and leg effort were assessed during the CLT by means of a 20-cm visual analog scale ranging from 0 (none) to 10 (maximal exertion).[16]

Quadriceps muscle contractility was determined with electrical femoral nerve stimulation producing a quadriceps twitch torque (Q_{TW}). Participants were seated in a semi-supine position with knees flexed at 90° and the ankle of the dominant leg was fixed with a non-elastic strap and connected to a force transducer (strain gage LC4102-K060, A&D CO, Tokyo, Japan). Participants performed three 5-s MVCs with 5 s breaks in between. In a relaxed state, after the MVCs, the femoral nerve was stimulated by a 100 Hz double stimulation (doublets), 10 Hz doublets and a single stimulation (see supplementary data for details). This was followed by two blocks consisting of an MVC and three stimulations, one 100 Hz doublets, one 10 Hz doublets and a single stimulation. Mean torque response was obtained for each type of stimulation (i.e. the average of the three Q_{TW1} for single stimulation, Q_{TW10} for 10 Hz doublets or Q_{TW100} for 100 Hz doublets respectively). Changes in quadriceps contractility (ΔQ_{TW}) were calculated as the percent-difference from baseline to post-exercise. Day-to-day changes in baseline MVC and Q_{TW} expressed as a coefficient of variation are within 6–11%. Within day variations, relevant for the current protocol, are likely smaller than these figures.

Inspiratory muscle contractility was assessed by means of changes in mouth pressure twitches ($\Delta P_{m,TW}$) elicited by cervical magnetic stimulation (CMS) of the phrenic nerve using a circular 90 mm coil powered by a magnetic stimulator at 100% stimulator output (MagStim 200 stimulator, Whitland, UK). Three blocks of one 5-s maximal inspiratory muscle contractions interspaced by three magnetic stimulations were performed (for methodological details, see supplementary information). $\Delta P_{m,TW}$ were calculated as the percent-difference from baseline to post-exercise. In this cohort, day-to-day changes in baseline $P_{m,TW}$ expressed as a coefficient of variation was 15.3%, while within day variation in our laboratory is below 10%.[17]

Responses to the CLT (3rd day) were compared between the males and females using unpaired t-tests. The presence of fatigue following the CLT was tested for each sex using one sample t-tests where post-CLT values were expressed as a percentage of baseline and compared to 1.0. Changes in peak-to-peak M-Wave amplitude within sexes before and after the CLT were compared using paired t tests. Due to the asymmetrical distribution of values when using the VAS scale at the very ends of the scale (i.e. minimal or maximal effort, where values are respectively close to 0 or 10), perception of breathlessness, respiratory and leg exertion were also analyzed using non-parametric Mann–Whitney ranks tests. As these yielded similar results to the unpaired t-tests, the later are reported here. Relationship between different variables were tested using linear regression. Effect sizes are reported as Cohen's D. All tests were performed using Prism 9.3 (Graphpad, La Jolla, CA). The level of significance was set at $P < 0.050$ for all statistical comparisons.

3. Results

Time to exhaustion from the CLT was 11.1 ± 1.9 min for males and 10.2 ± 2.6 min for females ($t_{(32)} = 1.123$, $p = 0.270$, 95% CI −2.4 –

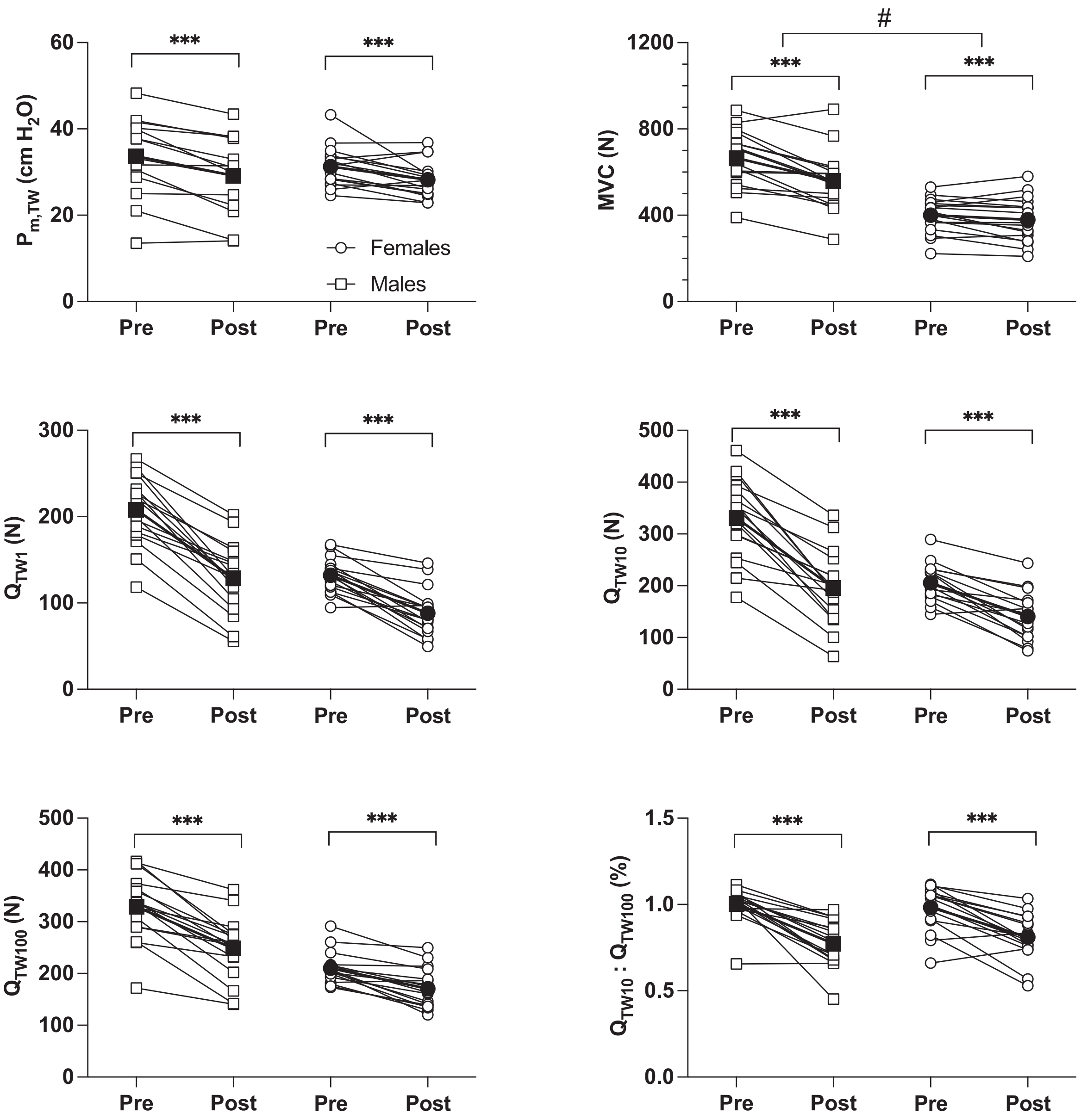

Fig. 1. Variables of respiratory and quadriceps muscle fatigue assessed Pre- and Post-cycling for males and females. $P_{m,TW}$, mouth pressure; MVC, maximal voluntary contraction; Q_{TW1}, single twitches; Q_{TW10}, 10 hz doublets; Q_{TW100}, 100 hz doublets. *** $P < 0.001$ for pre vs. Post differences with sexes; # $P < 0.05$ for the relative delta ((Post-Pre)/Pre) between males and females.

0.7 min, ES = 0.38). During the final 30 s of the CLT, $\dot{V}_E$ as a fraction of MVV was 73 ± 10% for males and 79 ± 13% for females ($t_{(32)} = 1.331$, p = 0.192, 95% CI −13 – 3%, ES = 0.46). HR during the final 30 s of the CLT test was 182 ± 8 bpm for males and 183 ± 8 bpm for females ($t_{(30)} = 0.422$, p = 0.676, 95% CI -5 – 7 bpm, ES = 0.14). $[La^-]$ at the end of the CLT was 13.1 ± 2.3 $mmoL \cdot L^{-1}$ for males and 11.6 ± 2.5 $mmoL \cdot L^{-1}$ for females ($t_{(30)} = 1.812$, p = 0.079, 95% CI -3.2 – 0.2, ES = 0.63). When $[La^-]$-values were normalized to those measured at the end of the incremental test, the effect size decreased to 0.01 (p = 0.979). At the end of the CLT breathlessness was 3.7 ± 3.7 for males and 2.2 ± 3.0 for females ($t_{(32)} = 1.303$, p = 0.202, 95% CI −3.9 – 0.8, ES = 0.44); respiratory exertion was 6.7 ± 2.4 for males and 7.0 ± 2.5 for females ($t_{(32)} = 0.361$, p = 0.720, 95% CI −1.4 – 2.0, ES = 0.12) and leg exertion was 9.4 ± 1.0 for males and 9.3 ± 1.0 for females ($t_{(32)} = 0.559$, p = 0.956, 95% CI −0.7 – 0.7, ES = 0.02).

Measures of EMG activity and NIRS values in the VASTUS during the final 30 s of the CLT are presented in Supplemental Table 2. The difference in EMG activity between males and females did not reject the null hypothesis of equal activation between sexes (p = 0.103, ES = 0.58), and a similar picture was seen for HHb concentration (p = 0.208, ES = 0.47). On the other hand, females showed an increase in O_2Hb concentration while males showed a decrease (p = 0.009, ES = 1.07).

Measures of EMG activity and NIRS values in the STERNO and INTER during the final 30 s of the CLT are presented in Supplemental Table 2. The difference between males and females in EMG activity (p = 0.289, ES = 0.38) and O_2Hb (p = 0.262, ES = 0.40) of the STERNO did not reject the null hypothesis of similar changes between sexes, while males showed a larger increase in HHb concentration at the end of the CLT (P < 0.001, ES = 1.52). Males showed a higher EMG activity of the INTER (p = 0.005, ES = 1.09), while the differences of neither the concentration of O_2Hb (p = 0.679, ES = 0.14) nor HHb (p = 0.279, ES = 0.38) at the end of the CLT rejected the null hypothesis of equal changes between sexes.

Comparisons of responses to the CLT between sexes are presented in Fig. 1 (for relative data, see Supplemental Fig. 1) and detailed statistical comparisons in Supplemental Table 3. Both measures of Q_{TW}, $P_{m,TW}$ and MVC showed the presence of fatigue following the CLT protocol with reduction from baseline in both sexes for all measures (all P < 0.001). At the end of the CLT, comparisons of muscle fatigue between and females did not reject the null hypothesis for $\Delta P_{m,TW}$ ($p = 0.312$, $ES = 0.37$), ΔQ_{TW1} ($p = 0.314$, $ES = 0.35$), ΔQ_{TW10} ($p = 0.161$, $ES = 0.49$), ΔQ_{TW100} ($p = 0.211$, $ES = 0.44$) or $Q_{TW10:100}$ ($p = 0.240$, $ES = 0.41$). Males showed a larger decrease in MVC force following the CLT ($p = 0.018$, $ES = 0.85$). The level respiratory muscle fatigue developed was unrelated (Fig. 2) to the extent of peripheral fatigue measured with single twitches ($r^2 = 0.034$, $p = 0.347$), the decrease in MVC ($r^2 = 0.067$, $p = 0.181$) or the increase in EMG activity of the VASTUS during the CLT ($r^2 = 0.001$, $p = 0.829$). The level of MVC decrease was related (Fig. 3) to the extent of peripheral fatigue developed measured as single twitches ($r^2 = 0.397$, $P < 0.001$) and followed a very similar pattern between sexes ($r^2 = 0.473$, $p = 0.002$ for males and $r^2 = 0.325$, $p = 0.017$ for females). It was not associated with the absolute workload of the CLT test ($r^2 = 0.002$, $p = 0.777$), the changes in EMG activity of the VASTUS ($r^2 = 0.097$, $p = 0.072$) or the HHb concentration in the VASTUS ($r^2 = 0.001$, $p = 0.838$) or STERNO ($r^2 < 0.001$, $p = 0.938$).

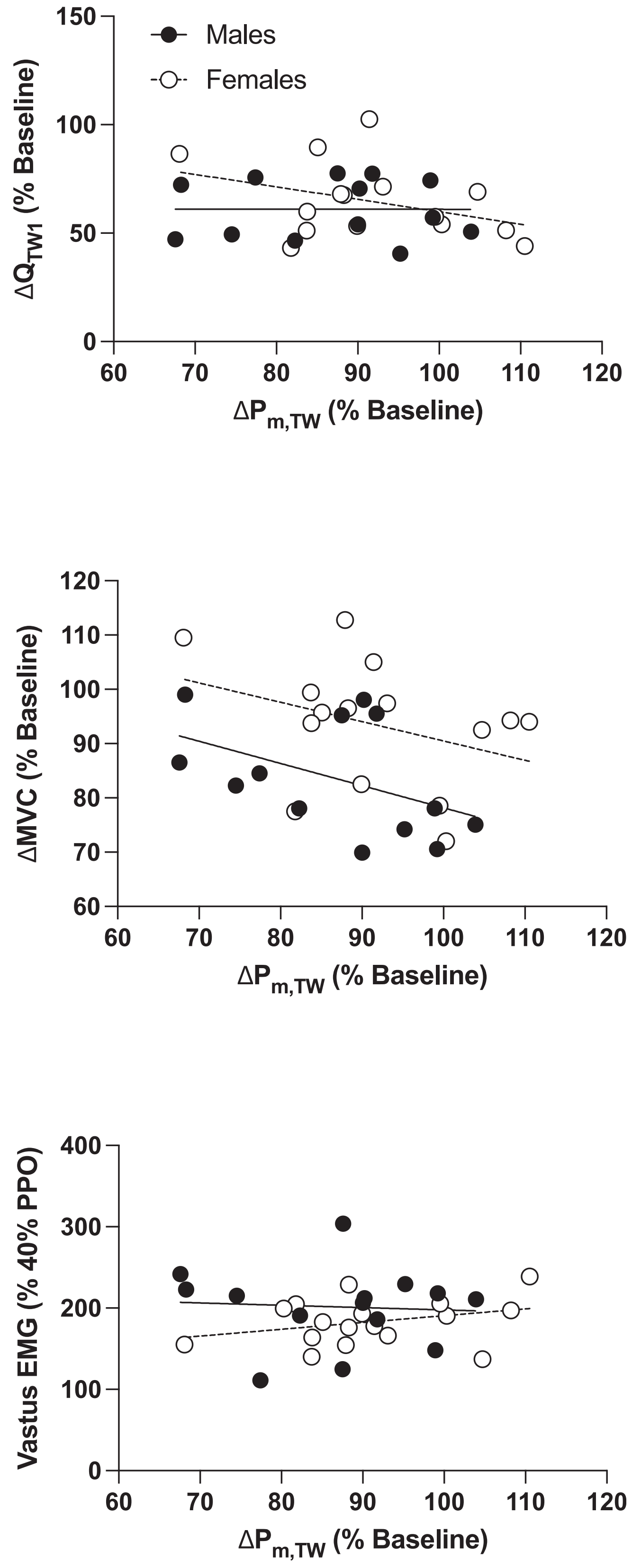

Fig. 2. Relationship between changes in mouth twitch pressure ($\Delta P_{m,TW}$) and different markers of quadriceps fatigue.All values refer to end-exercise (final 30-s) or pre to post differences. Q_{TW1}, single twitches of the quadriceps; MVC, maximal voluntary contraction of the quadriceps.

4. Discussion

Most studies comparing sex differences in fatigability between sexes show that females have either similar or enhanced endurance on a wide range of tasks and intensities when small muscle masses are exercised.[10,18,19] Our study supports the view that these differences seem to disappear when whole-body exercise is compared, leading to similar times to exhaustion during cycling at similar relative intensities,[5,7,11,12,20] where presumably a wider range of factors act to limit exercise tolerability.

We found very similar decrements of $P_{m,TW}$ between sexes (95% CI of differences −4.0 – 2.3 percent-points of baseline twitch), which is in agreement with investigations using changes in MIP as a measure of respiratory muscle fatigue,[11,21] but not to studies using transdiaphragmatic pressures.[7,12,22] The reason for contradicting results between the different studies are not immediately clear, as $P_{m,TW}$ is in fact much more similar to the transdiaphragmatic pressures as opposed to MIP maneuvers, which rely on volitional maximal maneuvers and therefore do not measure exclusively peripheral fatigue. Although $P_{m,TW}$ is a good indicator of esophageal and transdiaphragmatic pressure[23,24] and is sensitive to diaphragmatic fatigue,[25] this methodological difference could nonetheless account for the lack of agreement between studies.

Females did not show less quadriceps peripheral fatigue compared with males, but were better able to maintain volitional force as determined from MVC maneuvers, in line with other investigations.[5,18,19] Since volitional force was better preserved for females (95% CI 1.8–18.3 percent-points from baseline, $p = 0.018$) but neither Q_{TW1}, Q_{TW10} nor Q_{TW100} could be asserted as different between sexes, it could be argued that by extension females showed less central fatigue compared with males. Indeed, less central diaphragmatic fatigue has been reported in females following high-intensity cycling.[22] However, it must be noted that decrements in MVC were well related to decrements in Q_{TW1} in both sexes (Fig. 3, top left panel), with very similar slopes. This would not be expected if a different factor – for instance central fatigue –affected the drop in MVC more prominently for only one sex. Finally, although the assessment of central fatigue via voluntary activation estimation is popular in the literature, it has inherent flaws that render interpretation of data uncertain, namely because values of central activation can vary independent of changes above the neuromuscular junction, which is why we opted for not evaluating it.[26–28]

Fatigue of the lower limbs and of the respiratory muscles are intertwined during whole-body exercise, where one can have an influence on the other.[5,12,29] As such, it has been hypothesized that females, due to their smaller airways and lung volumes, could be more predisposed to an effect of inspiratory fatigue on the force production of the lower limbs.[30] At the end of the CLT no large differences were noted for EMG activity of the VASTUS between sexes, but the confidence interval for the difference was very large, which urges caution on the data interpretation.

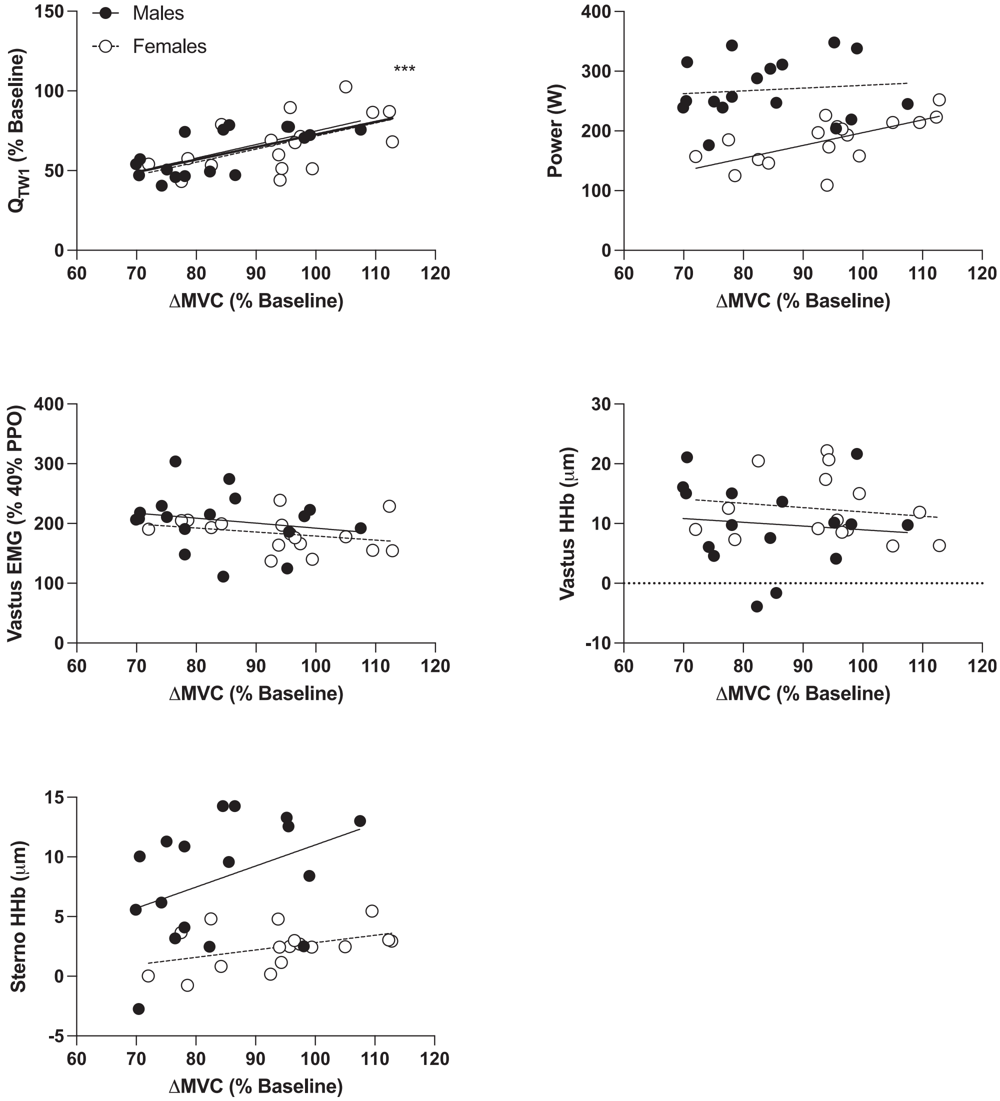

Fig. 3. relationship between changes in maximal voluntary contraction (MVC) of the quadriceps and different variables for males and females. All values refer to end-exercise or pre- to post-exercise differences. Q_{TW1}, single twitches pf the quadriceps; HHb, deoxyhemoglobin. *** Significant relationship at $P < 0.001$. For the top left panel, the bold line represents the relationship pooling both sexes.

On the other hand, while the concentration of HHb of the VASTUS was similar between sexes at task failure, males and females showed distinctively different responses for O_2Hb, with higher concentration for males and lower for males, in line with the concept of better vasodilatory responses for females during exercise.[31,32] Alternatively, the latter results could be a reflex from the higher adipose tissue of females compared to males, which decreases the amplitude of the NIRS signal.[33] Together, these data argue against any noticeable deleterious effects of respiratory muscle fatigue on quadriceps function of females at the end of the CLT. For the accessory respiratory muscles (STERNO and INTER), generally males showed higher EMG activity and a larger increase in HHb concentration at exhaustion, which supports the higher absolute work of breathing caused by the much larger absolute pulmonary ventilation in males.[5]

The extent of $P_{m,TW}$ reductions after the CLT, however, was not related to the changes in O_2HB or HHb of the respiratory muscles (data not shown) and neither to the changes in quadriceps fatigue and EMG (Fig. 2). As previously mentioned, the changes in MVC were closely associated with the extent of peripheral fatigue developed, but not to the level of EMG activity of the VASTUS or the HHb concentration of the VASTUS or respiratory muscles. A similar picture was noted for Q_{TW1} (data not shown). As it has also been suggested that the extent of fatigue developed depends on the absolute force being produced,[34] we tested whether the drop in MVC was related to the absolute workload during the tests, which was not the case (Fig. 3, top right panel). Although alleviating the respiratory system during exercise has been shown to elicit changes in exercise performance for both males and females[12] and to attenuate quadriceps fatigue,[5] the present data does not allow identification of a clear link between inspiratory muscle fatigue and that developed in the lower limbs during unimpeded high-intensity cycling.

When interpreting our results, it should be acknowledged that we used quadriceps fatigue as a surrogate for leg muscle fatigue, thus oversimplifying muscle fatigue in a complex motor task that activates different extensor and flexor muscles, negating for instance possible sex-differences in the fatigability of plantar flexors and its contribution to exhaustion.[2] Furthermore, we assessed quadriceps fatigue before inspiratory muscle fatigue (i.e., 2 min post-exercise vs. 10 min post-exercise). Quadriceps fatigue recovers substantially within the first 8 min of recovery,[35] although apparently without sex differences for MVC and Q_{TW1},[36] whereas diaphragmatic fatigue seems to remain stable for at least 10 min.[37] While this evidence supports our choice for protocol order, an effect of timing cannot be fully excluded. Finally, within-individual variability in the measurements, particularly in $P_{m,TW}$, might have hindered physiological differences from being detected given our sample size and the magnitude of these differences. While larger sample sizes and more precise techniques might be useful to detect smaller physiological differences, in the context of training decisions such minute differences might not be relevant.

5. Conclusion

The similarities in endurance capacity and peripheral fatigue developed by the inspiratory and quadriceps muscles between women and men does not seem sufficient to warrant particularly different exercise training strategies or interventions despite anatomical and physiological differences between sexes. Other aspects of sex differences might be more relevant in this context and should be further explored.

Funding Information

Zürcher Kantonalbank (ZKB) and the Commission for Technology and Innovation (CTI, project no. 15650.1 PFLS-LS).

Confirmation of ethical compliance

Participants gave written informed consent when enrolling in the study, which was approved by the local ethics committee (2014-N-02) and was performed according to the Declaration of Helsinki 2008.

CRediT authorship contribution statement

Fernando G. Beltrami: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Visualization. **Corina E. Schaer:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Project administration. **Christina M. Spengler:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Interest Statement

The authors have no conflict of interest to disclose.

Acknowledgements

The authors thank the Zürcher Kantonalbank (ZKB) and the Commission for Technology and Innovation (CTI, project no. 15650.1 PFLS-LS) for financial support of this study. They are also grateful to Dr. Jan Stutz, Mrs. Desirée Erne, Mrs. Dina Tageldin and Mr. Donat Roduner (Exercise Physiology Lab, ETH Zurich) for assisting with data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsams.2023.02.006.

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