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Task failure during sustained low-intensity contraction is not associated with a critical amount of central fatigue

Robin Souron^{1,2}, Anne-Cloé Voirin¹, Djahid Kennouche¹, Loïc Espeit¹, Guillaume Y Millet^{1,3}, Thomas Rupp⁴, Thomas Lapole¹

¹ Univ Lyon, UJM-Saint-Etienne, Inter-university Laboratory of Human Movement Biology, EA 7424, F-42023, Saint-Etienne, France.

² Laboratory of Impact of Physical Activity on Health (IAPS), UR n°201723207F, University of Toulon, France

³ Institut Universitaire de France (IUF)

⁴ Inter-university Laboratory of Human Movement Biology (LIBM), University Savoie Mont Blanc, EA 7424, 73000 Chambéry, France

Running title: Central fatigue kinetics in knee extensors

Corresponding author:

Thomas LAPOLE

Laboratoire Interuniversitaire de Biologie de la Motricité

Bâtiment IRMIS

10 rue de la Marandière

42270 Saint Priest en Jarez

04 77 42 18 91

thomas.lapole@univ-st-etienne.fr

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ABSTRACT

Fatigue-related mechanisms induced by low-intensity prolonged contraction in lower-limb muscles are currently unknown. This study investigated central fatigue kinetics in the knee extensors during a low-intensity sustained isometric contraction. Eleven subjects sustained a 10% maximal voluntary contraction (MVC) until task failure (TF) with neuromuscular evaluation every 3 min. Testing encompassed transcranial magnetic stimulation to evaluate maximal voluntary activation (VA_{TMS}), motor evoked potential (MEP) and silent period (SP), and peripheral nerve stimulation to assess M-wave. Rating of perceived exertion (RPE) was also recorded. MVC progressively decreased up to 50% of the time to TF (i.e. 50%_{TTF}) then plateaued, reaching ~50% at TF ($p < 0.001$). VA_{TMS} progressively decreased up to 90%_{TTF} then plateaued, the decrease reaching ~20% at TF ($p < 0.001$). SP were lengthened early (i.e. from 20%_{TTF}) during the exercise then plateaued ($p < 0.01$). No changes were reported for MEP evoked during MVC ($p = 0.87$), while MEP evoked during submaximal contractions decreased early (i.e. from 20%_{TTF}) during the exercise then plateaued ($p < 0.01$). RPE increased linearly during the exercise to be almost maximal at TF. M-waves were not altered ($p = 0.88$).

These findings confirm that TF is due to the subjects reaching their maximal perceived effort rather than any particular central event or neuromuscular limitations since MVC at TF was far from 10% of its original value. It is suggested that strategies minimizing RPE (e.g. motivational self-talk) should be employed to enhance endurance performance.

Keywords: central fatigue; sustained contraction; task failure; transcranial magnetic stimulation; voluntary activation; RPE

INTRODUCTION

In some sport activities (e.g. hiking sailing), muscles are continuously contracted at low intensities, which can subsequently induce neuromuscular fatigue. The latter is defined as an exercise-induced reduction in maximal voluntary contraction (MVC) force or the inability to produce a certain expected force or power.¹ Despite fatigue, the target force can still be maintained,²⁻⁴ and fatigue should not be confounded with the moment of task failure (TF). The development of fatigue during a prolonged fatiguing task can be tracked by regularly performing brief maximal MVCs during exercise. When peripheral electrical nerve stimulation⁵ or transcranial magnetic stimulation (TMS)⁶ are used during these MVCs to evoke superimposed twitches (SIT) and calculate the maximal voluntary activation (VA) level, it is possible to investigate the occurrence of central fatigue, which refers to the processes within motoneurons and/or the other components of the central nervous system that may influence force reduction.⁷

While many studies have examined central fatigue during maximal or submaximal contractions,⁸ studies that investigated low-intensity contractions are scarce. This is important because fatigue is known to be task dependent.⁸ While muscles are frequently contracted at low levels for prolonged periods (as it is the case in some sport activities, e.g. hiking sailing), neural drive³ as well as peripheral consequences (influenced by the level of ischemia) associated with this type of effort may differ from the fatigue induced by stronger contractions.

To the authors' knowledge, only two studies have investigated central fatigue kinetics during low-intensity sustained isometric contraction.^{3,4} A gradual increase in TMS-induced SIT has been reported during a 43-min elbow flexion at 15% MVC.⁴ The same group also reported a gradual decline in VA assessed through TMS (i.e. VA_{TMS}) during a 70-min elbow flexion at 5% MVC.³ The results of the last two-cited studies led to the hypothesis that suboptimal output from the motor cortex could explain, at least in part, the progressive decline in maximal-force generating capacities during a prolonged submaximal effort in upper limbs. Yet, no similar findings exist for locomotor muscles, although our group recently showed that fatigue etiology may differ between upper and lower limb muscles.⁹ Moreover, it is important to study sustained low-intensity contraction until TF, because setting a given contraction duration, as previously performed,^{3,4} may have prevented the capture of the changes that occurred close to TF.¹⁰

Therefore, the main purpose of the current study was to provide a comprehensive description of central fatigue appearance in knee extensors during a very low intensity sustained contraction performed to TF. We hypothesized that reduced neural drive would partly explain the gradual decrease in MVC throughout the sustained submaximal contraction.

MATERIALS AND METHODS

Subjects

Eleven recreationally active healthy men (age: 24 ± 5 yr; height: 181 ± 6 cm; weight: 71 ± 8 kg) volunteered for this study. The sample size was calculated using G*Power (version 3.1.9.2; Kiel University, Kiel, Germany), based on an expected 'moderate effect size ($f^2 = 0.25$) for MVC PRE-POST differences, with an α level of 0.05, power ($1 - \beta$) of 0.8 and correlation among repeated measures of 0.85. Written informed consent was obtained from all subjects before their participation. This study conformed to standards from the latest revision of the Declaration of Helsinki and was approved by the University of Saint Etienne ethics committee. All subjects were free of lower-limb injury during the previous three months, had no contraindications to TMS (as assessed through a safety checklist for the use of TMS¹¹ prior to the beginning of any testing) and had no acute or chronic neurological disorders and trauma. Subjects were instructed to avoid the consumption of caffeine on the day of the experiment and avoid performing any strenuous exercise for 48 h before testing.

Experimental Design

During a separate visit, subjects were familiarized with the correct development of knee extension maximal isometric force as well as magnetic and electrical stimulations. Then, subjects were tested during a single experimental session (Figure 1). The experimental sessions consisted of a sustained isometric contraction at 10% MVC (based on the PRE MVC, see below) force until TF, i.e. when the subject was unable to maintain the submaximal voluntary contraction target for 3 consecutive seconds. Neuromuscular evaluation (NME) was performed before (PRE), every 3 min during the submaximal sustained contraction, and immediately at TF (see experimental procedures section for further details).

Force and electromyographic recordings

Subjects were seated upright in a custom-built chair with knees and hips at 90° of flexion. A noncompliant strap connected to a force transducer was attached 3–5 cm above the subject's lateral malleolus. Subjects were instructed to push against the strain gauge (i.e. knee extension) with their dominant (right) leg, determined as the preferred leg used to kick a ball. Force data were acquired using a PowerLab data acquisition system (16/30–ML880/P, ADInstruments, Bella Vista, Australia) at a sampling rate of 2 kHz. Movements of the upper body were minimized using two belts across the thorax. During all measurements, subjects were provided with real-time feedback of their force trace on a screen, and guidelines were plotted when subjects had to maintain a targeted percent of MVC. Strong verbal encouragements were given during MVCs as well as during the sustained fatiguing contraction. EMG signals were recorded from rectus femoris (RF), vastus lateralis (VL) and vastus medialis (VM) muscles with pairs of self-adhesive surface electrodes (Meditrace 100; Covidien, Mansfield, MA) in a bipolar configuration with a 30-mm interelectrode distance. According to SENIAM recommendations, RF electrodes were placed at 50% on the line from the anterior spina iliaca superior to the superior part of the patella; VL electrodes at 2/3 on the line from the anterior spina iliaca superior to the lateral side of the patella; VM electrodes at 90% on the line between the anterior spina iliaca superior and the joint space in front of the anterior border of the medial ligament. Electrodes were also placed on the antagonist biceps femoris (BF) at 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia. The ground electrode was positioned on the patella. Low impedance ($<5\text{ k}\Omega$) between electrodes was obtained by shaving and gently abrading the skin and then cleaning it with isopropyl alcohol. Signals were amplified with an octal bio-amplifier (ML138, ADInstruments, Bella Vista, Australia), bandpass filtered (5–500 Hz) and analogue-to-digitally converted at a sampling rate of 2 kHz by PowerLab System (16/30, ADInstruments). All data were analysed offline using Labchart 7 software (ADInstruments).

Peripheral nerve stimulation

Single rectangular electrical pulses with 0.2-ms duration and 400 V maximal output voltage were delivered via constant-current stimulator (DS7AH, Digitimer, Hertfordshire, UK) to the right femoral nerve via a 30-mm diameter surface cathode

(Meditrace 100) taped to the skin into the femoral triangle and a 50 × 90 mm anode (Durastick Plus; DJO Global Vista, CA) in the gluteal fold. To determine the optimal intensity of stimulation, single stimuli were delivered incrementally by steps of 10 mA until resting M-wave and twitch amplitudes plateaued. The optimal intensity was then increased by 20% to ensure supramaximality. The mean intensity for peripheral nerve stimulation (PNS) was 370 ± 120 mA.

Transcranial magnetic stimulation

The left motor cortex was stimulated by a magnetic stimulator (Magstim 2002, The Magstim Company Ltd, Whitland, UK) with a 110-mm double-cone-coil (maximum output of 1.4 T). The coil was positioned to induce a postero-anterior current and manually controlled by the same investigator throughout all the testing sessions. A cervical collar was worn during all TMS measures to stabilize the head and neck and a swim cap was worn to ensure consistent coil placement relative to the optimal position. To determine this site, six marks were drawn on the cap: the vertex, 1 and 2 cm posterior to the vertex and 1 cm to the left of these 3 marks along the midline. Optimal coil position was determined as the site eliciting the largest SIT as well as VL, VM and RF MEP amplitudes, with a small MEP amplitude in the antagonist BF in response to stimulation at a known suprathreshold stimulator output (50% of maximal stimulator output) during a 10% MVC knee extension. When optimal agonist MEP and peak force were not recorded at the same coil position, the optimal coil position was chosen according to MEP amplitude, because the evoked peak force may be influenced by activation of other muscles.¹² This position was marked on the swim cap and was the same for RF, VL and VM muscles.

The optimal stimulus intensity was determined from SIT and MEP stimulus-response curves obtained during brief (2-3 s) voluntary contractions at 20% MVC. In brief, intensities of 40, 50, 60, 70 and 80% of maximal stimulator output were tested in random order. At each intensity, four contractions were performed at 10-s intervals. A rest period of 10 s separated each intensity. The optimal stimulation intensity was considered as the one that elicited maximal MEP on VL, VM and RF with minimal MEP on the antagonist BF. Since no M-waves were recorded on the BF, a low BF MEP was arbitrary fixed at an amplitude <10% of VL MEP.¹³ The mean TMS intensity ($62 \pm 6\%$ stimulator output) allowed to record MEP >50% M-wave, as recently recommended for VA_{TMS} calculation.¹²

Experimental procedures

The experimental procedures are illustrated in Figure 1. First, the optimal configuration (i.e. position and intensity) was determined for PNS. After a standardized warm-up consisting of 3 brief (~3 s) knee extensor isometric voluntary contractions at 20, 40, 60 and 80% of the MVC recorded during the former and separated familiarization session, subjects performed 2 brief (~3 s) MVCs interspersed by 1 min. Optimal coil position and intensity for TMS were then established. VA_{TMS} was then calculated based on a continuous method where subjects were asked to perform a single voluntary contraction including an initial ~3 s MVC followed by a voluntary reduction in force output to match 75% MVC and then 50% MVC with no rest period in-between (Figure 2A).¹⁴ This was done using a specific macro on the LabChart software that automatically calculated 75% and 50% of the preceding MVC once the TMS stimulation was delivered. Single TMS pulses were delivered during each level of contraction and a single PNS pulse was delivered during the 50% MVC contraction. To permit accurate determination of the SP, subjects were instructed to momentarily (<1 s) re-contract as quickly as possible immediately after delivery of the single TMS pulse. This procedure was performed twice during PRE, and once during measurements at the other time points. For PRE and TF measurements, single and double electrical (i.e. 100 and 10 Hz) nerve stimulations were delivered on the relaxed muscle after the MVC (Figure 2A). Immediately after the beginning of the task and twenty seconds before each NME during the sustained submaximal contraction (Figure 1), subjects were asked to verbally report their rating of perceived exertion (RPE, not pain), i.e. how hard they perceived the exercise, using a 100-mm visual analogue scale, with “no effort” on one end (0 mm) and “exhaustion” on the other (100 mm). NME during and at TF were performed as an extension of the prolonged submaximal voluntary contraction, i.e. subjects were not permitted to relax and went straight into the MVC at the moment of TF (Figure 1).

Data analysis

Because the exercise duration and thus the number of completed NMEs were different between subjects, interpolation was used to present the data. First, each actual NME was considered to refer to a given percentage of the total exercise duration, assuming the last evaluation (i.e. TF) corresponds to 100% of the time to task failure (TTF). For instance, a subject maintaining the task for 33 min performed 11 NMEs throughout the

exercise, the first NME then corresponding to 9.1% of the total duration, the 5th and the 6th NMEs respectively corresponding to 45.5 and 54.5%_{TTF} and the last NME corresponding to 100%_{TTF} (i.e. TF; exhaustion). Data were then linearly interpolated between actual NMEs to obtain values corresponding precisely, for each subject, to 10% (10%_{TTF}), 20 (20%_{TTF}), etc. until TF.

Areas of the evoked MEP and M-waves were measured offline. Evoked EMG data (M-waves, MEP and SP) are presented as the average values of all responses collected for each time points. A representative trace of the three types of evoked potentials obtained during maximal and submaximal voluntary contractions is displayed in Figure 2A.

PNS. M-wave areas (M_{sup}) were measured from electrical nerve stimulations in VL, RF and VM muscles during voluntary contractions at 50% MVC during each NME. The amplitudes of the potentiated peak twitch (P_t), as well as low- and high frequency doublets (Db_{10} and Db_{100} , respectively) were determined only for PRE and TF measurements. Low-frequency fatigue was then assessed from the change in the ratio Db_{10} to Db_{100} ($Db_{10:100}$).

Force and voluntary EMG. Maximal force was considered as the peak value recorded before the first TMS stimulus. At PRE, the highest MVC over the two trials was chosen for further analysis. Maximal root mean square EMG (RMS_{MAX}) was calculated for VL, RF and VM muscles over a 500-ms period during MVC before TMS delivery. RMS EMG was also measured during the 10% MVC sustained voluntary contraction over 500 ms before brief MVCs (i.e. $RMS_{10\%MVC}$). RMS recorded on each muscle was then normalized to the peak-to-peak amplitude of the maximal M-wave.

TMS. MEP areas were recorded during maximal (MEP_{MVC}) and submaximal voluntary contractions at 75 (MEP_{75}) and 50% MVC (MEP_{50}) for VL, RF and VM, and normalized to M_{sup} areas.

VA_{TMS} was measured by the modified twitch interpolation technique.¹⁴ Estimated resting twitch (ERT) was determined by linear regression of the relation between superimposed twitch (SIT) amplitude evoked when TMS was delivered at MVC, 75% and 50% MVC (Figure 2B) and voluntary force. This relation was extrapolated, and the y-intercept was interpreted as the ERT amplitude (Figure 2C). At PRE, the highest VA_{TMS} from the two trials performed was retained. VA_{TMS} was calculated as follows:

$$VA_{TMS} = (1 - SIT_{MVC}/ERT) \times 100$$

where SIT_{MVC} is the superimposed twitch evoked during contraction at 100% MVC. VA_{TMS} was considered appropriate when (i) TMS delivered over the motor cortex at 100% MVC produced a large MEP in the agonist muscles with a small MEP in the antagonist muscle, i.e. $<10\%$ of VL, VM and RF MEP,¹³ and (ii) the regression of voluntary force and the SIT force evoked during the contractions was linear ($r^2 > 0.9$). Based on these two criteria, one subject was excluded for VA_{TMS} analysis because of $r^2 < 0.9$.

SP durations were recorded during maximal (SP_{MVC}) and submaximal voluntary contractions at 75 (SP_{75}) and 50% MVC (SP_{50}) for VL, RF and VM. SP were determined visually and defined as the duration from the TMS stimulus to the return of continuous voluntary EMG, i.e. when clear EMG bursts could be identified (Figure 2A).

Statistical Analysis

Statistical analyses were performed with Statistica software (StatSoft Inc., Tulsa, OK). All variables were normally distributed (Kolmogorov-Smirnov normality test). Shapiro-Wilk and Mauchly tests were used to ensure the assumptions of normality and sphericity, respectively for all dependent variables. Greenhouse-Geisser correction factor was applied when the assumption of sphericity was violated. For ANOVA analyses, homogeneity of variance was verified by Levene's test. A one-way analysis of variance (ANOVA) for repeated measures was performed for MVC, VA_{TMS} and RPE to test for time effects during the prolonged submaximal voluntary contraction (i.e. PRE, 10% $_{TTF}$, 20% $_{TTF}$, 30% $_{TTF}$, 40% $_{TTF}$, 50% $_{TTF}$, 60% $_{TTF}$, 70% $_{TTF}$, 80% $_{TTF}$, 90% $_{TTF}$, TF). Two-way repeated measures ANOVA were performed for $RMS_{10\%MVC}$, RMS_{MAX} , M_{sup} , MEP and SP [muscle (VL, RF, VM) \times time]. Changes in peripheral function was not investigated during the fatiguing task (with the exception of M_{sup}) so paired t-tests were used to test the effect of time (PRE, TF) for Pt, Db10, Db100 and Db10/Db100 ratio (Db10:100). If significant main or interaction effects were detected, Bonferroni-corrected post hoc tests were performed. Pearson's correlations were used to determine relationships between MVC drop and VA_{TMS} changes during exercise. Partial eta square (η^2) was reported as an estimate of effect size, with $\eta^2 \geq 0.07$ and $\eta^2 \geq 0.14$ used as moderate and large effects, respectively.¹⁵ Statistical significance was set at $p < 0.05$. All data are presented in the text and figures as mean \pm standard deviation (SD).

RESULTS

The mean duration of the sustained voluntary contraction was 33 ± 23 min (range: 13–91 min). An increase in $\text{RMS}_{10\% \text{MVC}}$ was observed during the sustained low-intensity contraction for VL, VM and RF, as reported by a significant time effect ($p < 0.001$; $\eta^2 = 0.66$; Figure 3D). $\text{RMS}_{10\% \text{MVC}}$ recorded during the sustained low-intensity contraction was significantly increased from 30%_{TTF} and onward when compared to the first 10% of the task ($p = 0.001$ – 0.0001). The increase in $\text{RMS}_{10\% \text{MVC}}$ plateaued at 60%_{TTF} (i.e. the plateau was determined when the time point, in this specific case 60%_{TTF}, was not statistically different with the value recorded at TF).

MVC and central fatigue

A significant time effect was found for MVC ($p < 0.001$; $\eta^2 = 0.82$; Figure 3A). At TF, MVC was decreased by $49.2 \pm 17.1\%$ when compared to PRE. While MVC recorded at 10%_{TTF} was not different compared to baseline ($p = 0.97$), the decrease was found to be significant from 20%_{TTF} ($p < 0.001$). While MVC “visually” decreased up to 80%_{TTF}, values recorded from 50%_{TTF} were not statistically different from TF ($p = 0.49$ – 1).

The force decrease was accompanied by a decrease in VA_{TMS} as indicated by a significant time effect ($p < 0.001$; $\eta^2 = 0.60$; Figure 3B). At TF, VA_{TMS} was decreased by $20.8 \pm 18.1\%$. The decrease in VA_{TMS} was significant from 40%_{TTF} ($p = 0.04$) when compared to baseline. While VA_{TMS} seems to “visually” decrease until 90%_{TTF} before plateauing, there was no statistical difference between VA_{TMS} values from 40%_{TTF} and TF (e.g. $p = 0.07$ between 40%_{TTF} and TF). Yet, VA_{TMS} was lower at 90%_{TTF} than 40%_{TTF} ($p = 0.02$). The relationship between MVC drop and VA_{TMS} changes across exercise showed a strong and significant linear regression ($r = 0.97$; $p < 0.001$).

While there was no significant muscle \times time interaction for normalized RMS_{MAX} ($p = 0.55$; $\eta^2 = 0.09$), a significant time effect was reported ($p < 0.001$; $\eta^2 = 0.49$). At TF, the mean decrease in RMS_{MAX} was $35.3 \pm 25.9\%$ (pooled data for the three muscles). When compared to baseline and regardless of the investigated muscle, post-hoc analysis revealed a significant decrease in normalized RMS_{MAX} from 40%_{TTF} ($p = 0.03$ – 0.0001 ; Figure 3C).

Corticospinal excitability and inhibition

There was no significant muscle \times time interaction for any TMS-induced EMG parameters. A significant time effect was reported for MEP areas recorded during 75% ($p < 0.0021$; $\eta^2 = 0.34$) and 50% ($p < 0.001$; $\eta^2 = 0.50$) but not 100% ($p = 0.87$; $\eta^2 = 0.06$) MVC. When compared to baseline and regardless of the investigated muscle, post-hoc analysis revealed a significant decrease in MEP₇₅ and MEP₅₀ from 20%_{TF} ($p = 0.001$ – 0.0001 ; Figure 4A).

A significant time effect was also reported for SP recorded during MVC ($p < 0.001$; $\eta^2 = 0.62$), 75% MVC ($p < 0.001$; $\eta^2 = 0.59$) and 50% MVC ($p < 0.001$; $\eta^2 = 0.58$). When compared to baseline and regardless the investigated muscle, post-hoc analysis revealed a significant increase in SP duration from 20%_{TF} for MVC, 75% MVC and 50% MVC _{TF} ($p = 0.04$ – 0.0001 ; Figure 4B).

Rating of perceived exertion. A significant time effect was reported for RPE ($p < 0.001$; $\eta^2 = 0.92$) with an increase throughout the sustained exercise. When compared to the value recorded immediately after the beginning of the task, RPE increased almost linearly from 10%_{TF} (all $p < 0.001$; Figure 5).

Peripheral function. At TF, Pt, Db100 and Db10:100 were reduced by $34 \pm 10\%$ ($p < 0.001$; $\eta^2 = 0.82$), $19 \pm 7\%$ ($p < 0.001$; $\eta^2 = 0.72$), and $35 \pm 8\%$ ($p < 0.001$; $\eta^2 = 0.90$), respectively, when compared to PRE (Figure 6A). M_{sup} was not altered during the fatiguing exercise and at TF as reported by the non-significant time effect ($p = 0.16$; $\eta^2 = 0.13$) or muscle \times time interaction ($p = 0.88$; $\eta^2 = 0.06$; Figure 6B).

DISCUSSION

The present study investigated for the first time the time course of fatigue appearance during sustained low-intensity knee extensors contraction performed until TF. Our results showed a progressive decline in MVC up to 50%_{TF}, together with an increase in central fatigue as evidenced by the decline in VA_{TMS} up to 90%_{TF}. Changes in corticospinal excitability (i.e. MEP area) and inhibition (i.e. SP duration) do not seem to have a major influence on central fatigue as they plateaued early during exercise. Performance limitation is thought to be due to the subjects' perceived effort that was nearly maximal at TF.

Gradual decrease of maximal force generating capacity

A large variability was reported in the time to TF (TTF) in the present study (i.e. mean duration of 33 ± 23 min; range: 13–91 min). This variability cannot be explained by differences in the level of physical activity since only subjects with regular physical activity ranging between 2 and 6 hours were included. Differences in genetics, in training experience and in the nature of the activities performed by the subjects (e.g. resistance training vs endurance training) may explain the variability in TTF. Another explanation for this variability in TTF could be inter-subjects' differences in critical torque, i.e. the maximal sustainable work rate at which energy supply can be provided and sustained from oxidative metabolism.¹⁶ Such differences in critical torque (thus in TTF) could rely on several mechanisms, e.g. fiber type composition, muscle capillarity.¹⁶ The fact that subjects performed brief MVC every 3 min during the sustained low-intensity contraction could have influenced the development of fatigue. While this has been discussed by others that used similar protocols,^{3,4} our experimental design does not allow to draw any conclusion on this point. To shed light on this issue, future studies should compare fatiguing tasks with and without frequent MVCs performed during low-intensity contractions. Fatigue produced by the sustained submaximal knee extension was revealed by a ~50% decline in MVC at TF. Several studies have investigated fatigue immediately (i.e. without any resting period between TF and the last measurements) after a sustained submaximal contraction of the knee extensors performed up to TF.¹⁷⁻²⁰ They reported a decreased MVC of ~30%,¹⁸ ~35%^{17,20} and ~50%¹⁹ after sustained isometric contractions between 10–50% MVC. The greater fatigue level in the present study may be explained by the longer task duration in our study, i.e. mean duration of 33 min vs 2–14 min in the aforementioned studies. It has been demonstrated for the first dorsal interosseous that the lower the contraction intensity, the longer the task duration and the greater the amount of fatigue.² While already reported during long-duration cycling²¹ or running²² exercises, the plateau observed in MVC decline (i.e. MVC progressively decreased up to 50%_{TTF} with no more significant decline thereafter) is an original and interesting result when a sustained submaximal modality of exercise is used. The mechanisms behind such a plateau are not clear and warrant further investigations.

Changes in voluntary activation, corticospinal excitability and inhibition

To further explain the decrease observed during brief MVCs, the present study investigated for the first time the time course of central fatigue appearance on knee extensors using TMS during a sustained isometric very low-intensity contraction. VA_{TMS} decreased from 40% T_{TF} to reach a decrease of ~21% at TF (i.e. 96% vs 76% at PRE and POST, respectively). Similar results were reported in elbow flexors, with decrease of ~15%³ and ~22%⁴ observed at the end of sustained prolonged isometric contractions performed at 5% and 15% MVC, respectively. However, while these two studies performed on the elbow flexors are the only ones that investigated VA_{TMS} during prolonged and sustained isometric contraction, one should note that exercise duration was fixed (i.e. 70 min³ and 43 min⁴) while exercise was performed until failure in our study, limiting the comparison between results. Statistically, the decrease in VA_{TMS} plateaued (i.e. absence of significant differences with TF) at 40% T_{TF} . Yet, one should note that the decrease in VA_{TMS} was significant between 40% T_{TF} ($86 \pm 8\%$) and 90% T_{TF} ($75 \pm 11\%$), suggesting that the plateau occurred far after 40% T_{TF} . Interestingly, this plateau does not seem to occur in a similar-designed study involving the elbow flexors.³ As reported after a 2-min sustained MVC,⁹ additional work could be useful to investigate if central modulations differ between upper and lower limb muscles when a sustained low-intensity contraction is used.

As previously demonstrated for knee extensors,^{9,10} the relationship between force and VA_{TMS} remained linear with fatigue in our study. Thus, it was possible to estimate the contribution of central fatigue to the total force loss. For each subject, the linear force– VA_{TMS} relationship was determined immediately after TF^{3,9,10} as well as at each time points of the T_{TF} . Using the regression equation, the force corresponding to VA_{TMS} recorded at PRE was determined and compared with the real MVC recorded at every time points between 10% T_{TF} and TF included. Any additional force loss was interpreted to be due to central fatigue. As previously reported in some upper-³ and lower-limb¹⁰ muscles exercise, the contribution of central fatigue to the total force loss gradually increased throughout the sustained exercise, accounting for approximately 18, 22, 28, 33 and 38% of the total force loss at 20% T_{TF} , 40% T_{TF} , 60% T_{TF} , 80% T_{TF} and TF, respectively.

The sustained 10% MVC induced a lengthening in SP early during exercise, i.e. from 20% T_{TF} for SP recorded during both maximal and submaximal contractions. SP duration increases has widely been reported after sustained maximal^{9,14,23} and submaximal²⁴ voluntary contractions of various muscular groups. Because the initial

part of SP reflects both an inhibition of descending drive and reduced excitability of the motoneurons, while the latter part reflects intracortical inhibition-related processes, we believe that the increased SP duration reported in this study reflects increased intracortical inhibition. While subjects were instructed to contract as quickly as possible after the TMS, one should note that the aim was to reach a lower force level (i.e. after the MVC, subjects were asked to re-contract at 75% MVC, and after the 75% MVC subjects were asked to re-contract at 50% MVC; Figure 2). This could have influenced the results, likely causing longer SP duration. Further studies should investigate at which degree these experimental considerations could bias the SP-related results. Moreover, while no changes were reported in MEP_{MVC} during or at TF, agreeing with results obtained on elbow flexors during similar fatiguing exercises,^{3,4} we reported decreased MEP during the task when evoked during submaximal voluntary contractions at 75 and 50% MVC. Interestingly, this decreased corticospinal excitability was observed as soon as 20%_{TF} and then plateaued until TF. Such results, however, do not agree with previous studies on elbow flexors that reported increased corticospinal excitability when recorded during the low-intensity fatiguing contraction level (i.e. 5%³ and 15%⁴ MVC).^{3,4} The decrease in MEP recorded during contractions at 75% and 50% MVC may rely on the fact that RMS EMG was decreased during the exercise at these submaximal level of contractions (data not shown). While RMS_{MAX} was also decreased during the exercise, the fact that less motoneurons are in the refractory period during MVC could be a speculative explanation for why MEP recorded during MVC remained unchanged during the exercise and at TF. By combining TMS with corticospinal tract stimulation at the thoracic level, recent studies demonstrated that motoneuron excitability was quickly diminished (before plateauing) during sustained isometric knee extension performed at 25%²⁵ and 50%²⁶ of the RMS EMG associated with 25% and 50% MVC, respectively. Although not directly investigated in this study, the spinal contribution to the overall fatigue cannot be ruled out. The influence of spinal mechanisms on fatigue could relate on complex mechanisms occurring at both pre- and post-synaptic levels. Similar experimental designs along with the use of specific neurostimulation techniques²⁷ could allow to gain knowledge on the mechanisms of impaired spinal motoneuron excitability induced by this form of low-intensity prolonged exercises. Further studies should also investigate the origin of such force-dependent corticospinal excitability modulation with fatigue.

The repetitive activity within the motor pathway during the fatiguing exercise could be responsible for SP- and MEP-related changes,²⁸ leading to a decrease in the excitability of the corticospinal pathway (except during MVC when considering MEP-related data) that plateaued as early as at 20%_{TTF}, suggesting that this cannot explain the VA_{TMS} decrease up to 90%_{TTF}. The action of III and IV muscle afferents at the supraspinal level is known to greatly contribute to the decrease of VA_{TMS}.^{4,23,28} This is especially true in lower limb compared with upper limb muscles.⁹ The possible activation of such afferents in response to the increased metabolites concentration due to fatigue likely reduced VA_{TMS} without impacting MEP and SP after 20%_{TTF}. Firing of fatigue-sensitive muscle afferents likely exerted its effects upstream of the motor cortex explaining why VA_{TMS} was impaired up to 90%_{TTF} while MEP and SP were not. Such an hypothesis relies on results supporting that VA was still altered when a muscle was held ischemic after a fatiguing exercise (thus maintaining firing of group III and IV afferents), while changes in MEP and SP induced by the fatiguing exercise recovered.²³ Yet, explaining the present decrease in VA_{TMS} by the influence of group III and IV afferents remains speculative in the context of the present study.

The role of peripheral fatigue in MVC force loss

As shown above, central fatigue was found to contribute to almost 40% of force loss at TF, meaning that peripheral mechanisms contributed even more to the decline in force, what agrees with previous findings.¹⁹ However, since the present study was designed to better understand the central component of fatigue, peripheral fatigue was not assessed during the sustained and prolonged exercise for methodological reasons, i.e. Pt were not assessed during the task to avoid short resting periods that may have impacted central mechanisms.¹⁴ The presence of peripheral fatigue was evidenced by the decrease in Pt (-34%) and Db100 (-19%) at TF. Db10:100 also decreased at TF (-35%), suggesting the presence of low-frequency fatigue generally associated with an excitation-contraction coupling failure²⁹. The increase in the EMG required to maintain the submaximal target force overtime before TF suggests that increased temporal and/or spatial recruitment of motor units was necessary to maintain the target force when muscle fibers became fatigued.^{3,4} The absence of changes in M_{sup} areas, as already reported after a similar fatiguing protocol,¹⁹ suggests that phenomenon prior to the mechanisms that characterized excitation-contraction coupling are likely to be

preserved during such a fatiguing exercise (at least when assessed at 50% MVC as it was the case here).

Origin of TF

As reported in the previous sections, we observed that maximal force and central drive were both decreased throughout the first 50 and 90% of the prolonged submaximal fatiguing task, respectively, before plateauing. This suggests that the level of fatigue was not critical (i.e. subjects were able to sustain the contraction despite a plateau in central fatigue) when reaching TF. Rather, the moment of TF may rely on the fact that subjects perceived exertion near exhaustion. While it would have been difficult to expect a 90% decline in MVC in this study, even if it was asked to the subject to maintain a sustained 10% MVC until TF, one could have expected to record a larger decline in MVC than the one reported in the present study, i.e. ~50%. Our results are in line with a previous study reporting a 50% decrease in MVC at the end of a protocol that consisted in a sustained 20% MVC knee extension until TF.¹⁹ The first explanation could have been a substantial and rapid recovery of the neuromuscular system that could have allowed the capacity of the neuromuscular system to produce force to increase from ~52 N (i.e. which corresponds to the 10% MVC averaged for all subjects) to ~260 N (i.e. the mean MVC recorded at TF for all subjects). This explanation must be disregarded in this study since subjects were not permitted to relax and performed the MVC immediately upon reaching task failure. Second, one could consider a psychological explanation for this result. Indeed, there exists an effect of expected test duration on effort mobilization. In other words, subjects knew that the last MVC performed at TF would last only ~3 s, and such awareness likely motivated them to produce higher effort at TF compared to the sustained effort which had a longer and unknown duration.³⁰ As reported for dynamic exercises (e.g. Marcora et al.³⁰), our results go against the long-standing assumption that neuromuscular fatigue causes exercise failure during low-intensity prolonged exercise (although still being a large component). Then, while neuromuscular fatigue does not seem to limit exercise tolerance in this study, our results are in favor of the psychobiological model of exercise tolerance. The perception of effort, that was near to maximal at TF (9.8 ± 0.4 out of 10), was likely the “exercise terminator”. At some point, the central nervous system likely regulated skeletal muscle motor unit recruitment to maintain the required force

level,³¹ and increased motor unit recruitment and/or rate coding that should have been necessary to prolong the task was likely prevented by the fact that RPE was nearly at its maximal level.³² Then, the fact that subjects decided to prematurely stop the exercise due to high RPE could have prevented the recruitment of high threshold motoneurons, explaining why MVC at TF was far from the target force level, i.e. non-fatigued high-threshold motor units that were not recruited during the exercise allowed the subject to reach a high MVC. It is worth noting that even in the context of fatigue, higher-threshold motoneurons are further unlikely to be recruited during a low-intensity sustained contraction as performed in the present study. Our results strengthen the role of the brain in determining the end of the exercise,³³ including motivation-related mechanisms that could involve alterations in neurotransmitter function for instance.³⁴ Although not investigated in this study, the high RPE values could indicate the presence of mental fatigue, both variables being related and having an important influence on muscle endurance performance.³⁵ Indeed, it has been stated that prolonged and sustained exercise could include a cognitive demand such as a sustained attention to maintain the target force level in the context of low-intensity sustained contraction with force feedback.³⁶ This cognitive demand could have led to mental fatigue that increased RPE and decreased performance. While the influence of III and IV afferents on RPE has been largely suggested, other mechanisms than the sole information from these afferents may have influenced the intensity of perceived exertion such as corollary discharge associated with central motor command.³⁷ Yet, $RMS_{10\%MVC}$ plateaued during the submaximal sustained contraction, which does not support an increased central drive up to TF, contrary to one of the aforementioned argument. It is, however, conceivable that motoneuron excitability decreased during the task so reducing efficacy of descending drive to excite motoneurons, and greater descending drive would then be required to maintain motoneuron output.²⁵ Nonetheless, the plateau in $RMS_{10\%MVC}$ (Figure 3D) highlights the fact that the end of the exercise occurred way before a complete motor unit recruitment and/or a maximal motoneuron firing rates, influenced by mechanisms located within the central nervous system.¹⁹ For instance, $RMS_{10\%MVC}$ remained considerably lower than RMS_{MAX} (Figure 3C) throughout the fatigue task and this was still the case at TF. Although mechanisms related to amplitude cancellation might be involved,³⁸ these observations corroborate the aforementioned hypothesis of a prevention of additional motor unit recruitment

and/or increased discharge rate, likely because the subjects were reaching maximal RPE.

In conclusion, the current work is the first investigating the role of central indices in locomotor muscles performance during a very low intensity contraction sustained to TF. The present results show that task failure is not associated with a critical amount of central fatigue. We postulate that TF occurred in this study as a form of task disengagement and that exercise tolerance was ultimately limited by perception of effort (as reported in this study by the fact that subjects perceived exertion of near exhaustion).

PERSPECTIVES

We demonstrated that TF likely occurs when the required submaximal effort exceeds the limit of what subjects are willing to do, i.e. potential motivation.³⁵ The present results, that could also be true for long duration whole-body exercises such as cycling²¹ or running,²² strengthen the role that psychophysiological interventions may have in endurance performance. For instance, the use of mental strategies (e.g. motivational self-talk) may specifically target favorable changes in perception of exertion then enhancing endurance performance. We could first question if the increase in TTF duration reported during dynamic exercise when self-talk strategies are used³⁹ is also applicable to a sustained and submaximal modality of isometric exercise.

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Figures caption:

Figure 1. Experimental design of the study. Each subject performed a single session with neuromuscular evaluation (NME) performed before (PRE) and at task failure (TF) of the fatiguing protocol that consisted in a sustained submaximal voluntary contraction at 10% MVC until TF. NME (without the stimulations on the relaxed muscles) were also performed every 3 min during the time to exhaustion. Transcranial magnetic stimulations are represented by white arrows. Peripheral nerve stimulations are represented by single (single stimulation), double (double stimulations at 100 Hz) and double dotted black arrows (double stimulations at 10 Hz).

Figure 2. A: Typical force trace and EMG recordings for the vastus lateralis muscle before the fatiguing task. The bottom part of the panel A shows EMG background and the MEP and SP evoked during maximal (MVC) and submaximal voluntary contractions at 75% and 50% MVC and followed by the M-wave evoked at 50% MVC. Open arrows represent TMS and filled arrows represents PNS. The grey box represents the silent period duration, i.e. the time interval between TMS stimulus and the return of continuous voluntary EMG. B: Raw traces of the TMS superimposed twitches (SIT) evoked during MVC and submaximal contractions at 75% and 50% MVC. C: amplitude of SIT produced by TMS during maximal (white square) and submaximal contractions at 75% (white circle) 50% MVC (white triangle). The linear regression was extrapolated, and the y-intercept (dashed line) was interpreted as the ERT amplitude. Data are from a representative subject.

Figure 3. Changes in knee extensors maximal voluntary contraction (MVC) isometric force (A), voluntary activation (VA_{TMS} ; B) and maximal root mean square EMG (RMS_{MAX} ; C) during (10, 20, 30, 40, 50, 60, 70, 80, 90% of the time to task failure) and immediately at task failure (TF, performed as an extension of the prolonged submaximal voluntary contraction). Panel D displays the root mean square EMG recorded 500 ms before the brief MVCs during the sustained submaximal voluntary contraction. Data are presented as mean \pm SD. Significantly different from PRE: * $p < 0.05$. Significantly different from TF: # $p < 0.05$.

Figure 4. Changes in motor evoked potential (MEP; A) and silent period (SP; B) during (10, 20, 30, 40, 50, 60, 70, 80, 90% of the time to task failure) and immediately at task failure (TF, performed as an extension of the prolonged submaximal voluntary contraction). MEP and SP were recorded during maximal (MEP_{MVC} and SP_{MVC} , respectively) and submaximal voluntary contractions at 75 (MEP_{75} and SP_{75}) and 50%MVC (MEP_{50} and SP_{50}). Data are presented as mean \pm SD. Significantly different from PRE: * $p < 0.05$. Significantly different from TF: # $p < 0.05$.

Figure 5. Ratings of perceived exertion (RPE) recorded immediately after the beginning of the prolonged submaximal voluntary contraction (Start), during (10, 20, 30, 40, 50, 60, 70, 80, 90% of the time to task failure) and immediately at task failure (TF, performed as an extension of the prolonged submaximal voluntary contraction). Data are presented as mean \pm SD. Significantly different from Start: * $p < 0.05$. Significantly different from TF: # $p < 0.05$.

Figure 6. *Panel A* displays the electrically evoked force-related results with the amplitude of the potentiated peak twitch (Pt), potentiated peak doublet evoked at 100 Hz (Db100) and ratio between amplitude of the potentiated peak doublet evoked at 10 and 100 Hz (DB10:100). Pt, Db100 and Db10:100 were recorded before (PRE) the fatiguing contraction and immediately at task failure (TF). *Panel B* displays the results for M-waves recorded during 50%MVC (Msup) on vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM) muscles. Msup were recorded before (PRE), during (10, 20, 30, 40, 50, 60, 70, 80, 90% of the time to task failure) and immediately at task failure (TF, performed as an extension of the prolonged submaximal voluntary contraction). Data are presented as mean \pm SD. Significantly different from PRE: * $p < 0.05$.

Figure 1

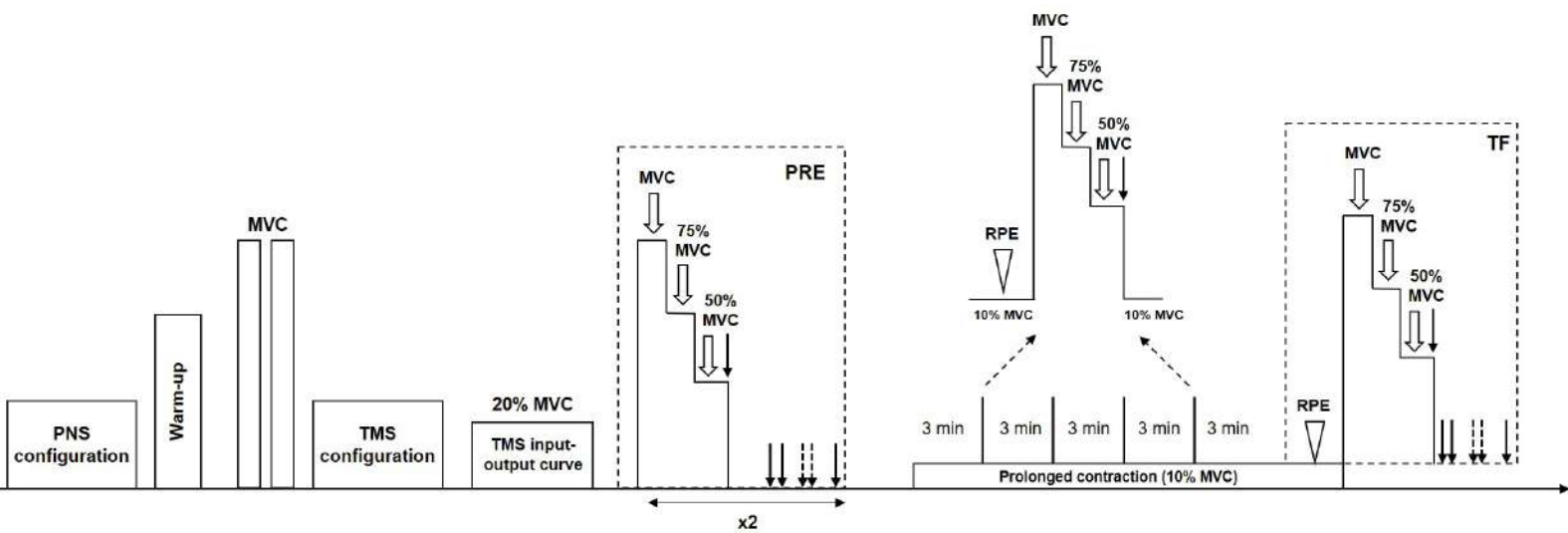


Figure 2

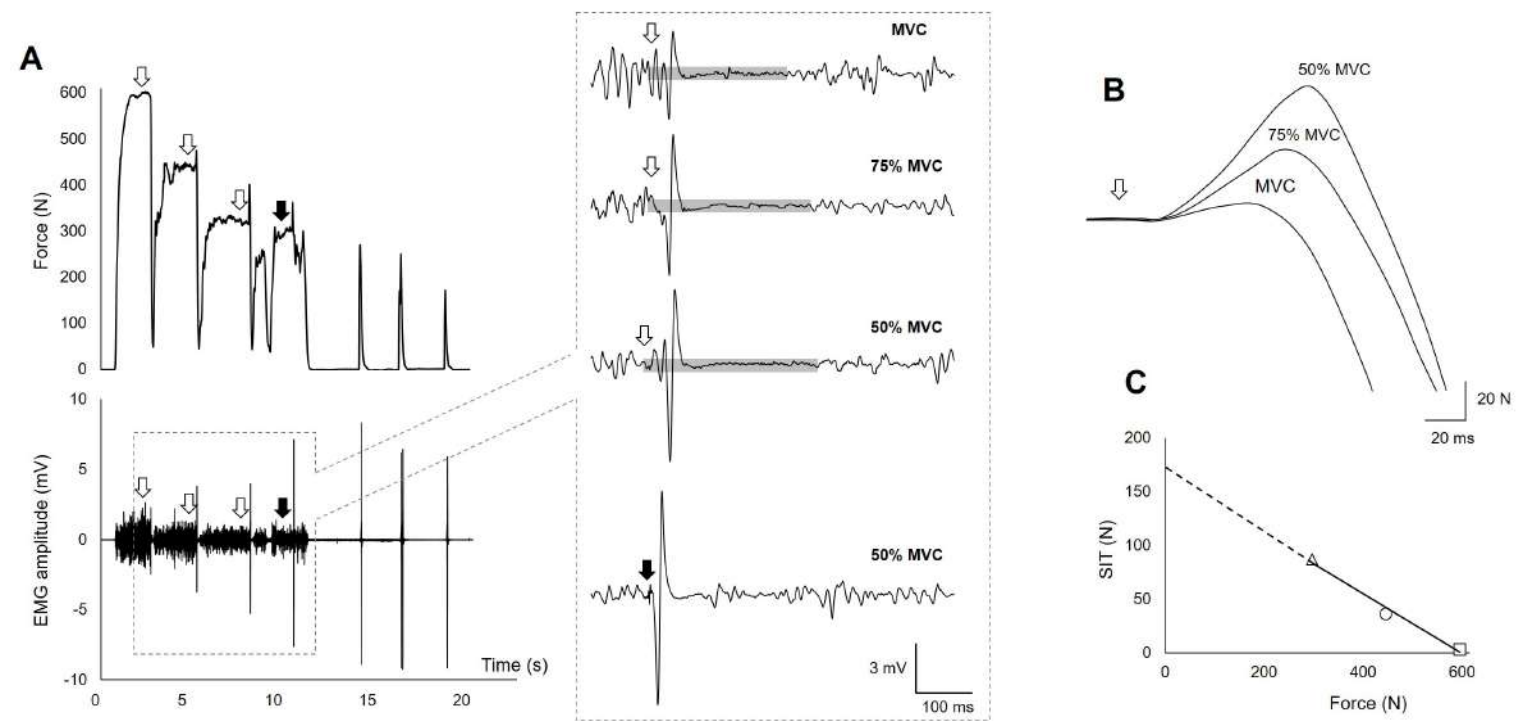


Figure 3

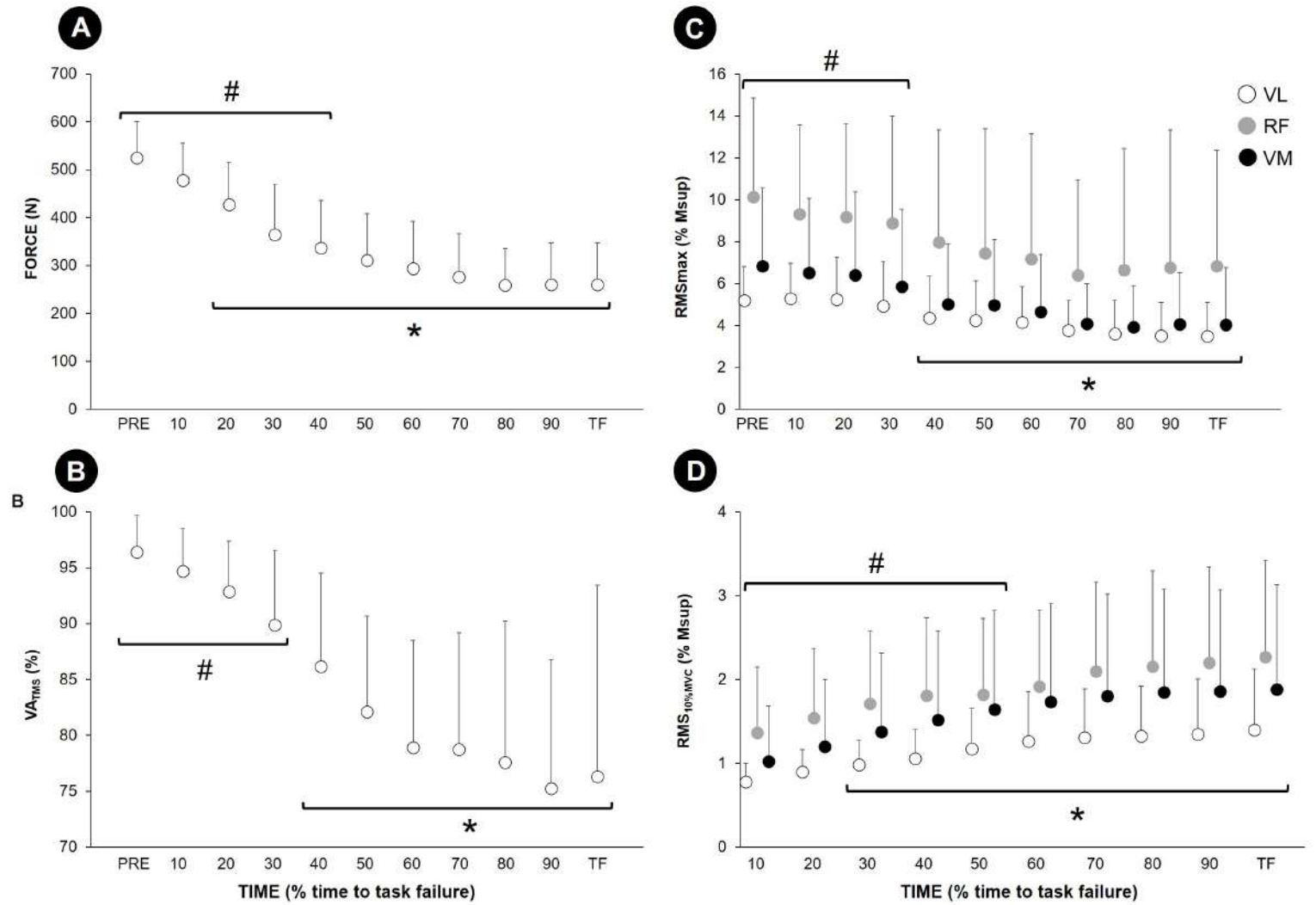


Figure 4

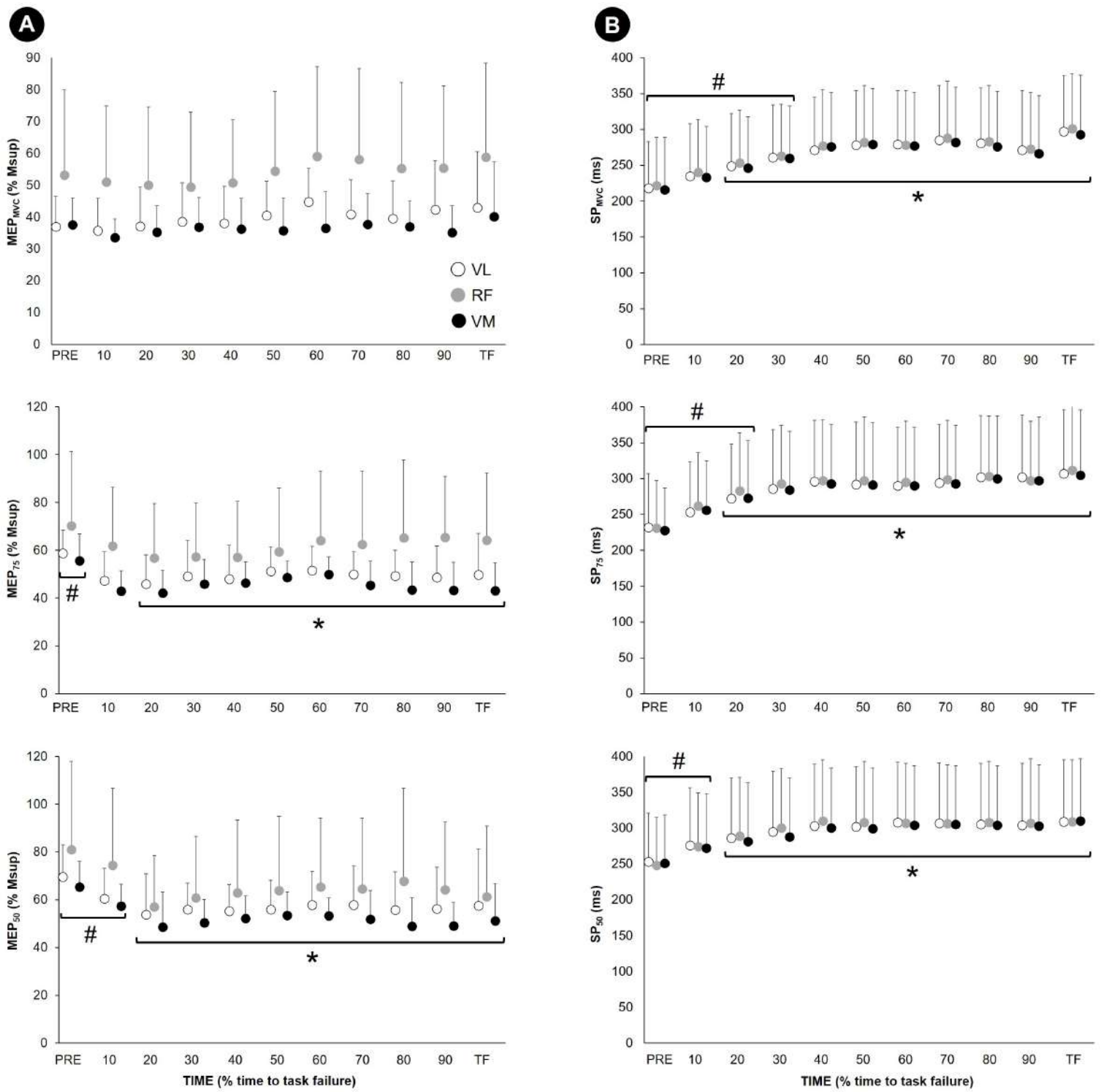


Figure 5

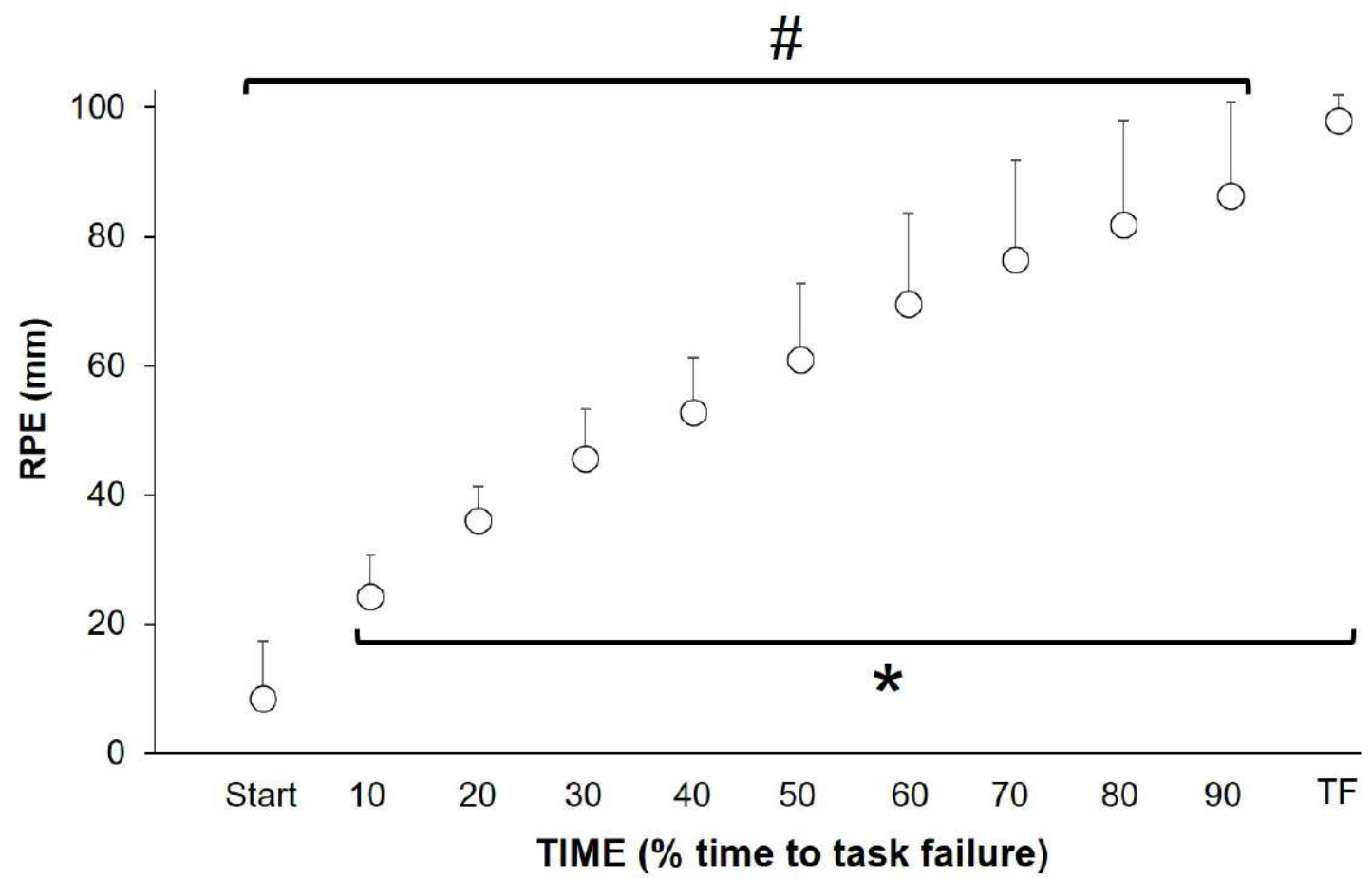


Figure 6

