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The Dynamics of Locomotor Neuromuscular Fatigue during Ramp-Incremental Cycling to Intolerance

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ABSTRACT

BALDWIN, M. M., M. R. CHADWICK, A. P. BENSON, H. B. ROSSITER, and C. FERGUSON. The Dynamics of Locomotor Neuromuscular Fatigue during Ramp-Incremental Cycling to Intolerance. *Med. Sci. Sports Exerc.*, Vol. 57, No. 4, pp. 700–709, 2025. **Introduction:** Traditional neuromuscular fatigue assessments are not task-specific and are unable to characterize neuromuscular performance decline during dynamic whole-body exercise. This study used interleaved maximal isokinetic cycling efforts to characterize the dynamics of the decline in neuromuscular performance during ramp-incremental (RI) cycle ergometry exercise to intolerance. **Methods:** Eleven young healthy participants (10 male/1 female) performed two RI cycle ergometry exercise tests to intolerance: 1) RI exercise with peak isokinetic power (Piso) at 80 rpm measured at baseline and immediately at intolerance from a maximal ~6 s effort, and 2) RI exercise where additional Piso measurements were interleaved every 90 s to characterize the decline in neuromuscular performance during the RI test. Muscle excitation was measured using EMG during all Piso assessments, and pulmonary gas exchange was measured throughout. **Results:** Baseline Piso was 832 ± 140 W and RI exercise reduced Piso to 349 ± 96 W at intolerance ($P = 0.001$), which was not different from flywheel power at intolerance (303 ± 96 W; $P = 0.292$). There was no reduction in Piso between baseline cycling and gas exchange threshold (GET; baseline Piso vs mean Piso below GET: 828 ± 146 vs 815 ± 149 W; $P = 1.00$). Piso fell progressively above GET until intolerance (Piso every 90 s above GET: 759 ± 139, 684 ± 141, 535 ± 144, 374 ± 117 W; each $P < 0.05$ vs baseline and mean Piso below GET). Peak muscle excitation (EMG) was also reduced only above GET (73% ± 14% of baseline, at intolerance; $P < 0.05$). However, the reduction in peak Piso preceded the reduction in peak muscle excitation. **Conclusions:** The dynamics of the decline in neuromuscular performance (reduction in Piso and EMG) during RI exercise are consistent with known intensity-dependent metabolic and traditional pre–post neuromuscular fatigue responses to discrete bouts of constant-power exercise. **Key Words:** EXERCISE INTOLERANCE, NEUROMUSCULAR FATIGUE, PEAK ISOKINETIC POWER, $\dot{V}O_{2MAX}$

Fatigue can be defined as a temporary reduction in the capacity for skeletal muscle to produce force or power that is reversible with rest. Following constant-power output exercise, the severity of exercise-induced neuromuscular fatigue is intensity dependent (1–4). After moderate-intensity constant-power output cycle ergometry below the gas exchange threshold (GET), both externally evoked contractions and isometric maximal voluntary contractions (MVC) identify only a small reduction in neuromuscular system function due to peripheral and central fatigue when exercise duration is <140 min (1–3). However, there is no reduction in task-specific maximal effort isokinetic cycling power (Piso) (4) or deleterious effects on subsequent exercise performance after moderate-intensity constant-power cycling terminated at 8 and 140 min, respectively (3). This is consistent with little to no meaningful locomotor neuromuscular fatigue that affects neuromuscular performance following exercise within the moderate-intensity domain when stored muscle substrates (e.g., glycogen) are not limited.

After exercise in the heavy-intensity domain (above the GET, but below critical power—the highest power output where a dynamic equilibrium (often referred to as a steady-state) can be achieved (5–7)), the severity of exercise-induced locomotor neuromuscular fatigue is greater compared with moderate-intensity

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exercise. Peripheral and central fatigue impair neuromuscular system function to a greater extent following exercise in this domain (1–3), leading to a reduction in cycling task-specific Piso (4) and a reduction in subsequent exercise performance (3). Thus, the severity of locomotor neuromuscular fatigue following heavy-intensity exercise reduces neuromuscular performance and typically has functional consequences that impair exercise performance.

Following cycle ergometry exercise above critical power in the very-heavy/severe-intensity domain to intolerance, the severity of exercise-induced locomotor neuromuscular fatigue is greater still compared with heavy-intensity exercise, as indicated by further declines in neuromuscular system performance (1,2,8). This is primarily a consequence of greater peripheral fatigue that further reduces cycling task-specific Piso (4) and substantially reduces subsequent exercise performance (e.g., (9,10)). Collectively, the intensity-dependent severity of locomotor neuromuscular fatigue following discrete bouts of constant-power output exercise is consistent with the known magnitude and time course of perturbations in intramuscular and circulating metabolites evoked during moderate-, heavy-, and very-heavy-intensity exercise (1,11–13).

The ramp-incremental power output forcing function is the integral of the constant-power output function (14). Ramp-incremental exercise is the gold-standard cardiopulmonary exercise test performed to interrogate the integrated physiologic function of the neuromuscular, cardiovascular, and pulmonary systems under stress. Cardiopulmonary exercise test variables, for example, GET, $\Delta\dot{V}O_2/\Delta$work rate, minute ventilation/carbon dioxide output ($\dot{V}_E/\dot{V}CO_2$) slope, and peak oxygen uptake ($\dot{V}O_{2peak}$) (15,16), quantify impairment, contribute to prognostic assessments, and discriminate among proximal causes of symptoms or exercise limitations, among other uses (17). Data describing metabolic perturbations *during* ramp-incremental exercise emphasize the importance of the GET as a threshold in this regard (18,19). Externally evoked isometric contractions identify substantial neuromuscular fatigue following ramp-incremental intolerance (20,21). However, it is unknown how the dynamics of the decline in locomotor neuromuscular performance develop during ramp-incremental exercise, from rest to peak exercise, and influence the point of exercise intolerance (22). Therefore, the primary aim of this study was to use interleaved measurement of task-specific cycling Piso combined with electromyography (EMG; muscle excitation) to characterize the decline in neuromuscular performance instantaneously at discrete intervals *during* ramp-incremental exercise (23–25). We hypothesized that Piso and EMG measured during these maximal isokinetic efforts would be unchanged from baseline during ramp-incremental exercise below GET, but both variables would decline precipitously above GET such that, at intolerance, Piso would not differ from the ramp-incremental power, that is, no power reserve: a Piso that does not exceed the upper 95% prediction limit of the power fluctuation during cycling in hyperbolic mode (24). If observed, these responses would be consistent with no decline in locomotor neuromuscular performance during sub-GET ramp-incremental exercise, followed by a progressive decline in neuromuscular performance that increases in magnitude as the point of tolerance is reached. A reduction in Piso and EMG would indicate both muscle fatigue and reduced muscle excitation contribute to the decline in neuromuscular performance (23–25).

METHODS

Ethical Approval and Participants

This study was approved by The Faculty of Biological Sciences (University of Leeds) Research Ethics Committee (BIOSCI 18-004). Eleven healthy, recreationally active participants volunteered (10 male, 1 female; age, 24 ± 3 yr; height, 179 ± 8 cm; body mass, 73 ± 8 kg) and provided written informed consent to participate in this study. Participants were screened using the Health and Physical Activity Status Questionnaire and confirmed as having no known contraindications to high-intensity exercise. Before visiting the exercise laboratory, participants were instructed to abstain from strenuous exercise in the preceding 24 h and to refrain from food and caffeine intake for at least 3 h.

Equipment and Measures

Cycle ergometry. Exercise tests were performed on an electromagnetically braked cycle ergometer (Excalibur Sport PFM, Lode, Groningen, the Netherlands). This computer-controlled ergometer can instantaneously switch from hyperbolic (cadence-independent) to isokinetic modes to allow measurement of maximal effort isokinetic cycling power (Piso) (4,23–27). Cycling power produced at the crank was measured every 2° of angular rotation from the product of force (N·m) and angular velocity (rad·s^{-1}). These measures were made using strain gauges located within the bottom bracket of the crank assembly and three independent light sensors sampling flywheel velocity in series that come built into the commercially available ergometer (4).

Pulmonary gas exchange. Breath-by-breath pulmonary gas exchange and ventilation were measured during all exercise tests from a mouthpiece that housed the flow sensor and gas sample umbilical (Cardio2, Medgraphics; Medical Graphics Corporation, St Paul, MN). Before testing, a pitot tube volume sensor was calibrated across the expected physiologic flow range using a 3 L syringe. Similarly, the infrared CO_2 and galvanic O_2 gas analyzers were calibrated across the physiologic range using two gas mixtures of known concentrations (tank 1: O_2 = 21%, CO_2 = 0%; tank 2: O_2 = 12%, CO_2 = 5%). Calibration gases were resampled after the test to confirm analyzer stability across the exercise test. During all tests, heart rate was recorded from the R-R interval of a 12-lead ECG that was integrated with the gas exchange system to record heart rate with a breath-by-breath sampling frequency (Mortara X12+; Mortara Instrument, Milwaukee, WI).

Electromyography. Surface EMG was measured in five muscles of the right leg: gastrocnemius lateralis, biceps femoris, vastus lateralis, rectus femoris, and vastus medialis. Two self-adhesive 42 × 24-mm electrodes (Kendall H93SG electrodes; Covidien, Minneapolis, MN) were placed on the

muscle belly with a 20-mm interelectrode distance, guided by Surface EMG for the Non-Invasive Assessment of Muscles (SENIAM) recommendations. Before electrode placement, sites were shaved, abraded, and cleaned using 70% isopropyl alcohol to minimize skin impedance. EMG signals were recorded at 1500 Hz (Noraxon TeleMyo 2400T G2; Noraxon USA Inc, Scottsdale, AZ) and transferred wirelessly from the transmitter worn by participants on a waist belt to the receiver using a radio system.

Exercise Protocols

All participants completed two exercise protocols: 1) a maximal ramp-incremental exercise test, and 2) a ramp-incremental exercise test with assessments of Piso at baseline and interleaved during the ramp-incremental phase to measure neuromuscular performance during ramp-incremental exercise (Fig. 1A). Each test was performed on a separate visit to the laboratory, with the order in which they were performed randomized.

The general procedures for both protocols were the same. Before the start of the ramp-incremental phase, participants performed two short (~6 s) bouts of maximal effort isokinetic cycling at 80 rpm to determine baseline Piso. Following these efforts, participants completed a minimum of 2 min of rest and 4 min of unloaded pedaling (20 W) with each phase continued until a clear dynamic equilibrium was attained. Next, the ramp-incremental phase was initiated with an incrementation rate of 20 or 25 $W \cdot min^{-1}$ (for females and males, respectively) and continued to intolerance, determined as the point at which participants were unable to maintain a cycling cadence greater than 50 rpm despite strong verbal encouragement. At the point of intolerance, the cycle ergometer was immediately switched from hyperbolic to isokinetic mode using the ergometer computer controller and ~6 s of maximal effort isokinetic cycling at 80 rpm completed to measure Piso at intolerance.

During the ramp-incremental exercise test with interleaved assessments of Piso, every 90 s the ergometer was switched from hyperbolic to isokinetic mode and 6 s of maximal effort isokinetic cycling at 80 rpm was performed to measure Piso throughout the incremental phase. At the end of each isokinetic phase, the ergometer was switched back to hyperbolic mode and the ramp-incremental phase continued (Fig. 1B). Participants performed between 6 and 7 Piso efforts during the ramp-incremental phase, determined by the individual time to intolerance. Muscle excitation (EMG) was measured during all isokinetic efforts.

Data Analysis

Pulmonary gas exchange. Breath-by-breath $\dot{V}O_2$ was plotted against time, and 99% prediction limits were fitted to the local mean response. Individual breaths located outside these prediction limits were removed, as these breaths were considered "noise" and not reflective of the underlying physiologic response (28). GET was measured from the ramp-incremental test using the V-slope in combination with the end-tidal and ventilatory equivalent responses (18). GET was not identifiable in the ramp-incremental exercise test with interleaved assessments of Piso because of oscillations in $\dot{V}O_2$ and $\dot{V}CO_2$ evoked by the maximal Piso efforts. The $\dot{V}O_{2peak}$ was determined as the greatest 12-breath rolling average working back from the point of intolerance.

Cycling power. Throughout all tests, cycling power at the crank (i.e., the power the individual was producing at the pedals) was measured independently for left and right cranks every 2° of angular rotation. Left and right crank power every 2° of angular rotation was then summed and a mean calculated for each 360° of angular rotation. This provided a measure of cycling power for each pedal stroke throughout exercise.

During cadence-independent hyperbolic cycling, variations in crank power above and below the flywheel power, equivalent to the power programmed into the cycle ergometer computer controlled, are normal and expected. Using the cycling power measured at the crank, the mean and 95% prediction limits of these fluctuations were characterized relative to the flywheel power (24). This was used to determine whether any power reserve detected exceeded the typical variations observed in crank power throughout the test.

Peak voluntary isokinetic power (Piso). Following the instantaneous switch from hyperbolic to isokinetic modes, the first three pedal strokes that were constrained at 80 ± 1 rpm were used to calculate Piso.

Characterization of locomotor neuromuscular performance and fatigue. Four measures were used to describe the locomotor neuromuscular performance and fatigue evoked during ramp-incremental exercise (Fig. 1):

1. Baseline Piso: This refers to maximum isokinetic cycling power (Piso) at baseline before ramp-incremental exercise
2. Aerobic power index: (Ramp-incremental peak power output/Baseline Piso) × 100. This describes the ability of the aerobic system to support the available isokinetic cycling power (i.e., Baseline Piso) during the ramp-incremental test.
3. Fatigue index: [((Baseline Piso − Piso at a specific time point)/Baseline Piso)/Ramp-incremental flywheel power] × 100. This describes reduction in Piso from baseline (as a percentage) per watt of ramp-incremental work rate.
4. Power reserve: [(Piso at intolerance − Ramp-incremental flywheel power)/Ramp-incremental flywheel power] × 100. This describes the ability to produce Piso in excess of the demands of the exercise task at ramp-incremental intolerance and therefore whether locomotor neuromuscular performance limits ramp-incremental exercise. The power reserve was considered meaningful if the magnitude of this exceeded the upper 95% prediction limit for the mean fluctuation in crank power versus flywheel power (24).

Electromyography. A bandpass filter of 10–500 Hz was applied to raw EMG signals measured during Piso to reduce noise and artifact contamination. Raw EMG signals were then rectified, and root mean square (RMS) smoothed with a

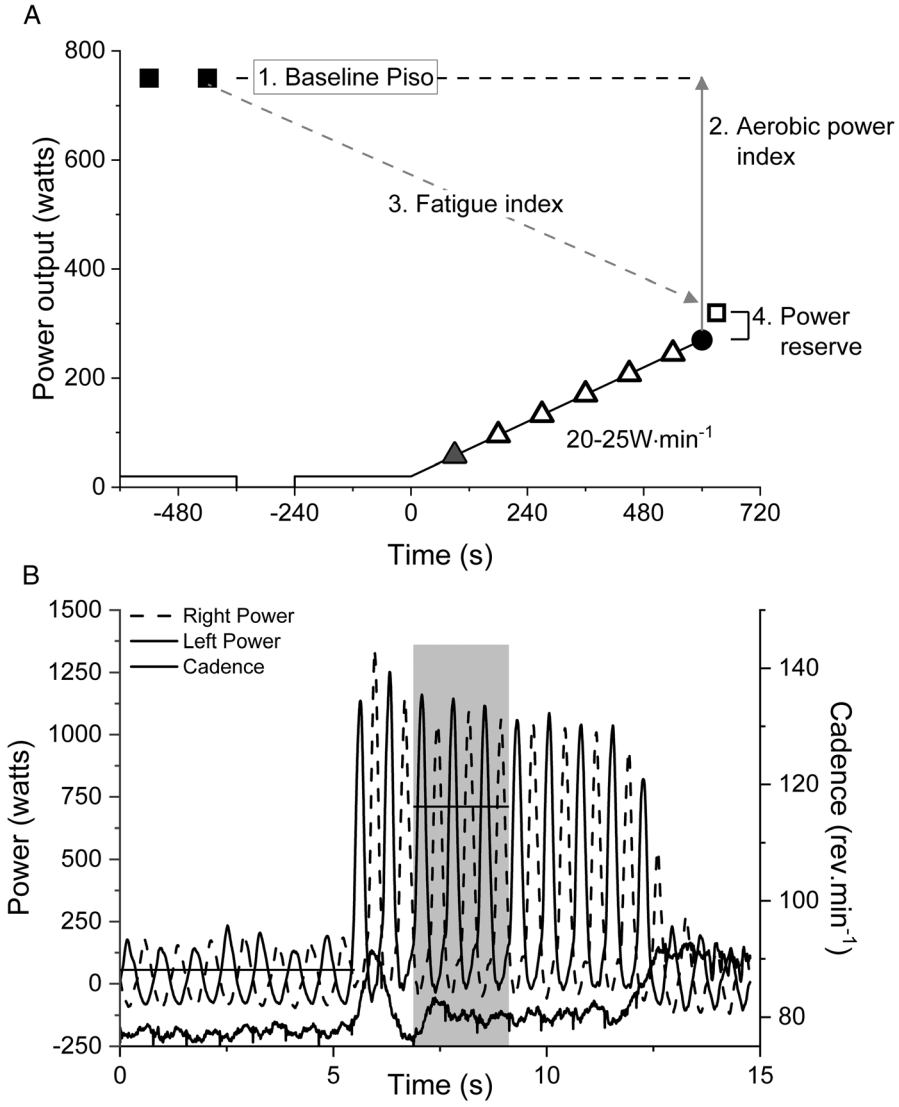

FIGURE 1—A, Schematic representation of the ramp-incremental exercise test with interleaved assessments of Piso. ■: measurement of baseline Piso. The solid black line describes flywheel power throughout the ramp-incremental test increasing at a rate of 20–25 W·min^{-1}. ●: peak ramp-incremental flywheel power. □: Piso measured at intolerance. Δ: Piso measured every 90 s during the ramp-incremental test. The four measures used to characterize locomotor neuromuscular performance, as described in the text, are also shown. B, A representative example the interleaved Piso measurement performed, as indicated by ▲ in panel A. Right and left powers every 2° of angular rotation from the ramp phase transitioning into the Piso phase with the corresponding cadence are shown. The gray box indicates the three pedal strokes from which Piso was calculated. The calculated Piso from these pedal strokes that is comparable with the flywheel power for this phase is shown by the thick black solid line.

100-ms time window. The three contractions corresponding to the three pedal strokes used to calculate each Piso measurement were identified. For each pedal stroke, the peak RMS-EMG of each of the five muscle groups was determined, and all values were summed. This derived a single RMS-EMG value for each of the three pedal strokes from which a mean was taken to derive an appropriate RMS-EMG datum to pair with each Piso measurement. All RMS-EMG values were normalized to baseline Piso (i.e., the visit maximum).

Work done. Pedal-by-pedal stroke power from both tests was plotted against time and integrated to calculate work done (work done [kJ] = (Power [W] × Time [s])/1000). Work done during Piso measures during ramp-incremental exercise test with interleaved assessments of Piso was also calculated and subtracted from the work done during the same time period in the ramp-incremental protocol to determine the additional work done performed during these interleaved Piso measurements.

Statistical Analyses

Before any statistical tests were conducted, data were checked for normality using Shapiro–Wilk tests. Characteristics

of the two different ramp-incremental protocols were compared using paired *t*-tests. To determine if a power reserve was present within each RI protocol, power measurements (Baseline Piso, Piso at intolerance, and peak ramp-incremental flywheel power) were compared using a one-way repeated-measures ANOVA with Dunnett's *post-hoc* test using peak ramp-incremental flywheel power as the reference variable (24). Changes in Piso and RMS-EMG with time during the ramp-incremental exercise test with interleaved assessments of Piso were analyzed using a one-way repeated-measures ANOVA. Where significant effects were identified, Bonferroni *post-hoc* tests were used to identify significant differences. Statistical significance was set at $P < 0.05$. Intraclass correlation coefficients (ICC) were calculated based on a mean-rating ($k = 2$), absolute agreement, two-way mixed-effects model. ICC values >0.90 are considered excellent, values between 0.75 and 0.90 indicate good repeatability, and values less than 0.50 indicate poor repeatability (29). Data are presented as mean ± SD.

RESULTS

Ramp-Incremental Exercise Test without Interleaved Assessments of Piso

Gas exchange responses. The ramp-incremental tolerable duration was 689 ± 65 s. GET was 1.86 ± 0.32 L·min^{-1} (51% ± 4% $\dot{V}O_{2peak}$), and $\dot{V}O_{2peak}$ was 3.66 ± 0.62 L·min^{-1} (50.8 ± 9.5 mL·min^{-1}·kg^{-1}).

Power output responses (baseline to intolerance). There was no difference between the first and second Baseline Piso measurements (833 ± 137 vs 830 ± 146 W, $P = 0.768$, test–retest variability = 3.5%; ICC = 0.98); therefore, the mean Baseline Piso (832 ± 140 W) was used in all subsequent analyses. The aerobic power index was 37% ± 4%; the aerobic system ($\dot{V}O_{2peak}$) was able to support 303 ± 36 W (peak ramp-incremental flywheel power) of the available Baseline Piso at intolerance. The fatigue index between baseline and ramp-incremental peak was 0.193% ± 0.038% reduction in Piso/watt, describing the mean rate at which Piso was lost during the ramp-incremental test per watt of ramp-incremental work. At the limit of tolerance, peak ramp-incremental flywheel power was 303 ± 36 W, and Piso at intolerance was 349 ± 96 W and was not different ($P = 0.292$): there was no power reserve (Fig. 2A). On average, the time between the last hyperbolic pedal stroke of the ramp-incremental test in hyperbolic mode and the first pedal stroke used to measure Piso was 2.7 ± 1.0 s. The lower and upper limits of mean fluctuation (95% prediction limits) in crank power during the ramp-incremental test were −27% ± 6% to +26% ± 6% of the required flywheel power. Over the duration of the ramp-incremental test, 97.8 ± 17.5 kJ of work was completed.

At the limit of ramp-incremental intolerance, muscle excitation (EMG) decreased from 100% during baseline Piso to 69% ± 15% during Piso at intolerance ($n = 9$ due to EMG failure in 2 subjects; $P = 0.001$).

Ramp-Incremental Exercise Test with Interleaved Assessments of Piso

Gas exchange responses. The tolerable duration of the test with interleaved Piso measurements was 631 ± 53 s, which was shorter than in the ramp-incremental exercise test ($P = 0.001$). At the limit of tolerance, $\dot{V}O_{2peak}$ was 3.78 ± 0.50 L·min^{-1} (52.3 ± 7.5 mL·min^{-1}·kg^{-1}), not different from that reached in the ramp-incremental test ($P = 0.160$), confirming that $\dot{V}O_{2max}$ was reached in both tests, by meeting the definition of a change in work rate at peak exercise without any change in $\dot{V}O_2$ (30,31).

Power output responses (baseline to intolerance). Similar to standard RI exercise, there was no difference between the first and second Baseline Piso measurements (829 ± 153 vs 827 ± 145 W; $P = 0.903$; test–retest variability = 4.9%; ICC = 0.964); therefore, the mean Baseline Piso (828 ± 146 W) was used in all subsequent analyses. This was not different from mean Baseline Piso in the ramp-incremental test without interleaved Piso measurements ($P = 0.753$). Interleaving Piso efforts during the ramp-incremental test reduced the flywheel power at intolerance compared with the standard ramp-incremental protocol (278 ± 30 vs 303 ± 36 W; $P = 0.001$). Consistent with no change in Baseline Piso and $\dot{V}O_{2max,}$ but a reduction in ramp-incremental flywheel power, the aerobic power index was 34% ± 5% and lower than in the ramp-incremental test ($P = 0.001$). Therefore, overall, the aerobic system was able to support a smaller fraction of the available muscle power at intolerance. Piso at intolerance of the ramp-incremental exercise test with interleaved Piso was 374 ± 117 W and not different from that of the standard ramp-incremental test (349 ± 96 W; $P = 0.225$). Similarly, the mean fatigue index was 0.201% ± 0.052% and not different from that of the ramp-incremental test (0.193% ± 0.038%; $P = 0.337$). Therefore, despite the reduction in ramp-incremental flywheel power at intolerance, the mean rate at which Piso decreased per watt of ramp-incremental work was the same. In other words, there was a similar magnitude of decline in neuromuscular performance (reduction in baseline to intolerance Piso) and rate of decline in neuromuscular performance per watt (mean fatigue index) in both tests. At the limit of tolerance, Piso was greater than the peak ramp-incremental flywheel power (374 ± 117 W vs 278 ± 30 W; $P = 0.033$): there was a power reserve (Fig. 2B). In addition, muscle excitation (EMG) decreased from 100% during baseline Piso to 73% ± 14% during Piso at intolerance ($P = 0.006$). The overall decline in muscle excitation in this test was not different from the decline during the standard ramp-incremental test (69% ± 15%; $P = 0.441$). Therefore, the main consequence of interleaving measurement of Piso during ramp-incremental exercise was a small reduction in ramp-incremental flywheel power at intolerance.

Locomotor neuromuscular performance during ramp-incremental exercise. A representative example of the crank power responses during ramp-incremental exercise with interleaved assessments of Piso is shown in

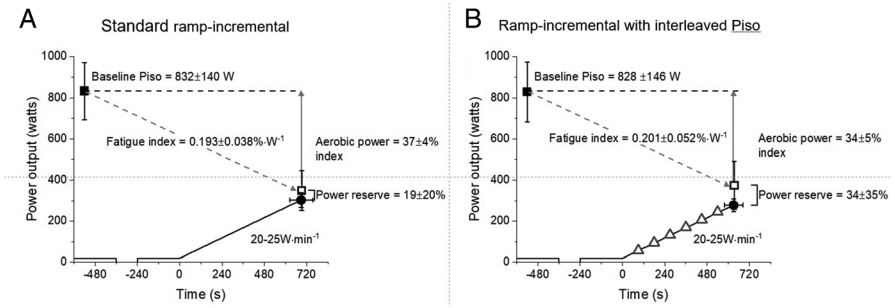

FIGURE 2—The mean power responses that characterize locomotor neuromuscular performance induced by ramp-incremental exercise at the limit of tolerance. A, Ramp-incremental exercise. B, Ramp-incremental exercise with interleaved Piso measurements. ■: Baseline Piso; Δ: Piso measured every 90 s during the ramp-incremental test; ●: peak ramp-incremental flywheel power; □: Piso at intolerance.

Figure 3A. All individuals had a similar profile of reduction in Piso during ramp-incremental exercise; Piso was stable early in the test, but the subsequent fall in Piso became increasingly large as the test progressed toward intolerance (Fig. 3B). Normalizing the responses to GET, we found no decrease in Piso below GET (Baseline Piso vs mean Piso below GET: 828 ± 146 vs 815 ± 149 W; $P = 1.00$), but a progressive reduction in Piso above GET for all time-point comparisons (759 ± 139 vs 684 ± 141 vs 535 ± 144 W; $P < 0.05$). In addition, the rate of decline in Piso (fatigue index) increased as the point of intolerance is approached (Fig. 3C), consistent with a progressively greater loss of neuromuscular performance above GET. Muscle activity showed a similar profile to Piso. There was no effect of exercise on maximal effort RMS-EMG activity below GET, but RMS-EMG reduced progressively above GET, although this reduction was not significantly different from baseline until the limit of tolerance ($P = 0.006$; Fig. 4A). The profile of the reduction in muscle excitation relative to the reduction in Piso is shown in Figure 4B.

Although the ramp-incremental tolerable duration and flywheel power at intolerance were less when Piso measurements were interleaved, total work done was greater with interleaved Piso measurements compared with the standard ramp-incremental test (standard 97.8 ± 17.5 vs Interleaved 102.3 ± 17.0 kJ; $P = 0.009$). This was a consequence of the additional work done during the interleaved Piso measurements (19.2 ± 6.5 kJ). The additional work done during the interleaved Piso measurements summed to equal the "missing" work done in the ramp phase of the standard ramp that had a longer tolerable duration (15.8 ± 7.6 kJ; $P = 0.103$).

DISCUSSION

The primary aim of this study was to characterize the decline in locomotor neuromuscular performance instantaneously at discrete intervals *during* ramp-incremental exercise. In agreement with our hypothesis, our novel findings identified that during ramp-incremental exercise there was no reduction in neuromuscular performance below the GET (i.e., no decrease in Piso or EMG compared with responses at baseline). Above the GET, there was a progressive reduction in neuromuscular performance (reduction in Piso) that increased in its rate of development as the ramp continued until the point of intolerance (Fig. 3). Furthermore, the time course of the reduction in Piso relative to the reduction in muscle excitation (RMS-EMG) suggests that muscle fatigue (reduction in force for a given excitation (23,32)) preceded the reduction in muscle excitation in these healthy participants. These data also agree with our previous studies in young healthy participants showing that ramp-incremental exercise of optimal duration (~8–12 min) (33) is limited by locomotor neuromuscular performance (23–25,34).

Neuromuscular performance and fatigue below the GET. During ramp-incremental exercise below GET

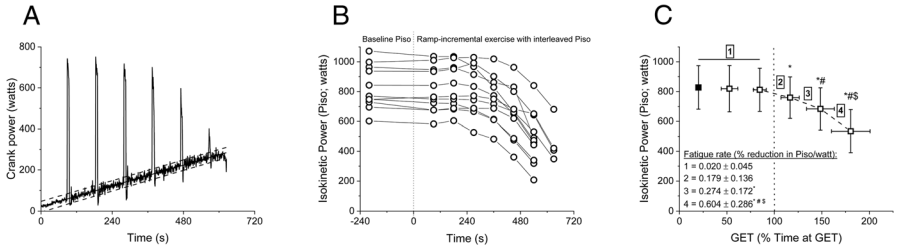

FIGURE 3—A, Representative participant's crank power during the ramp-incremental protocol with interleaved measurement of Piso every 90 s. Also shown is the mean crank power and 95% prediction limits of the power fluctuation while exercising in the cadence-independent hyperbolic mode, with the isokinetic phases excluded. B, Individual isokinetic power (Piso) responses during ramp-incremental exercise, following measurement of Baseline Piso. C, Group mean Piso during ramp-incremental exercise, using GET to demarcate moderate-intensity (<GET) from supra-GET exercise. Piso responses: *lower than below GET, #lower than the first post-GET Piso, $lower than the second post-GET Piso. Fatigue rate responses: *faster rate of fatigue than below GET (rate 1), #faster rate of fatigue than post-GET rate 2, $faster rate of fatigue than post-GET rate 3. ■: Baseline Piso. □: Piso during ramp-incremental exercise.

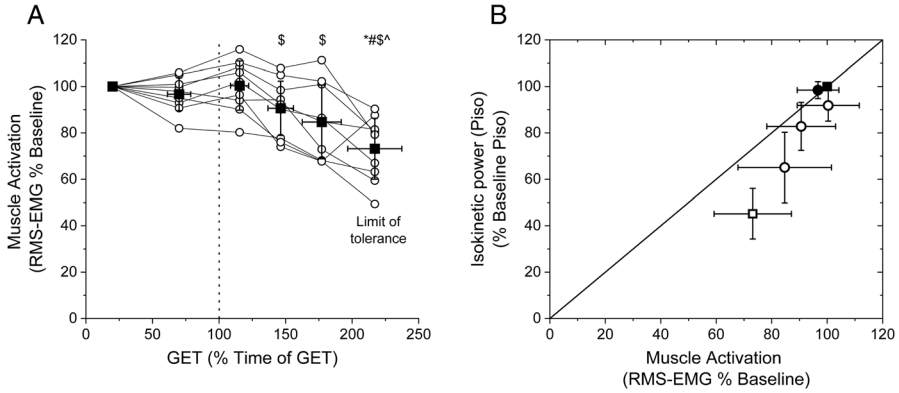

FIGURE 4—A, Individual (○) and group mean (■) muscle excitation responses during isokinetic power measurements (n = 9 due to EMG failure in 2 subjects). *Lower than baseline, #lower than below GET, $lower than post-GET 1, ^lower than post-GET 2. B, The relationship between the decrease in muscle activation (% baseline EMG) and the decrease in Piso (% Baseline Piso) during ramp-incremental exercise with interleaved measurements of Piso. ■: Baseline Piso; Piso below (●) and above (○) GET during ramp-interleaved exercise; □: Piso at intolerance.

(i.e., moderate-intensity), there was no reduction in Piso or muscle excitation (no reduction in RMS-EMG during maximal effort Piso; Figs. 3, 4). The absence of a reduction in neuromuscular performance below the GET is unsurprising in the context of the duration of the moderate-intensity phase of the ramp-incremental test (~5 min), and modest level of fatigue-related metabolite accumulation is expected during moderate-intensity (ramp or constant-power) exercise (e.g., Pi, H^+) (35,36) that is well described within the literature (1,19,37). Similarly, this finding is consistent with the absence of a reduction in neuromuscular performance (Piso) following constant-power output moderate-intensity exercise (4). Although the mechanisms for force reduction when measured by Piso and external stimulation techniques may differ, this finding also aligns with the minor reduction in neuromuscular system performance observed using externally evoked contractions (1–3) after constant-power output moderate-intensity exercise.

Thus, although there is a continued contribution to the rate of ATP turnover from nonoxidative pathways during ramp-incremental exercise below the GET (38), this does not approach or exceed any "critical threshold" hypothesized to initiate a cascade of biochemical changes that compromise neuromuscular function by inducing peripheral fatigue (Fig. 3) (1,38–41).

Neuromuscular performance above the GET. Above GET, Piso is lower during each of the subsequent interleaved efforts. The reduction in Piso increases in magnitude as the ramp-incremental test proceeds, reflecting a greater rate of decline in neuromuscular performance as the point of intolerance is approached (Fig. 3C). These interleaved ramp-incremental responses agree with the greater metabolic perturbation and accumulation of fatigue-related metabolites observed during discrete constant-power moderate- versus heavy-, and heavy- versus very-heavy/severe-intensity exercise (42,43). Similarly, a greater reduction in Piso followed by EMG during successive interleaved isokinetic measurements is consistent with the greater peripheral and central fatigue measured using externally evoked contractions and for Piso following discrete bouts of constant-power exercise in these domains (1,4).

Peripheral fatigue (reduction in evoked twitch force) and central fatigue (reduction in voluntary excitation) and reduction in Piso each occur within the first 5 min of heavy- and very-heavy/severe-intensity constant-power exercise (4,44,45). The severity of peripheral fatigue is greater after very-heavy/severe-intensity constant-power exercise compared with heavy-intensity, whereas the severity of central fatigue can be reduced (quantitatively, if not significantly) at intolerance (2). This suggests that a reduction in Piso may be identifiable before a reduction in EMG. Therefore, it was perhaps unsurprising that we found the reduction in Piso preceded the reduction in EMG during our ramp-incremental test above GET. It is unclear whether a reduction in Piso in the absence of a reduction in EMG (i.e., overt muscle fatigue) is a prerequisite for a later reduction in muscle excitation; potentially via group III/IV muscle afferent signaling (46–49). Regardless of the precise mechanism(s) that determine the time course, the responses characterized using interleaved Piso measurements during ramp-incremental exercise are consistent with the amalgamation of equivalent intensity constant-power tests and exceeding a critical threshold of fatigue-related metabolite accumulation (40) that propagates further fatigue and ultimately exercise intolerance.

Mechanisms of ramp-incremental intolerance. In the standard ramp-incremental test, the absence of a power reserve at intolerance is consistent with our previous work showing that exercise in young healthy participants is ultimately terminated by locomotor neuromuscular performance. In other words, neuromuscular fatigue has reduced Piso to the extent that, at the point of intolerance, the maximum voluntary cycling power is not statistically or meaningfully different from the flywheel power required by the ramp-incremental task (23–25). We consider Piso at intolerance to be meaningfully different from the peak flywheel power at intolerance if this exceeded the upper 95% prediction limit of the pedal-to-pedal stroke fluctuation in power while cycling in hyperbolic mode during the ramp-incremental phase of the test (Fig. 3A) (24). These data therefore provide a functional context for changes in the performance of the neuromuscular system

revealed by externally evoked and maximal isometric contractions following intolerance (20).

When interleaving measurements of Piso to characterize the dynamics of locomotor neuromuscular performance during ramp-incremental cycling, a key difference was a reduction in ramp-incremental flywheel power at intolerance. The lower flywheel power at intolerance, coupled with the same reduction in Piso at intolerance induced by ramp-incremental exercise, leads to a power reserve being present (Fig. 2B). This indicates the a decline in neuromuscular performance is insufficient to limit ramp-incremental exercise, and mechanisms in addition to reduced locomotor neuromuscular performance are contributory as physiologic capacity to produce the power required by the task remains (24,34). It is noteworthy that a power reserve is also present in clinical populations at the limit of maximal ramp-incremental exercise (34) and in healthy individuals when the ramp rate is reduced to extend the exercise time and reduce the ramp-incremental flywheel power at intolerance (24). In addition, results consistent with these findings have been observed with different ramp rates using electrically evoked and maximum voluntary isometric contractions (20).

The physiologic basis for the power reserve, its functional significance, and whether the mechanism(s) are the same in these different scenarios remain unknown. In this study, we found that the additional work done during the maximal Piso measurements during the interleaved ramp was equivalent to the additional work done at the end of the test, due to the longer tolerable duration. Although speculative, and potentially coincidental, it is possible that some of the finite supracritical power work capacity (i.e., W′) (5) was used during these Piso measurements, thereby curtailing tolerable duration in the interleaved test compared with the standard ramp. However, other mechanisms are likely to contribute to dissociating the locomotor neuromuscular capacity to perform exercise from the ultimate signal that results in exercise intolerance in scenarios with a power reserve (50,51). For example, greater cumulative work of breathing and sensations of dyspnea evoked by the hyperventilatory response to the interleaved Piso measurements may have consequences for the respiratory system that hastened reaching the point of intolerance (24). Understanding these mechanism(s) will undoubtedly be important for understanding how to effectively intervene to improve exercise tolerance and will be an important aim of future studies.

Technical considerations for the assessment of neuromuscular performance and fatigue. Assessments of neuromuscular performance and fatigue are traditionally performed using voluntary (MVC) and external magnetic or electrically evoked isometric contractions on an isokinetic dynamometer or chair instrumented with force transducers to measure changes in isometric force (20,52–54). For dynamic whole-body exercise, this necessitates interruption of the exercise task being performed and a delay before the assessments are made, as the participant is moved from the ergometer to the instrumented equipment for neuromuscular performance and fatigue assessments. This delay is critical, because recovery kinetics of neuromuscular performance are rapid (typically a large recovery is observed within 1 min), which can affect the interpretation of the measured peripheral (reduction in potentiated twitch force) and central (% voluntary excitation) mechanisms of fatigue relative to the exercise task (23,45,55–57).

Doyle-Baker et al. (55) developed an innovative ergometer to overcome the delay between exercise termination and neuromuscular performance and fatigue assessment (2,44,55). This recumbent cycle ergometer locks the pedals in place at a specific joint angle, allowing isometric MVC and externally evoked neuromuscular responses to be assessed. By eliminating the delay between exercise termination and assessment, this technique provided an important advance to our understanding of fatigue during exercise, but was, nonetheless, limited to assessing neuromuscular performance using isometric contractions. For dynamic exercise, reductions in isometric force and reductions in shortening velocity contribute to the reduction in power producing capacity (58). Thus, it is not possible to interpret from isometric measurement whether the severity of neuromuscular fatigue induced by the exercise is of sufficient magnitude to limit continued performance of the cycling task. However, making the distinction of whether neuromuscular performance, or some other mechanism(s), is limiting to the exercise task is vital for tailoring specific interventions to improve exercise tolerance (45).

Maximum effort isokinetic cycling power (Piso) can be measured at baseline, interleaved during the ramp-incremental protocol and measured immediately at intolerance to characterize neuromuscular performance (4,23–25,34). These Piso assessments have the advantage of using the same task-specific motor program and can be initiated instantaneously by switching the ergometer from standard hyperbolic to isokinetic cycling during and at the tolerable limit of any protocol to measure Piso without substantial delay. As these Piso measurements are velocity (accounting for the power–velocity relationship (23)) and task-specific, Piso can identify whether the reduction in locomotor neuromuscular performance is sufficient or not to limit cycling performance (23–25,34). The absence of evoked contractions precludes direct assessment of peripheral and central mechanisms contributing to changes in the neuromuscular system status that determine the reduction in the functional capacity to generate power. However, changes in EMG amplitude, as a measure of peak muscle excitation during Piso, relative to isokinetic power, provide useful insight into the mechanisms responsible for the reduction in neuromuscular performance (22,32). Therefore, this experimental paradigm identifies different facets of neuromuscular performance than externally evoked contractions. Specifically, the change in Piso during exercise, and at intolerance, can be used as an ecologically valid strategy to investigate the functional consequences of declines in neuromuscular system performance for limiting exercise tolerance in health and disease (22).

Limitations. The technique used to measure exercise-induced changes in neuromuscular performance in this study relies on participants providing a maximal voluntary effort and is not independently verified by the application of an external stimulation technique. As such, there is potential for Piso

measurements to be influenced by volitional effort. However, the simplicity of the protocol means that they can be integrated into whole-body exercise at any point, without inducing a time delay, providing an instantaneous measure of neuromuscular performance that represents the capacity of the individual to continue the task. The consistency of the Piso profile among individuals (Fig. 3B) suggests that all participants were able to give a good maximal effort when instructed, and responses indicate little cumulative effect of the repeated Piso measurement during the test.

Surface EMG was used to provide a noninvasive indication of muscle excitation. This apparatus is unable to determine the origin of reduced muscle excitation within the central nervous system, limiting insight into the mechanisms underpinning exercise-induced fatigue development during ramp-incremental exercise. Although external stimulation techniques can evaluate neuromuscular system performance, as previously discussed, these techniques cannot currently be implemented into dynamic whole-body exercise. Therefore, despite this limitation, EMG was chosen because 1) it can be easily integrated into dynamic whole-body exercise, and 2) it was interpreted during maximal isokinetic efforts, which may reduce some of the concerns for surface EMG interpretation during fatigue (22).

CONCLUSIONS

In young healthy participants, during ramp-incremental exercise, there is no reduction in neuromuscular performance below GET. Above GET, a decline in neuromuscular performance becomes evident and increases in rate as the point of intolerance is approached. Both muscle fatigue and excitatory mechanisms are contributory, but the initial reduction in Piso in the absence of a reduction in EMG suggests that muscle fatigue (reduction in force for a given excitation) is the initiating mechanism for the reduction in power producing capacity that precipitates exercise intolerance. Furthermore, task-specific Piso measurements can be used during exercise and at the limit of intolerance to investigate changes in neuromuscular performance during exercise and determine the primary mechanism(s) of exercise intolerance.

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