Mechanisms of neuromuscular fatigability in people with cancer-related fatigue

Callum G Brownstein[1], Rosemary Twomey[2,4,5], John Temesi[2,6], Mary E. Medysky[2], S. Nicole Culos-Reed[2,3], Guillaume Y Millet[1,2,7]

[1]Univ Lyon, UJM-Saint-Etienne, Inter-university Laboratory of Human Movement Biology, EA 7424, F-42023, Saint-Etienne, France; [2]Faculty of Kinesiology, University of Calgary, Calgary, Canada; [3]Department of Oncology, Cumming School of Medicine, University of Calgary; [4]Ohlson Research Initiative, Arnie Charbonneau Cancer Institute, Cumming School of Medicine, University of Calgary, AB, T2N 4Z6, Canada; [5]O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, AB, T2N 4Z6, Canada; [6]Faculty of Health & Life Sciences, Northumbria University, Newcastle upon Tyne, United Kingdom; [7]Institut Universitaire de France (IUF).

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Address for correspondence:

Professor Guillaume Y Millet

Laboratoire Interuniversitaire de Biologie de la Motricité

Bâtiment IRMIS

10 rue de la Marandière

42270 Saint Priest en Jarez

France

+33 652 963 810

Email: guillaume.millet@univ-st-etienne.fr

ABSTRACT

Introduction: Cancer-related fatigue (CRF) is a debilitating symptom that affects around one-third of people for months or years after cancer treatment. In a recent study, we found that people with post-treatment CRF have greater performance fatigability. The aim of this secondary analysis was to examine the aetiology of performance fatigability in people with post-treatment CRF. **Methods:** Ninety-six people who had completed cancer treatment were dichotomized into two groups (fatigued and non-fatigued) based on a clinical cut-point for fatigue. Alterations in neuromuscular function (maximal voluntary contraction peak force, MVC; voluntary activation, VA; potentiated twitch force, $Q_{tw,pot}$; electromyography, EMG) in the knee extensors were assessed across three common stages of an incremental cycling test. Power outputs during the fatigability test were expressed relative to gas exchange thresholds to assess relative exercise intensity. **Results:** The fatigued group had a more pronounced reduction in MVC peak force and $Q_{tw,pot}$ throughout the common stages of the incremental cycling test (main effect of group: $p<0.001$, $\eta_p^2=0.18$ and $p=0.029$, $\eta_p^2=0.06$, respectively). Electromyography was higher during cycling in the fatigued group (main effect of group: $p=0.022$, $\eta_p^2=0.07$). Although the relative intensity of cycling was higher in the fatigued group at the final common stage of cycling, this was not the case during the initial two stages, despite the greater impairments in neuromuscular function. **Conclusion:** Our results suggest that the rapid impairments in performance fatigability in people with CRF was primarily due to disturbances at the level of the muscle, rather than the central nervous system. This could impact the ability to tolerate daily physical activities.

Key words: Contractile function; Cycling; Electromyography; Voluntary activation.

INTRODUCTION

Cancer-related fatigue (CRF), defined as a distressing, persistent sense of physical, emotional and/or cognitive tiredness or exhaustion (1), is the most common and debilitating symptom for people living with cancer (2, 3). CRF affects almost every person during cancer treatment, and around one-third report persistent CRF for months or years after cancer treatment (4, 5). This post-treatment CRF is of interest because it negatively impacts health-related quality of life and the ability to return to work (6). Given its high prevalence as well as the burden of CRF and the potential economic impact, understanding the aetiology of CRF is a pertinent issue. While the precise underpinnings of CRF are unclear, it is thought that CRF is a multifactorial symptom that is associated with several biological and psychosocial factors (7-9). Impaired exercise tolerance is another potentially important contributor to CRF, and likely contributes to reported difficulties in performing physical activities of daily living among people with CRF (10, 11). As such, the physiological (e.g. cardiopulmonary, metabolic and neuromuscular) alterations contributing to impaired exercise tolerance in people with CRF warrant further investigation, particularly given that these impairments could be reversible through exercise training.

One physiological alteration which could hinder the ability to perform physical activities of daily living is neuromuscular fatigability, defined as the reduction in neuromuscular function measured following exercise of a discrete time-period (12). In a recent study (8), we assessed neuromuscular fatigability in response to a standardised cycling test (13), with incremental stages interspersed with the assessment of neuromuscular function of the knee extensors, including isometric maximal voluntary contractions (MVC), voluntary activation (VA) and potentiated twitch force ($Q_{tw,pot}$). Using a clinical cut-point to identify people with moderate-severe CRF (14), we found that the reduction in isometric muscle force-generating capacity at the final common stage (the final stage completed by all participants) was higher in people with

CRF compared to a non-fatigued group (the latter group being people post-cancer treatment who did not have clinically meaningful CRF based on the clinical cut-point). Moreover, we reported that alongside reduced peak oxygen uptake ($\dot{V}O_{2peak}$), CRF severity was associated with neuromuscular fatigability measured at the final common stage of cycling exercise (8). While it remains unclear whether neuromuscular fatigability is causally related to CRF, greater fatigability could impede the ability to perform everyday physical tasks, cause an avoidance of physical activity and thus further deconditioning, and/or cause fatigue to accumulate throughout the day. Accordingly, gaining an understanding of the mechanisms underpinning the greater fatigability in people with CRF could help provide targets for future interventions to reduce this symptom.

In our previous study (8), the primary aim was to identify the physiological correlates of CRF from a comprehensive group of physiological measures, including neuromuscular fatigability. While this analysis identified neuromuscular fatigability as being independently associated with CRF severity, such an analysis could not provide insight into the mechanisms of fatigability or how fatigability manifests during incremental cycling. Additional analyses of our dataset can help to provide such insight. First, analysis of the kinetics of fatigability can reveal the temporal manifestation of impaired neuromuscular function during exercise. This is of interest as it can shed light on the potential contribution of fatigability towards impairments in the ability to perform physical activities of daily living, and can also facilitate understanding of the mechanisms contributing to impaired neuromuscular function. Second, the contribution of reductions in the capacity of the nervous system to activate muscle and/or impairments within the contractile machinery, as well as their kinetics of change during exercise, can be assessed using neurostimulation methods to determine the site(s) of impaired neuromuscular function (15, 16). Third, we set power outputs relative to body mass during our incremental cycling test. This approach was used since body mass influences the power requirements of

daily activities such as walking and climbing stairs, and thus provides an ecologically valid approach to assess neuromuscular fatigability. Understanding the relative intensity of these power outputs with respect to the gas exchange threshold (GET) and respiratory compensation point (RCP) is of interest, particularly because metabolic and neuromuscular disturbances are exacerbated during exercise above these thresholds (17). Such an analysis can provide insight into whether the greater fatigability in people with CRF is a result of surpassing metabolic thresholds earlier during the neuromuscular fatigability test, or due to other mechanisms. Finally, the assessment of electromyography (EMG) during cycling can be used to determine exercise-induced alterations in neuromuscular activity and how these might relate to the greater fatigability in people with CRF. Together, these analyses can provide a more comprehensive understanding of the aetiology of fatigability in individuals with CRF. Accordingly, the overarching aim of the present study was to examine the aetiology of greater neuromuscular fatigability in people with post-treatment CRF. We hypothesized that (i) in comparison to a non-fatigued group, impairments in neuromuscular variables would be higher during a neuromuscular fatigability test in people with CRF and (ii) given that our previous study (8) showed lower $\dot{V}O_{2peak}$ in the fatigued than non-fatigued group with GET and RCP occurring at similar relative intensities, the greater impairment in neuromuscular variables would be related to people with CRF exceeding metabolic thresholds.

METHODS

Participants

The data presented herein are a secondary analysis, using data collected as part of a larger study that investigated the physiological and psychosocial correlates of CRF (8). The study received ethical approval from the Conjoint Health Research Ethics Board and the Health Research

Ethics Board of Alberta Cancer Committee (REB14-0398 and HREBA.CC-16-10-10, respectively), and was conducted in accordance with all aspects of the *Declaration of Helsinki*, apart from registration in a database. All participants provided written informed consent to take part in the study. Participants were eligible if they were adults who had received a cancer diagnosis of any type and had completed any type of active treatment (surgery, chemotherapy and radiation therapy; people on long-term hormonal therapy were eligible to participate). Participant recruitment is described in detail in Brownstein et al. (8). A health screening was conducted to assess for contraindications to exercise, including arrhythmias, uncontrolled hypertension and physical activity readiness (8). The data from 96 of the 97 participants recruited for our previous study were included in the present analysis, with one participant excluded due to missing cardiopulmonary exercise test (CPET) and neuromuscular fatigability data.

Experimental Design

Participants visited the laboratory on two occasions separated by ~two weeks. During the first visit, participants performed a CPET, followed by a familiarisation with the neuromuscular assessment procedures. During the second visit, participants performed incremental cycling exercise interspersed with measurements of neuromuscular function.

Cancer-Related Fatigue

Fatigue was measured using the FACIT-F scale (18), which is widely recommended for the assessment of CRF (19). Participants were classified as fatigued if they scored ≤ 34, based on recommendations for the diagnosis of CRF derived from diagnostic interviews (14). All participants with scores ≥ 35 were allocated to the non-fatigued group.

Cardiopulmonary Exercise Test

Following the measurement of stature (cm) and mass (kg), a CPET was conducted using a custom-built recumbent ergometer, using an electromagnetically-braked Velotron system (RacerMate Inc., Seattle, WA). Breath-by-breath pulmonary gas exchange and ventilation was measured throughout the test (Quark CPET, COSMED, Rome, Italy). Prior to each visit, the Cosmed was calibrated, following manufacturer guidelines, to gases of known concentrations (oxygen, O_2: 15.15%, carbon dioxide, CO_2: 5.03%). Ventilatory volumes were calibrated using a three-litre syringe. The starting power output (25-50 W) and increment (8-20 W) were estimated and adjusted on an individual basis for a desired test duration of 8-12 min. Participants were permitted to select their own cadence (≥ 60 rpm), and were instructed to maintain this cadence during cycling assessments. The power output was increased at 1 min intervals until task failure, defined as a reduction in cadence of ≥ 5 rpm for ≥ 5 s. Verbal encouragement was provided by the same experimenters throughout the assessment.

Neuromuscular Fatigability Test

The neuromuscular fatigability test was also performed on the recumbent cycle ergometer, which permits the immediate assessment of neuromuscular function after cycling (13). Each stage of the cycling test lasted 3 min, beginning with a power output of 0.3 $W \cdot kg^{-1}$, with an increment of 0.3 $W \cdot kg^{-1}$ for the next four stages and 0.4 $W \cdot kg^{-1}$ for the following five stages. Isometric force and force during pedal rotations was measured using a wireless PowerForce system (Model PF1.0.0; Radlabor GmbH, Freiburg, Germany). Pre-exercise, between each stage, and following task-failure, a neuromuscular assessment was performed (described below). During cycling, participants received real-time feedback of cadence and were given verbal instruction to maintain their self-selected cadence when it drifted by ≥ 4 rpm.

Neuromuscular Function

For the neuromuscular assessments during the neuromuscular fatigability test, the seat position was adjusted to ensure that knee and hip were at 90º flexion when the pedal was locked. Whilst on the cycle ergometer, participants were secured at the hip and chest with non-compliant straps. The pre-exercise neuromuscular assessment began with two isometric maximal voluntary contractions (MVCs) without stimulation to ensure potentiation of subsequent evoked twitches. Subsequently, two ~3 s MVCs were performed, separated by 1 min. Supramaximal electrical stimulation of the femoral nerve was delivered at the plateau in force, with the same stimulation delivered 2 s following the MVC while at rest to measure voluntary activation (VA) and potentiated twitch force ($Q_{tw,pot}$). Between cycling stages and at task failure, the pedal was locked instantly, and participants immediately performed one MVC with stimulations delivered during and following the MVC. Isometric force was measured during voluntary and evoked contractions using a wireless PowerForce pedal force analysis system (Model PF1.0.0, Radlabor GmbH, Freiburg, Germany) (20) situated between the pedal and crank. A detailed description of the settings associated with the innovative cycle ergometer can be found in Doyle-Baker et al. (13).

Electromyography

Electromyographic activity was recorded during neuromuscular assessments and throughout cycling. Self-adhesive surface electrodes (10 mm recording diameter; Meditrace 100, Covidien, Mansfield, MA) were placed on the *vastus lateralis* (VL) and *rectus femoris* (RF) of the right knee extensors using a bipolar configuration with a 30 mm inter-electrode distance. As a high number of participants (13) either had missing data or displayed no discernible compound muscle action potential (Mwave) in the RF, EMG data from this muscle are not reported. A reference electrode was placed on the patella. Prior to applying the electrodes, the skin was shaved, gently abraded and cleaned using isopropyl alcohol. The EMG signals were analogue-to-digitally converted at a sampling rate of 2000 Hz using a PowerLab system (16/35,

ADInstruments, Bella Vista, Australia) and octal bio-amplifier (ML138, ADInstruments, gain = 500) with bandpass filter (5-500 Hz), and were analysed offline using Labchart 8 software (ADInstruments).

Motor Nerve Stimulation

Single electrical stimuli (1 ms duration) were delivered to the right femoral nerve using a constant current stimulator (DS7A, Digitimer, Welwyn Garden City, Hertfordshire, UK). The cathode electrode (10 mm stimulating diameter; Meditrace 100, Covidien) was secured with tape and a gauze plug to apply pressure on the inguinal triangle and a 50 × 90 mm rectangular anode electrode (Durastick Plus, DJO Global, Vista, CA) was placed on the gluteal fold. The optimal stimulus intensity was determined as the minimum current that elicited a maximum resting twitch response (Q_{tw}) and maximal compound muscle action potential (M_{max}) in both the VL and RF, with the intensity subsequently multiplied by 1.3 to ensure the stimulus was supramaximal for all neuromuscular assessments.

Data analysis

Relative Exercise Intensity during the Neuromuscular Fatigability Test

To determine the relative intensity of the three common stages of the fatigability test for the present analysis, the power outputs associated with the GET and RCP were first determined. To do so, the power outputs were adjusted to take into account the mean rise time of $\dot{V}O_2$ during step incremental exercise, which approximates two-thirds of the rate of step increment (21). Subsequently, the power outputs during the three common stages of the fatigability test were expressed as percentages of the power outputs associated with the GET and RCP.

Neuromuscular Responses during the Neuromuscular Fatigability Test

In our previous study (8), the relative change in MVC peak force, $Q_{tw,pot}$ and VA between baseline and the final common stage of the test (stage 3), as well as at task failure, was assessed. For the present analysis, the kinetics of the changes in MVC peak force, $Q_{tw,pot}$, VA and the amplitude of the negative phase of M_{max} (22) were assessed across all three common stages of exercise. Alterations in these variables were expressed in percentages relative to the baseline value. Voluntary activation was determined using the twitch interpolation method (15), quantified by comparing the amplitude of the superimposed twitch (SIT) to the $Q_{tw,pot}$ using the following equation: $VA\ (\%) = [1 - (SIT/Q_{tw,pot}) \times 100]$. In instances when superimposed stimuli were not delivered at peak force, a correction was applied using the force at stimulation (F_{atstim}), the peak force, the amplitude of the SIT and the $Q_{tw,pot}$, with the following equation applied: $VA\ (\%) = [1 - (SIT \times (F_{atstim}/MVC)/(Q_{tw,pot}) \times 100)]$ (23). For the EMG measurements during cycling, the EMG onset and offset of the rectified signal during pedal rotations was visually determined. The root-mean square EMG (EMG_{RMS}) was recorded between EMG onset and offset, and the average EMG_{RMS} was taken from 10-40 s of stage 1 and 1 min 50 s to 2 min 50 s of each stage. The first 10 s of stage 1 and final 10 s of each stage were not analysed so as not to include acceleration and deceleration phases, respectively, in the EMG analysis. The EMG_{RMS} was normalized to the maximum EMG_{RMS} obtained over a 0.5 s epoch during the plateau in the baseline MVC. The amplitude of the negative phase of M_{max} amplitude was calculated from EMG responses to single femoral nerve stimulation in the relaxed muscle.

Statistical analysis

Jamovi statistical software (jamovi, version 1.0, 2019, the jamovi project; retrieved from https://www.jamovi.org) was used for all statistical analyses. All data are presented as mean ± standard deviation (SD). Statistical significance was set at an α of 0.05. Normality of the data

was assessed by the Shapiro-Wilk test, with no data requiring transformation. To test our first hypothesis, group differences in neuromuscular changes from baseline after the three common stages of the neuromuscular fatigability test were assessed using a two-way mixed-design ANOVA (group × time). Similarly, to test our second hypothesis, a two-way mixed-design ANOVA was used to assess group differences in relative exercise intensity (with respect to GET and RCP) during the three common stages of the neuromuscular fatigability test. Assumptions of sphericity were explored using Mauchly's test, and controlled for using the Greenhouse-Geisser adjustment in instances where the α for Mauchley's test was < 0.05. In the event of a significant interaction or main effect, *post-hoc* comparisons were performed with Bonferroni correction. Independent sample t-tests, or a Mann-Whitney U test if Levene's test revealed unequal variance, were used to assess between-group differences in power outputs associated with GET and RCP (expressed in absolute units and relative to body mass) and baseline neuromuscular variables. Partial eta squared (η_p^2; ANOVA) was calculated to estimate effect sizes, with values representing small ($\eta_p^2 < 0.13$), medium ($\eta_p^2 \geq 0.13, < 0.26$) and large ($\geq 0.26$) (24). Cohen's *d* effect size (t-test) was calculated, with values interpreted as small ($d \geq 0.2, < 0.6$), moderate ($d \geq 0.6, < 1.2$) and large (≥ 1.2) (24).

RESULTS

Participant Characteristics

Participant characteristics are displayed in Table 1. Of the 96 included participants, 54 were in the fatigued group and 42 were in the non-fatigued group based on scores derived from the FACIT-F scale. There were no statistical differences in age ($p = 0.097$, $d = 0.39$) or body mass ($p = 0.088$, $d = 0.36$) between groups (Table 1).

Neuromuscular fatigability test

One participant from the non-fatigued group did not complete neuromuscular fatigability testing. Due to the discomfort associated with motor nerve stimuli, seven participants (4 fatigued, 3 non-fatigued) did not receive stimuli between stages, and instead only performed MVCs, while the stimulation data from two participants (both from the fatigued group) was not included due to a lack of discernible M-waves. Thus, for the analysis of $Q_{tw,pot}$ and VA at stages 1-3, 48 and 38 participants from the fatigued and non-fatigued groups were included. For baseline M_{max} data, seven participants (five and two from fatigued and non-fatigued groups, respectively) demonstrated either no discernible M-wave in the VL or had missing data. For EMG during cycling, 13 participants (seven and six from fatigued and non-fatigued groups, respectively) had missing data.

Baseline measures

At baseline, no differences were found for knee extensor MVC peak force between the fatigued and non-fatigued groups (239 ± 160 vs. 205 ± 67 N respectively, $U = 1050$, $p = 0.822$, $d = 0.28$), $Q_{tw,pot}$ (90 ± 69 vs. 78 ± 27 N, respectively, $U = 957$, $p = 0.426$, $d = 0.19$) or VA (94 ± 6% vs. 95 ± 5%, respectively, $U = 982$, $p = 0.544$, $d = 0.17$).

Neuromuscular fatigability

Raw values for neuromuscular variables are presented in Table 2. For the percentage reduction in MVC peak force during the neuromuscular fatigability test (Figure 1A), there was a main effect of time ($F_{1.5,128.7} = 34.6$, $p < 0.001$, $\eta_p^2 = 0.29$) and group ($F_{1,93} = 17.9$, $p < 0.001$, $\eta_p^2 = 0.18$) and no interaction effect ($F_{2,186} = 0.05$, $p = 0.953$, $\eta_p^2 < 0.01$). In other words, the reduction in MVC peak force was more pronounced in the fatigued group throughout the fatigability test, with MVC reduced by 10, 12 and 17% in the fatigued group, and 2, 4 and 10% in the non-fatigued group at stages 1, 2 and 3, respectively. For the decrease in $Q_{tw,pot}$ from

baseline during the neuromuscular fatigability test (Figure 1B), there was a main effect of time ($F_{1.7,138.4}$ = 42.35, p < 0.001, η_p^2 = 0.34) and group ($F_{1,85}$ = 4.92, p = 0.029, η_p^2 = 0.06) and no interaction effect ($F_{2,170}$ = 0.93, p = 0.397, η_p^2 = 0.01). In line with maximal force, the reduction in $Q_{tw,pot}$ was more pronounced in the fatigued group, being reduced by −12, −19 and −28% in the fatigued group and −8, −12 and −20% in the non-fatigued group at stages 1, 2 and 3, respectively. For the decrease in VA from baseline during the neuromuscular fatigability test (Figure 1C), there was a main effect of time ($F_{1.8,138.9}$ = 3.72, p = 0.045, η_p^2 = 0.05) with no effect of group ($F_{1,85}$ = 1.22, p = 0.273, η_p^2 = 0.02) and no group × time interaction ($F_{2,170}$ = 2.27, p = 0.114, η_p^2 = 0.03). For the amplitude of the negative phase of M_{max}, there was a main effect of time ($F_{1.8,139.0}$ = 6.42, p = 0.002, η_p^2 = 0.08), and no group ($F_{2,164}$ = 1.02, p = 0.316, η_p^2 = 0.012) or interaction ($F_{2,164}$ = 2.47, p = 0.088, η_p^2 = 0.03) effects.

EMG during cycling

For EMG_{RMS} expressed as a percentage of maximum EMG_{RMS} (Figure 2), there was a main effect of time ($F_{1.5,109.8}$ = 168.12, p < 0.001, η_p^2 = 0.69) and group ($F_{1,78}$ = 5.47, p = 0.022, η_p^2 = 0.7), with no group × time interaction ($F_{1.5,109.8}$ = 2.48, p = 0.062, η_p^2 = 0.03). Thus, EMG_{RMS} increased during cycling and was, overall, higher in the fatigued group, but the rate of increase did not differ between groups.

Power Outputs at GET and RCP

For peak power output and power outputs associated with the GET and RCP, no differences were found when expressed in absolute units (W; Table 3). However, when expressed relative to body mass ($W \cdot kg^{-1}$), the power output associated with the GET was lower in the fatigued versus non-fatigued group (U = 701, p = 0.046, d = 0.44), with no difference between the peak power output or the power output associated with the RCP.

Relative Exercise Intensity during the Neuromuscular Fatigability Test

During the three common stages of the neuromuscular fatigability test, at which time the power outputs were 0.3, 0.6 and 0.9 $W \cdot kg^{-1}$, the absolute power outputs did not differ between the fatigued and non-fatigued groups (no main effect of group: $F_{1,90} = 2.67$, $p = 0.106$, $\eta_p^2 = 0.03$). For exercise intensity relative to the GET, there were main effects of time ($F_{1,85} = 416.8$, $p < 0.001$, $\eta_p^2 = 0.83$) and group ($F_{1,85} = 4.9$, $p = 0.029$, $\eta_p^2 = 0.06$; Figure 3) and a group × time interaction ($F_{1,85} = 4.9$, $p = 0.029$, $\eta_p^2 = 0.06$). In *post-hoc* analysis, the relative intensity of stage 3 (the last common stage) with respect to the GET was significantly higher in the fatigued compared with non-fatigued group ($p = 0.039$, $d = 0.49$, Figure 3). Similarly, for exercise intensity relative to RCP, there were main effects of time ($F_{1.0,85.2} = 817.0$, $p < 0.001$, $\eta_p^2 = 0.91$) and group ($F_{1,85} = 4.8$, $p = 0.031$, $\eta_p^2 = 0.05$) and a group × time interaction ($F_{1.0,85.2} = 4.6$, $p = 0.034$, $\eta_p^2 = 0.05$). *Post-hoc* analysis showed that the relative intensity of stage 3 with respect to the RCP was significantly higher in the fatigued compared with the non-fatigued group ($p = 0.046$, $d = 0.49$). When expressed relative to the RCP, the power output at the final common stage was 75 ± 24% and 68 ± 18% in the fatigued and non-fatigued groups, respectively.

DISCUSSION

A number of key and novel findings from the present study help to shed light on the aetiology of fatigability in people with post-treatment CRF. First, and in line with our first hypothesis, people with post-treatment CRF had a more pronounced reduction in maximal and evoked force in the knee extensors during an incremental cycling test compared to a non-fatigued group. Second, the concurrently higher reduction in $Q_{tw,pot}$ in the fatigued group, together with the lack of differences between groups in maximal voluntary activation, suggest that the greater fatigability in people with CRF is primarily due to greater disturbances at the muscle level.

Third, although the fatigued group were exercising at a higher relative intensity with respect to the GET during stage 3 of the fatigability test, this was not the case during the first two stages, nor were there any differences in absolute power outputs. Thus, differences in the relative intensity of exercise at a given power output relative to body mass are unlikely to explain the greater fatigability in people with CRF during the early stages of exercise. Finally, the higher EMG_{RMS} in the fatigued group throughout neuromuscular fatigability assessment indicates that a higher level of muscle activation during cycling was required to maintain power output compared to the non-fatigued group. The results from this study provide important insight into the aetiology of fatigability in people with post-treatment CRF.

Impairments in contractile function are responsible for greater neuromuscular fatigability in people with post-treatment CRF

During the incremental neuromuscular fatigability assessment, the fatigued group demonstrated greater impairments in neuromuscular function compared to the non-fatigued group throughout the fatigability test. Following stage 3, the reduction in MVC peak force relative to baseline was −17 ± 9% and −10 ± 10% in the fatigued and non-fatigued groups, respectively. To allow comparison to other populations, using the same ergometer and protocol we have previously observed that the magnitude of reduced peak force in the fatigued group after stage 3 is higher than that observed in healthy young participants (~−5%) (13), similar to that observed in highly fatigued people with multiple sclerosis (~−18%) (24), but lower than that observed in people with head and neck cancer who had recently completed radiation and chemotherapy (−29%) (25). The overall reduction in $Q_{tw,pot}$ was greater in the fatigued group (−20 ± 14% and −13 ± 11% across stages 1-3 in the fatigued and non-fatigued groups, respectively), with no between-group difference in the reduction in VA. By using dynamic,

whole-body exercise, the present study improves on previous designs by utilising a more ecologically valid exercise-mode compared to previous literature on neuromuscular fatigability in people with CRF, which have utilised isometric exercise protocols (26, 27). Thus, during exercise with greater relevance to activities of daily living, the results from the present study indicate that greater fatigability in people with CRF can primarily be attributed to perturbations occurring within the contractile machinery rather than deficits in muscle activation.

Greater impairments in neuromuscular function are evident early during whole-body exercise in people with CRF

For the present study, the kinetics of altered neuromuscular function were assessed across the three common stages of the fatigability test. Following just three min of exercise, during which the power output was 0.3 $W \cdot kg^{-1}$ (i.e. ~20-25 W), the fatigued group demonstrated a reduction in MVC peak force which was five-fold greater than the non-fatigued group (−10 ± 10% and −2 ± 11% reduction in MVC peak force, respectively). Such a rapid decline in neuromuscular function in response to exercise of low power output, as expressed either in absolute terms, relative to body mass or relative to the GET (see below), has potentially important implications for the physiological and perceptual impact of typical daily physical activities. For example, the low intensity during the initial stages of the fatigability test is likely to correspond with low-intensity activities of daily living, such as walking, housework, gardening, or slowly climbing stairs. In turn, higher impairments in contractile function during such activities might necessitate a greater compensatory increase in muscle activity (28), as indicated by the elevated EMG_{RMS} in the fatigued group (see below), and thus an increased sense of effort (29) and perception of fatigue (30).

During cycling exercise, impairments in contractile function are determined by perturbations in metabolic homeostasis (17). Specifically, increases in the concentrations of metabolites which inhibit the excitation-contraction coupling and/or cross-bridge force, such as inorganic phosphate (Pi) and hydrogen (H^+) (31, 32), induce impairments in the capacity of muscle to produce force in response to neural input. In turn, these metabolic perturbations are exacerbated when exercising above the GET (i.e. in the heavy domain), and are further exacerbated when exercising above critical power or the RCP (i.e. in the severe domain) (17). In order to gain insight into the relative intensities of exercise during the fatigability test, the power outputs were expressed relative to that associated with the GET and RCP. This analysis revealed that the fatigued group were exercising at a higher intensity relative to the GET in comparison with the non-fatigued group at stage 3 (141 ± 64% and 113 ± 45%, respectively). Although the intensity relative to the RCP was also higher in the fatigued group at stage 3, the vast majority of participants were exercising well below the RCP (75 ± 24% and 64 ± 19% of RCP, respectively). Accordingly, the greater neuromuscular fatigability in the fatigued group at the final common stage might have been due, at least in part, to the higher relative exercise intensity being performed and the greater proportion of participants exercising within the heavy domain compared with the non-fatigued group.

While the higher exercise intensity relative to the GET presents a conceivable explanation for the exacerbated fatigability in the fatigued group at the final common stage, there were no statistical differences in the relative exercise intensity during the first or second stage of the fatigability test, despite fatigability being exacerbated across all stages (main effect of group). In fact, both the fatigued and non-fatigued groups were exercising firmly within the moderate-intensity domain (i.e. below the GET) during the first stage of the task (47 ± 21% and 38 ± 14% of GET in the fatigued and non-fatigued groups, respectively). These results could point towards slower $\dot{V}O_2$ on-kinetics as a plausible explanation for the exacerbated deficits in

neuromuscular function during the initial stages of the fatigability assessment. Specifically, slower $\dot{V}O_2$ on-kinetics are associated with a greater reliance on substrate level phosphorylation and metabolites which impair contractile function (33). Indeed, our group has previously demonstrated that the speed of $\dot{V}O_2$ on-kinetics are negatively associated with reductions in twitch force (34). Although $\dot{V}O_2$ on-kinetics were not measured in the present study, it is known that the time constant of the $\dot{V}O_2$ on-response is related to physical activity levels (35) and $\dot{V}O_{2peak}$ (36), both of which were found to be lower in the fatigued group in our previous study on the same group of participants (8). Accordingly, slower $\dot{V}O_2$ on-kinetics represents a plausible mechanism contributing to the higher impairment in neuromuscular function in the fatigued group during the initial stages of the fatigability assessment in the present study. Given that transitions between different steady-state energetic levels are commonplace during everyday activities, a greater consideration for the role of $\dot{V}O_2$ on-kinetics in fatigability is warranted in individuals with CRF in order to provide insight into factors which could limit functional capacity.

Electromyography during whole-body exercise is greater in people with post-treatment CRF

Concurrent with the higher impairments in MVC peak force and $Q_{tw,pot}$, the fatigued group also demonstrated higher EMG_{RMS}/maximum-EMG_{RMS} of the VL throughout the neuromuscular fatigability test, likely due to higher muscle activation. A higher muscle activation might be a consequence of the greater impairments in contractile function in the fatigued group. Indeed, the greater EMG_{RMS}/maximum-EMG_{RMS} concurrent with the higher reduction in $Q_{tw,pot}$ is indicative of a compensatory increase in motoneuron output owing to an impaired capacity of the muscle to respond to neural input in people with CRF. In turn, activation of higher threshold

motor units of a lower fatigue resistance could have further compounded these impairments due to their low oxidative, high glycolytic metabolic profile and their slower $\dot{V}O_2$ kinetics (37). Thus, the higher EMG_{RMS} activity in the fatigued group might have been both a cause and consequence of their higher fatigability. Moreover, the higher level of activation coupled with greater metabolic disturbances, even when exercising at low intensities, has potential implications for the perception of effort associated with performing activities of daily living.

Limitations

The present study performed a secondary analysis using data collected as part of a larger study that investigated the physiological and psychosocial correlates of CRF. The protocol for the cycling exercise in the present study was designed with the objectives of the previous study in mind. Thus, there were some limitations with the approaches used in the present study in order to better understand the aetiology of fatigability. Specifically, to facilitate the interpretation of factors behind the greater fatigability in the fatigued group, the present study determined the power outputs associated with the GET and RCP during the step incremental cardiorespiratory exercise test to assess the relative intensity of exercise during the neuromuscular fatigability test at the three common stages. However, differences were present between the fatigability and cardiorespiratory exercise tests in terms of the starting power output (24 ± 7 W vs. 36 ± 16 W, respectively), increment (24 ± 7 W vs. 11 ± 3 W, respectively) and stage duration (3 min vs. 1 min, respectively). It has previously been demonstrated that a stage duration of 3 min is associated with a lower power output at the GET relative to 1 min (38). Conversely, steeper increments in power output are associated with a higher power output at GET (39). Thus, calculating the power output during the fatigability test relative to that at the GET during the cardiorespiratory exercise test might have resulted in imprecise estimates in relative exercise

intensity. Using measurement of gas exchange during the cycling used for the neuromuscular fatigability test would have permitted more accurate determination of relative exercise intensity, whilst also allowing for $\dot{V}O_2$ kinetics to be assessed. Nevertheless, the results provide novel insight into the aetiology and temporal manifestation of neuromuscular fatigability in response to locomotor exercise in people with CRF, which can be used to guide future research. Finally, because this was a secondary analysis and therefore convenience sample, we may have been underpowered to detect small effects in variables such as VA.

CONCLUSION

The present findings provide important insight into the aetiology of fatigability in people with post-treatment CRF. Specifically, findings indicate that the greater fatigability in a fatigued vs. non-fatigued group of people living beyond cancer can be attributed to exacerbated disturbances at the muscle level, rather than differences in the level of voluntary activation. The substantially greater level of fatigability following just 3 min of relatively low-intensity exercise in the fatigued versus non-fatigued group, when the relative intensity of exercise did not differ between groups, suggests a potential role of slower $\dot{V}O_2$ on-kinetics in people with CRF, which has potential implications on fatigability during daily physical activities. Similarly, the higher EMG_{RMS} in the fatigued group during cycling, which might have occurred to compensate for impairments in contractile function, has potential implications for perceptions of effort during activities of daily living, and may be a contributing factor to the difficulties in performing such activities in people with CRF.

Table and figure legends

Table 1. Participant characteristics.

Table 2. Raw neuromuscular values including isometric maximal voluntary contraction (MVC; fatigued n = 54, non-fatigued n = 41) peak force, potentiated twitch force ($Q_{tw,pot}$; fatigued n = 48, non-fatigued n = 38), voluntary activation (VA; fatigued n = 48, non-fatigued n = 38) and the amplitude of the negative phase of the maximum compound muscle action potential (M_{max}) during step-incremental cycling exercise in fatigued and non-fatigued groups.

Table 3. Power output variables derived from step-incremental cycling exercise and performance fatigability test in fatigued and non-fatigued groups. Data expressed as mean ± SD.

Figure 1. Changes in isometric maximal voluntary contraction peak force (MVC; Panel A; fatigued n = 54, non-fatigued n = 41), potentiated twitch force ($Q_{tw,pot}$; Panel B; fatigued n = 48, non-fatigued n = 38) and voluntary activation (VA; Panel C; fatigued n = 48, non-fatigued n = 38) during an incremental performance fatigability test in participants with and without cancer related fatigue.* $p = 0.029$, ** $p < 0.001$ significant main effect of group. Data expressed as mean ± SD.

Figure 2. Root-mean-squared electromyography (EMG_{RMS}) measured in the vastus lateralis (VL) normalized to baseline maximum EMG_{RMS} during an incremental performance fatigability test in participants with and without cancer related fatigue fatigued (fatigued n = 40, non-fatigued n = 32). Measurements were taken from 10-40 s of stage 1, and 1 min 50 s to 2 min 50 s of stages 1, 2 and 3. * $p < 0.05$ significant main effect of group. Data expressed as mean ± SD.

Figure 3. Power outputs during the three common stages of the performance fatigability test expressed relative to the power output at gas exchange threshold (GET). Black horizontal lines

represent the means, while blue and red circles represent individual data points for the fatigued and non-fatigued groups, respectively (fatigued n = 52, non-fatigued n = 35). * p = 0.039, significant between-group difference. Data expressed as mean ± SD.

Additional information

Conflicts of interest

No conflicts of interest, financial or otherwise. The results of the present study do not constitute endorsement by ACSM. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Author contributions

G.Y.M and C.G.B conceived and designed the study; R.T, J.T, T.M and M.M performed experiments; C.G.B, R.T, and J.T analysed data; C.G.B and G.Y.M interpreted results of experiment; C.G.B drafted manuscript; R.T, J.T, T.M, M.M, N.C.R and G.Y.M edited and revised manuscript. C.G.B, R.T, J.T, T.M, M.M, N.C.R and G.Y.M approved final version of manuscript.

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Data availability

Data available upon request.

References

1. Berger AM, Mooney K, Alvarez-Perez A et al. Cancer-Related Fatigue, Version 2.2015. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2015;13(8):1012-39.
2. Williams LA, Bohac C, Hunter S, Cella D. Patient and health care provider perceptions of cancer-related fatigue and pain. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2016;24(10):4357-63.
3. Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *Journal of the National Cancer Institute. Monographs*. 2004;(32):40-50.
4. Jones JM, Olson K, Catton P et al. Cancer-related fatigue and associated disability in post-treatment cancer survivors. *Journal of cancer survivorship : research and practice*. 2016;10(1):51-61.
5. Goedendorp MM, Gielissen MFM, Verhagen CAHHVM, Bleijenberg G. Development of fatigue in cancer survivors: a prospective follow-up study from diagnosis into the year after treatment. *J Pain Symptom Manage*. 2013;45(2):213-22.
6. Islam T, Dahlui M, Majid HA, Nahar AM, Mohd Taib NA, Su TT. Factors associated with return to work of breast cancer survivors: a systematic review. *BMC public health*. 2014;14 Suppl 3(Suppl 3):S8.
7. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nature reviews. Clinical oncology*. 2014;11(10):597-609.
8. Brownstein CG, Twomey R, Temesi J et al. Physiological and psychosocial correlates of cancer-related fatigue. *Journal of Cancer Survivorship*. 2021.

9. Saligan LN, Olson K, Filler K et al. The biology of cancer-related fatigue: a review of the literature. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2015;23(8):2461-78.

10. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-Related Fatigue: The Scale of the Problem. *The oncologist*. 2007;12(S1):4-10.

11. Curt GA, Breitbart W, Cella D et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *The oncologist*. 2000;5(5):353-60.

12. Enoka RM, Duchateau J. Translating Fatigue to Human Performance. *Medicine and science in sports and exercise*. 2016;48(11):2228-38.

13. Doyle-Baker D, Temesi J, Medysky ME, Holash RJ, Millet GY. An Innovative Ergometer to Measure Neuromuscular Fatigue Immediately after Cycling. *Medicine and science in sports and exercise*. 2018;50(2):375-87.

14. Van Belle S, Paridaens R, Evers G et al. Comparison of proposed diagnostic criteria with FACT-F and VAS for cancer-related fatigue: proposal for use as a screening tool. *Support Care Cancer*. 2005;13(4):246-54.

15. Merton PA. Voluntary strength and fatigue. *The Journal of physiology*. 1954;123(3):553-64.

16. Millet GY, Martin V, Martin A, Vergès S. Electrical stimulation for testing neuromuscular function: from sport to pathology. *European journal of applied physiology*. 2011;111(10):2489-500.

17. Black MI, Jones AM, Blackwell JR et al. Muscle metabolic and neuromuscular determinants of fatigue during cycling in different exercise intensity domains. *Journal of applied physiology (Bethesda, Md. : 1985)*. 2017;122(3):446-59.

18. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of pain and symptom management*. 1997;13(2):63-74.

19. Minton O, Stone P. A systematic review of the scales used for the measurement of cancer-related fatigue (CRF). *Annals of oncology : official journal of the European Society for Medical Oncology*. 2009;20(1):17-25.

20. Stapelfeldt B, Mornieux G, Oberheim R, Belli A, Gollhofer A. Development and evaluation of a new bicycle instrument for measurements of pedal forces and power output in cycling. *International journal of sports medicine*. 2007;28(4):326-32.

21. Wasserman K, Whipp BJ, Davis JA. Respiratory physiology of exercise: metabolism, gas exchange, and ventilatory control. *International review of physiology*. 1981;23:149-211.

22. Rodriguez-Falces J, Place N. Determinants, analysis and interpretation of the muscle compound action potential (M wave) in humans: implications for the study of muscle fatigue. *European journal of applied physiology*. 2018;118(3):501-21.

23. Strojnik V, Komi PV. Neuromuscular fatigue after maximal stretch-shortening cycle exercise. *Journal of applied physiology (Bethesda, Md. : 1985)*. 1998;84(1):344-50.

24. Coates KD, Aboodarda SJ, Krüger RL et al. Multiple sclerosis-related fatigue: the role of impaired corticospinal responses and heightened exercise fatigability. *Journal of neurophysiology*. 2020;124(4):1131-43.

25. Lavigne C, Lau H, Francis G, Culos-Reed SN, Millet GY, Twomey R. Neuromuscular function and fatigability in people diagnosed with head and neck cancer before versus after treatment. *European journal of applied physiology*. 2020;120(6):1289-304.

26. Cai B, Allexandre D, Rajagopalan V et al. Evidence of significant central fatigue in patients with cancer-related fatigue during repetitive elbow flexions till perceived exhaustion. *PloS one*. 2014;9(12):e115370.

27. Yavuzsen T, Davis MP, Ranganathan VK et al. Cancer-related fatigue: central or peripheral? *J Pain Symptom Manage*. 2009;38(4):587-96.

28. Amann M, Dempsey JA. Locomotor muscle fatigue modifies central motor drive in healthy humans and imposes a limitation to exercise performance. *The Journal of physiology*. 2008;586(1):161-73.

29. Marcora SM, Bosio A, de Morree HM. Locomotor muscle fatigue increases cardiorespiratory responses and reduces performance during intense cycling exercise independently from metabolic stress. *American journal of physiology. Regulatory, integrative and comparative physiology*. 2008;294(3):R874-83.

30. Twomey R, Aboodarda SJ, Kruger R, Culos-Reed SN, Temesi J, Millet GY. Neuromuscular fatigue during exercise: Methodological considerations, etiology and potential role in chronic fatigue. *Neurophysiologie clinique = Clinical neurophysiology*. 2017;47(2):95-110.

31. Fitts RH. The cross-bridge cycle and skeletal muscle fatigue. *Journal of applied physiology (Bethesda, Md. : 1985)*. 2008;104(2):551-8.

32. Allen DG, Lamb GD, Westerblad H. Skeletal muscle fatigue: cellular mechanisms. *Physiological reviews*. 2008;88(1):287-332.

33. Grassi B. Skeletal muscle VO2 on-kinetics: set by O2 delivery or by O2 utilization? New insights into an old issue. *Medicine and science in sports and exercise*. 2000;32(1):108-16.

34. Temesi J, Mattioni Maturana F, Peyrard A, Piucco T, Murias JM, Millet GY. The relationship between oxygen uptake kinetics and neuromuscular fatigue in high-

intensity cycling exercise. *European journal of applied physiology*. 2017;117(5):969-78.

35. Cerretelli P, Pendergast D, Paganelli WC, Rennie DW. Effects of specific muscle training on VO2 on-response and early blood lactate. *Journal of applied physiology: respiratory, environmental and exercise physiology*. 1979;47(4):761-9.

36. Inglis EC, Iannetta D, Murias JM. The relationship between the time constant of [Formula: see text]O(2) kinetics and [Formula: see text]O(2max) in humans. *European journal of applied physiology*. 2021;121(9):2655-6.

37. Han YS, Proctor DN, Geiger PC, Sieck GC. Reserve capacity for ATP consumption during isometric contraction in human skeletal muscle fibers. *Journal of applied physiology (Bethesda, Md. : 1985)*. 2001;90(2):657-64.

38. Roffey DM, Byrne NM, Hills AP. Effect of stage duration on physiological variables commonly used to determine maximum aerobic performance during cycle ergometry. *Journal of sports sciences*. 2007;25(12):1325-35.

39. Weston SB, Gray AB, Schneider DA, Gass GC. Effect of ramp slope on ventilation thresholds and VO2peak in male cyclists. *International journal of sports medicine*. 2002;23(1):22-7.

Table 1. Participant characteristics.

Variable	Fatigued (*N* = 54)	Non-fatigued (*N* = 42)
Age (years)		
Mean (SD)	54 (9)	58 (12)
Stature (cm)		
Mean (SD)	170 (11)	169 (11)
Mass (kg)		
Mean (SD)	82 (21)	75 (18)
Sex, *N* (%)		
Male	21 (39)	19 (45)
Female	33 (61)	23 (55)
Time since treatment (months)		
Mean (SD)	34 (34)	44 (28)*
Cancer type, *N* (%)		
Breast	24 (44)	19 (45)
Prostate	5 (9)	12 (29)
Head and Neck	7 (13)	2 (5)
Colon	5 (9)	3 (7)
Haematological	1 (2)	0 (0)
Other	14 (26)	7 (17)
Multiple cancer types	2 (4)	1 (2)
Treatment received, *N* (%)		
Surgery	42 (78)	32 (76)
Radiotherapy	23 (43)	13 (31)
Chemotherapy	25 (46)	15 (36)
Single-modality	31 (59)	29 (69)
Multi-modality	22 (41)	13 (31)
Fatigue (FACIT-F score)		
Mean (SD)	26 (6)	44 (5)*
Median	27	45
Range	10-34	35-51

Note: Single modality refers to chemotherapy or radiotherapy only, multi-modality refers to chemotherapy and radiotherapy. * between-group difference ($p < 0.05$).

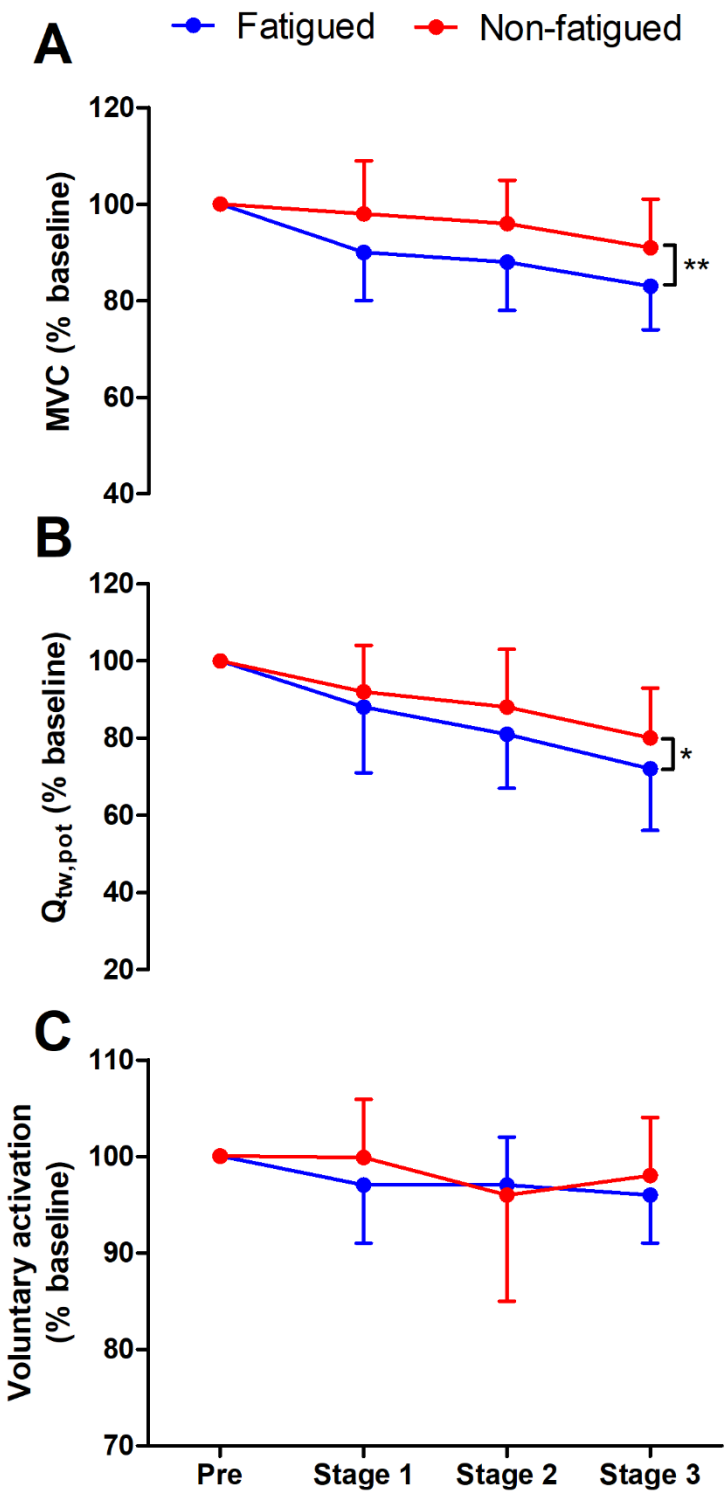
Table 2. Raw neuromuscular values including isometric maximal voluntary contraction (MVC; fatigued n = 54, non-fatigued n = 41) peak force, potentiated twitch force ($Q_{tw,pot}$; fatigued n = 48, non-fatigued n = 38), voluntary activation (VA; fatigued n = 48, non-fatigued n = 38) and the amplitude of the negative phase of the maximum compound muscle action potential (M_{max}) during step-incremental cycling exercise in fatigued and non-fatigued groups.

		Pre-exercise	Stage 1	Stage 2	Stage 3
MVC (N)	Fatigued	239 ± 159	218 ± 144	214 ± 145	204 ± 145
	Non-fatigued	205 ± 67	200 ± 65	192 ± 66	185 ± 67
$Q_{tw,pot}$ (N)	Fatigued	88 ± 68	78 ± 60	73 ± 58	66 ± 58
	Non-fatigued	78 ± 27	71 ± 24	66 ± 22	60 ± 20
VA (%)	Fatigued	94 ± 6	92 ± 8	90 ± 14	90 ± 10
	Non-fatigued	95 ± 5	95 ± 4	91 ± 11	93 ± 6
M_{max} (mV)	Fatigued	3.3 ± 2.1	3.2 ± 2.1	3.3 ± 2.1	3.4 ± 2.1
	Non-fatigued	4.4 ± 1.6	4.3 ± 1.5	4.4 ± 1.5	4.4 ± 1.5

Table 3. Power output variables derived from step-incremental cycling exercise and performance fatigability test in fatigued and non-fatigued groups.

Variable			*p* value	*d effect size*
CPET PO	Fatigued (*N* = 53)	Non-fatigued (*N* = 38)		
Absolute PO (W)				
PPO	158 ± 54	161 ± 53	0.757	0.06
PO at RCP	112 ± 44	115 ± 40	0.524	0.07
PO at GET	65 ± 26	70 ± 27	0.226	0.23
Relative PO ($W \cdot kg^{-1}$)				
PPO	2.0 ± 0.6	2.2 ± 0.6	0.090	0.33
PO at RCP	1.4 ± 0.4	1.5 ± 0.5	0.076	0.22
PO at GET	0.8 ± 0.3	0.9 ± 0.4	0.046	0.28
Fatigability PO (% GET)	Fatigued (*N* = 52)	Non-fatigued (*N* = 35)		
Stage 1	47 ± 21	38 ± 14	0.100	0.50
Stage 2	94 ± 15	75 ± 30	0.642	0.80
Stage 3	141 ± 64	113 ± 45	0.039	0.51
Fatigability PO (% RCP)	Fatigued (*N* = 52)	Non-fatigued (*N* = 35)		
Stage 1	25 ± 8	21 ± 6	1.00	0.56
Stage 2	50 ± 16	43 ± 13	0.641	0.48
Stage 3	75 ± 24	64 ± 19	0.046	0.51

CPET, cardiopulmonary exercise testing; PO, power output; PPO, peak power output; RCP, respiratory compensation point; GET, gas exchange threshold.



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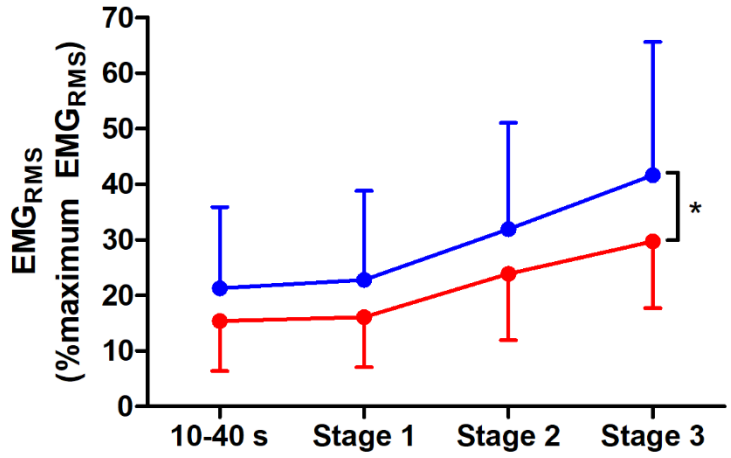

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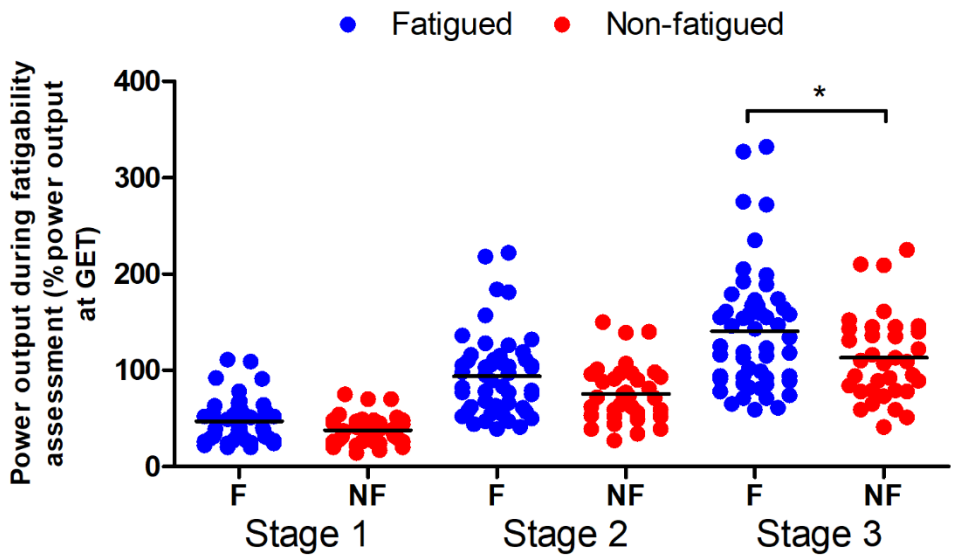

Figure 3. Power outputs during the three common stages of the performance fatigability test expressed relative to the power output at gas exchange threshold (GET). Black horizontal lines represent the means, while blue and red circles represent individual data points for the fatigued and non-fatigued groups, respectively (fatigued n = 52, non-fatigued n = 35). * p = 0.039, significant between-group difference. Data expressed as mean ± SD.