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Research Paper

Voluntary muscle and motor cortical activation during progressive exercise and passively induced hyperthermia

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New findings

- **What is the central question of this study?**
  We examined whether passive hyperthermia exacerbates central fatigue due to an increase in peak muscle relaxation rate, and whether exercise-induced hyperthermia attenuates this response because of a reduction in contractile speed related to peripheral fatigue.
- **What is the main finding and its importance?**
  Exercise and passive hyperthermia increase muscle relaxation rate. An increase from moderate to severe passive hyperthermia enhances this rate, but without exacerbating force loss or voluntary muscle and cortical activation, relative to exercise. The centrally mediated rate of activation appears sufficient to overcome the increase in peak muscle relaxation.

This study examined whether central fatigue was exacerbated by an increase in muscle contractile speed caused by passive hyperthermia (PaH) and whether exercise-induced hyperthermia (ExH) combined with related peripheral fatigue influenced this response. The ExH was induced by cycling at 60% of maximal oxygen uptake in 38°C conditions and the PaH by sitting in a 48°C climate chamber. Ten men performed brief (∼5 s) and sustained (30 s) maximal voluntary isometric contractions (MVCs) of the knee extensors at baseline (CON, ∼37.1°C) and during moderate (MOD, ∼38.5°C) and severe (SEV, ∼39.5°C) hyperthermia. Motor nerve and transcranial magnetic stimulation were used to assess voluntary muscle and cortical activation level, along with contractile properties. Brief MVC force decreased to a similar extent during SEV-ExH (−8%) and SEV-PaH (−6%; $P < 0.05$ *versus* CON). Sustained MVC force also decreased during MOD-ExH (−10%), SEV-ExH (−13%) and SEV-PaH (−7%; $P < 0.01$ *versus* CON). Motor nerve and cortical activation were reduced on reaching MOD (∼3%) and SEV (∼5%) ExH and PaH during the brief and sustained MVCs ($P < 0.01$ *versus* CON). Peak twitch force decreased on reaching SEV-ExH and SEV-PaH ($P < 0.05$ *versus* CON). Following transcranial magnetic stimulation, during the brief and sustained MVCs the peak muscle relaxation rate increased in ExH and PaH ($P < 0.01$ *versus* CON). The increase was greatest during the sustained contraction in SEV-PaH ($P < 0.01$), but this did not exacerbate central fatigue relative to ExH. These results indicate that during fatiguing cycling exercise in the heat, quadriceps peak relaxation rate increases. However, the centrally mediated rate of activation appears sufficient to overcome even the largest increase in muscle relaxation rate, seen during SEV-PaH.

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Experimental Physiology

Introduction

Moderate increments in body core and especially muscle temperature are known to improve contractile rate processes (e.g. substrate flux; Bennett, 1984; Fitts, 1994; Allen *et al.* 2008) and shorten the muscle twitch response (i.e. reduce time to peak force and half-relaxation time; Davies & Young, 1983; De Ruiter & De Haan, 2000). These temperature-induced adjustments contribute to enhanced performance in activities that require brief explosive muscle contractions, such as jumping and sprinting (Racinais *et al.* 2010). In contrast, large increments in core temperature (>39.0°C) have been associated with impaired aerobic performance and increased development of fatigue during sustained (≥10 s) maximal voluntary isometric contractions (MVCs; Nybo & Nielsen, 2001; Périard *et al.* 2011*b*). This exacerbated force loss has previously been attributed to a progressive hyperthermia-induced reduction in central drive to the exercising muscle, leading to its incomplete activation (i.e. central fatigue; Nybo & Nielsen, 2001; Morrison *et al.* 2004; Thomas *et al.* 2006), typically evaluated via twitch interpolation using motor nerve stimulation (MNS). More recently, however, it was demonstrated that the reduction in force-generating capacity following passive and exercise-induced hyperthermia is modulated by both central and peripheral fatigue components (Périard *et al.* 2011*a*). Indeed, central fatigue accounted for a similar fraction of the loss in force, but the rate of decline was greater following exercise (Périard *et al.* 2011*a*). This is likely to be due to adjustments originating beyond the neuromuscular junction in response to prolonged contractile activity (i.e. peripheral fatigue).

Likewise, Todd *et al.* (2005) demonstrated decrements in voluntary torque and cortical activation using transcranial magnetic stimulation (TMS) during a sustained (120 s) MVC following passive hyperthermia (38.5°C). They reported that peak muscle relaxation rate measured during the silent period in response to TMS was ∼20% faster during hyperthermia, compared with normothermia. This led to the suggestion that the additional central fatigue observed during sustained contractions in hyperthermia may be indicative of a failure of descending drive (i.e. insufficient motor unit firing rate) to compensate for the faster relaxation rate. Conversely, during brief MVCs it was proposed that motor unit firing rates could be transiently increased, thus compensating for the hyperthermic increase in contractile speed. This observation was supported by an uncompromised cortical voluntary activation during these brief contractions (Todd *et al.* 2005). However, it raises an interesting question as to the mechanism of failure within hot muscles, because the modified contractile condition may exceed the centrally mediated rate of activation during sustained contractions (Thompson, 2006). In contrast, muscle fatigue originating from repeated contractile activity is known to reduce relaxation rate (Fitts, 1994; Allen *et al.* 2008). As such, the development of skeletal muscle fatigue during exercise should offset the potential increase in central fatigue stemming from a hyperthermia-induced enhancement of contractile function.

Therefore, this study sought to verify the hypotheses that a passive increase in whole-body temperature exacerbates the development of central fatigue due to an increase in peak muscle relaxation rate and that exercise-induced hyperthermia attenuates this response due to the development of peripheral fatigue (i.e. a reduction in contractile speed).

Methods

Subjects

Ten recreationally active male volunteers participated in this study. The subject characteristics were as follows (means ± SD): age, 34.1 ± 7.9 years; body mass, 80.1 ± 13.5 kg; height, 181.0 ± 8.0 cm; and maximal oxygen uptake ($\dot{V}_{O_2\,max}$), 4.4 ± 0.6 l min^{-1}. Subjects were fully informed of the experimental procedures and potential risks prior to giving written informed consent. They were also required to complete a Medical History Questionnaire and Physical Activity Readiness Questionnaire (PAR-Q) before being admitted to the study. The protocol was approved by the Shafallah Medical Genetics Centre Ethics Committee. All procedures conformed to the standards of the Declaration of Helsinki. Subjects participated in three sessions, i.e. a pre-experimental session and two counterbalanced experimental sessions.

Pre-experimental session

This familiarization session commenced with the determination of height and body mass measured using a precision stadiometer and balance scales (Seca 769, Hamburg, Germany). Skin-fold thickness over the site of muscle temperature measurement (on the right vastus lateralis) was also measured. The $\dot{V}_{O_2\,max}$ was then determined on an electronically braked cycle ergometer (Excalibur Sport, Lode, The Netherlands) using an online breath-by-breath cardiopulmonary system (Quark b2; Cosmed, Rome, Italy). The protocol consisted of cycling for 5 min at four submaximal power outputs (100, 130, 160 and 190 W) followed by an increase in power output (25 W min^{-1}) until volitional fatigue. The power output corresponding to 60% $\dot{V}_{O_2\,max}$ was calculated from the $\dot{V}_{O_2}$–power output relationship. This intensity of exercise was chosen to induce hyperthermia while eliciting fatigue at the skeletal muscle level (Nybo & Nielsen, 2001; Périard *et al.* 2011*a*). The environmental conditions were set to 20–22°C and ∼50% relative

humidity (RH), with a wind speed of 12.5 km h^{-1}. Saddle and handlebar position were adjusted by the subject to their preferred cycling position and replicated during the exercise-induced hyperthermia trial. After the $\dot{V}_{O_2\,max}$ test, the subjects performed a series of isometric knee-extensor contractions until they felt accustomed to the equipment and were capable of reproducing an MVC with a stable plateau. They were then thoroughly familiarized with MNS and TMS in order to establish the maximal and estimated twitches, muscle compound action potential (M-wave) and motor evoked potential (MEP) stimulus intensities (see '*Stimulation*' section below). A coefficient of variation in three successive contractions of <5% constituted familiarization for each phase of the neuromuscular function protocol.

Experimental session

Subjects arrived at the laboratory at the same time of day on two occasions separated by 3–5 days. On arrival (∼60 min prior to testing) they emptied their bladder and provided a urine sample for the measurement of urine osmolality (Osmocheck, Pal-Osmo; Vitech Scientific Ltd, Horsham, UK). They were then weighed before changing into sporting attire and inserting a rectal thermistor probe (MRB rectal probe; Ellab, Hilleroed, Denmark). Subjects then rested in the seated position in temperate (20–22°C, 50% RH) conditions while being instrumented with muscle and skin temperature sensors. After this time, each subject moved to a custom-built adjustable chair to perform the neuromuscular function protocol (see '*Neuromuscular function*' section below). A standardized warm-up was carried out, which consisted of 10 isometric knee extensions of 4 s in duration, interspaced with ∼10 s of recovery. Contraction intensity was progressively self-adjusted by the subject to attain 100% MVC in the last three contractions. Neuromuscular function was then assessed at baseline/control core temperature (CON) before moving into the climate chamber (Tescor, Warminster, PA, USA). Once in the chamber, subjects undertook one of two experimental trials to induce exercise-induced hyperthermia (ExH) and passive hyperthermia (PaH). Exercise-induced hyperthermia was induced by cycling at 60% $\dot{V}_{O_2\,max}$ in conditions of 38°C and 45% RH, with an airflow of 12.5 km h^{-1}. Passive hyperthermia was induced by sitting upright in conditions of 48°C and 45% RH. Neuromuscular function during each intervention was assessed during moderate (MOD) and severe (SEV) hyperthermia, characterized by rectal temperatures of 38.5 and 39.5°C, respectively. During the ExH trial, subjects were moved from the ergometer to the custom-built chair to perform the neuromuscular function assessment protocol. Once the protocol was completed, they remounted the ergometer and resumed cycling. In the PaH trial, the subjects were moved between being seated upright to the custom-built neuromuscular function assessment chair. The environmental conditions during the assessment were standardized to 44°C and 45% RH by increasing (for ExH) or decreasing room temperature (for PaH) for the duration of testing (∼5 min). Subjects also received facial fanning (7.5 km h^{-1}) during the assessment. During all tests, subjects wore shorts and socks. Shoes were removed during the contractions.

Neuromuscular function

The neuromuscular function assessment protocol is illustrated in Fig. 1. It was initiated by a brief (∼5 s) MVC, on which an evoked doublet at 100 Hz and a single twitch (1 Hz) were superimposed via MNS. A doublet was then evoked on the relaxed muscle and followed by three single twitches. After a 60 s rest period, brief contractions were performed at 75 and 50% MVC, with TMS and MNS manually delivered at ∼2 s intervals once a force plateau was established. The target force levels were calculated from the preceding MVC, and the force to attain was displayed on a computer monitor. A brief MVC on which TMS was superimposed then followed. This sequence (75–50% MVC) was performed twice. After the second sequence, subjects rested for 60 s and then executed a 30 s MVC. The length of contraction was chosen based on the repeated nature of the protocol and in consideration that after 30 s, pain becomes increasingly severe during a sustained MVC, which alters perceived sensations from the active musculature and leads to uncertainty regarding the level of force being exerted (Bigland-Ritchie *et al.* 1978). The TMS and MNS (doublet) were delivered at the onset (2 s), middle (15 s) and the end (28 s) of the sustained MVC. A doublet was also evoked 5 s after the end of the sustained MVC. During all MVCs, subjects were verbally encouraged to sustain maximal force. To enhance motivation, they were further aided by a visual display of force production (Gandevia, 2001).

Force and EMG recordings

Isometric knee-extensor force of the right leg was measured during voluntary and evoked contractions using a custom-built adjustable chair and dynamometer (Captels, St Mathieu de Treviers, France). The force signals were amplified, sent through an A/D board and sampled at 2000 Hz by data acquisition hardware and software (MP35 and BSL Pro Version 3.6.7; Biopac Systems Inc., Santa Barbara, CA, USA). Subjects were seated upright, with the hips and knees flexed at 90 deg. Straps placed across the chest and hips secured the subjects in the chair to prevent extraneous movement. Electromyographic activity of the vastus lateralis was recorded via bipolar Ag–AgCl electrodes (Ambu Blue sensor T; Ambu A/S, Ballerup, Denmark) with a diameter of 9 mm and an interelectrode distance of 30 mm. The electrodes were fixed lengthwise

over the muscle belly. A reference electrode was attached to the right wrist. Electrode positions on the leg were marked with indelible ink to ensure that placement was reproducible between trials. Low impedance between the two electrodes was obtained by shaving and cleaning the skin with alcohol. The EMG signals were amplified, filtered (bandwidth frequency, 5–500 Hz) and recorded by commercially available hardware and software (MP35 and BSL Pro version 3.6.7; Biopac Systems Inc.).

Stimulation

Motor nerve stimulation. A high-voltage stimulator (Digitimer DS7AH; Digitimer, Welwyn Garden City, UK) was used to deliver a square-wave stimulus of 0.2 ms duration with a maximal voltage of 400 V. A monopolar cathode ball electrode (0.5 cm diameter) was manually pressed into the femoral triangle by a trained experimenter to ensure consistency in placement and pressure application. The anode, a self-adhesive pad (5 cm × 10 cm; Medicompex SA, Ecublens, Switzerland), was located on the gluteal fold. During the pre-experimental familiarization session, a passive isometric recruitment curve was drawn to individualize the optimal stimulus intensity. Briefly, the current was progressively increased in 10–20 mA increments until a plateau in electrophysiological (M-wave peak-to-peak amplitude) and concomitant mechanical response (peak twitch force) was observed. To ensure that the supramaximal twitch and doublet stimulation intensity was supramaximal, this intensity was further increased by 50% above the level required to elicit peak twitch force in unpotentiated muscle, and kept constant for each subject throughout all subsequent experimental trials.

Transcranial magnetic stimulation. A concave double-cone coil (13 cm diameter) was used to elicit single magnetic stimuli (1 ms duration) using a mono-pulse magnetic stimulator (Magstim 200; The Magstim Company Ltd, Whitland, UK). The junction of the figure-of-eight coil was aligned tangentially with the sagittal plane, with the centre of the coil 1–2 cm to the left of the vertex. This optimal coil position was marked on the scalp with indelible ink to ensure reproducibility of the stimulation conditions for each subject throughout the entire experiment. The active motor threshold was identified during the pre-experimental session by constructing a stimulus–response curve during submaximal contractions (i.e. 50% MVC). Stimulator output was increased in 3% increments from 30% until an MEP response $\geq$50 μV was visible in more than three consecutive stimuli. The motor threshold occurred at 48.2 ± 5.6% of maximal stimulator output. During each of the experimental trials, TMS was delivered at 140% of the active motor threshold (i.e. 67.5 ± 15.8% of stimulator output) identified during the pre-experimental session and kept constant throughout the trials (Ross *et al.* 2012). This intensity of stimulation falls within the range (i.e. 130–170% of resting motor threshold) that has been shown to elicit a plateau in MEP amplitude (Suzuki *et al.* 2012). In the present study, the stimulator output resulted in large MEPs at baseline (CON) in the vastus lateralis of 78% (ExH) and 72% (PaH) of maximal M-wave amplitude (M_{max}) during contractions at 50% MVC.

Data analysis

Contractile properties were calculated from the mean of the three potentiated twitches; these properties included peak twitch force, contraction time to peak force and half-relaxation time. Voluntary muscle and cortical activation were quantified using evoked supramaximal doublets (MNS) and single twitches (TMS), as follows: voluntary activation (%) = [1 – (superimposed twitch/resting potentiated twitch)] × 100 (Merton, 1954). In order to calculate cortical voluntary activation, it was necessary to estimate, rather than measure directly, the amplitude of the resting twitch evoked by motor cortex stimulation, owing to the fact that corticospinal excitability increases during voluntary contractions (Rothwell *et al.* 1991). According to the method developed by Todd *et al.* (2003), the estimated resting twitch was determined as the *y*-intercept of the linear regression between the amplitude of superimposed twitches evoked by TMS and voluntary force recorded before TMS during 50, 75 and 100% MVCs (Fig. 2). The reliability of the TMS protocol for the determination of cortical activation has been established in the knee extensors (Goodall *et al.* 2009; Sidhu *et al.* 2009).

Peak muscle relaxation rate during the sustained MVC was calculated immediately following TMS by measuring the steepest rate of decline in force during the silent period (Todd *et al.* 2005) using Spike2 Software (Cambridge Electronic Design, Cambridge, UK). The rate was normalized to the total force (i.e. the sum of the MVC and TMS stimulation) evoked prior to the silent period (%P_o ms^{-1}; percent force/tension per unit time). The peak-to-peak amplitudes of M-wave (M-amplitude) and MEP were measured offline (Fig. 3). The MEP amplitude was normalized to that of the M-amplitude (MEP/M) elicited with the same temperature, conditions and contraction intensity to account for activity-dependent changes in muscle-fibre action potentials (Gandevia *et al.* 1999). During voluntary efforts, root mean square activity (RMS activity) of the EMG signal was calculated for 0.5 s during the plateau of force production (~0.5 s before delivering TMS or MNS). The RMS activity was also normalized to M_{max} (RMS/M) of the MVC performed in the same conditions to account for any

temperature-related changes in muscle-fibre action potentials (Todd *et al.* 2005).

Exercise measurements

Body core temperature was monitored with a rectal temperature probe inserted 12 cm beyond the anal sphincter. Muscle temperature was monitored using a flexible thermistor (MAC flexible probe; Ellab, Hilleroed, Denmark) inserted to a depth of 3 cm into the vastus lateralis of the right leg. The flexible thermistor was autoclaved according to the manufacturer's recommendations and inserted via a catheter (16 gauge) after local anaesthesia of the skin (2 ml of xylocaine). Skin-fold thickness over the site of measurement was 4.4 ± 1.3 mm. Skin temperatures of the chest, upper arm, thigh and lower leg were monitored via wireless dermal adhesive temperature patches (VitalSense® system, Mini Mitter; Respironics, Herrsching, Germany) and used to calculate mean skin temperature (Ramanathan, 1964). All temperatures were recorded at 5 min intervals. Heart rate was monitored telemetrically with a Polar transmitter–receiver (T-31; Polar Electro, Lake Success, NY, USA) and recorded every 5 min. Thermal comfort scores were recorded on a seven-point scale (Bedford, 1936) at 5 min intervals, as were ratings of perceived exertion (RPE) during exercise (Borg, 1982). Subjects were permitted to drink *ad libitum*. Body mass changes, corrected for fluid ingested and sweat trapped in clothing, were evaluated at the conclusion of each trial. The subjects also kept a 24 h food diary prior to testing and replicated their diet before the second trial.

Statistical analysis

All statistical calculations were performed using PASW software version 18.0 (SPSS Inc., Chicago, IL, USA). Repeated-measures ANOVAs were performed to test significance between and within treatments. Where significant interaction effects were established, pairwise differences were identified using the Bonferroni *post hoc* analysis procedure adjusted for multiple comparisons. Significant differences in hydration status were identified using Student's paired *t* tests. The significance level was set at $P < 0.05$. All values are expressed as means ± SD.

Results

Exercise measurements

The time to reach MOD-ExH (47.7 ± 15.5 min) and MOD-PaH (50.0 ± 13.1 min) was similar, as was the time to reach SEV-ExH (95.2 ± 26.5 min) and SEV-PaH (103.3 ± 16.3 min). Rectal and muscle temperature increased significantly from CON to MOD and SEV hyperthermia during both ExH and PaH (Table 1; $P < 0.005$). However, no differences were noted between conditions. The rise in skin temperature during PaH was significantly greater than in ExH ($P < 0.001$). Thermal comfort scores were similar between the ExH and PaH trials, increasing significantly throughout each condition from CON ($P < 0.05$). Heart rate also increased significantly throughout each trial ($P < 0.05$). The increase in heart rate was greater in the ExH than in the PaH trial ($P < 0.001$). The RPE rose

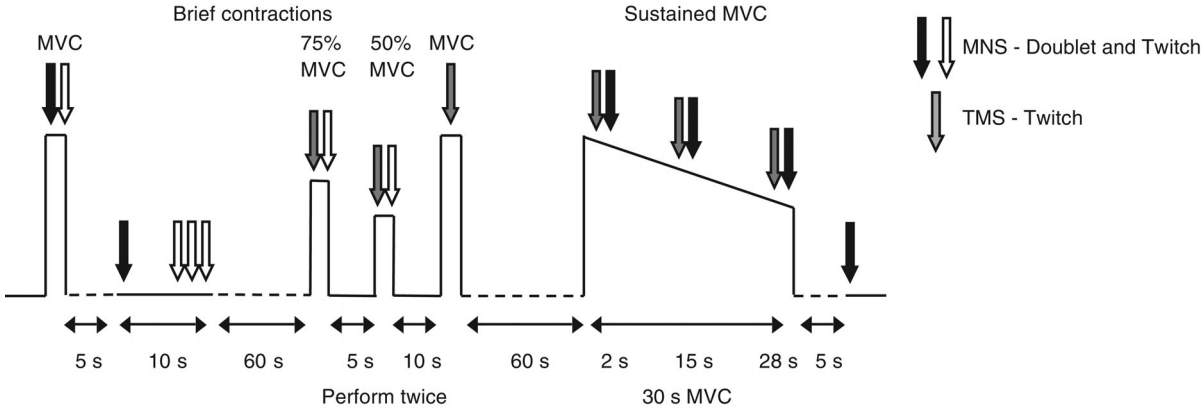

Figure 1. Force production and voluntary activation protocol in which motor nerve stimulation (MNS) and transcranial magnetic stimulation (TMS) are applied during brief (∼5 s) and sustained (30 s) maximal voluntary isometric contractions (MVCs).
The initial brief MVC is followed by one doublet and three single twitches on the relaxed muscle. Then two submaximal contractions and one MVC are performed and superimposed with TMS and MNS. After the series is repeated, a sustained MVC is performed and superimposed with TMS and MNS at 2, 15 and 28 s. The MNS and TMS at each stimulation interval are separated by ∼2 s. The sustained MVC is followed by MNS. The entire protocol was performed at baseline/control and during moderate (38.5°C) and severe (39.5°C) exercise-induced hyperthermia and passively induced hyperthermia. Arrows indicate the type and timing of stimulation.

to 15.3 ± 2.2 (MOD-ExH) and then to 17.0 ± 2.3 (SEV-ExH; $P < 0.003$). Pretrial hydration status was comparable between conditions, with a urine osmolality of 412.5 ± 256.7 mosmol kg^{-1} in the ExH trial and 392.0 ± 254.5 mosmol kg^{-1} in PaH. Body mass losses were also similar between ExH (1.6 ± 0.7 kg) and PaH (1.7 ± 0.7 kg).

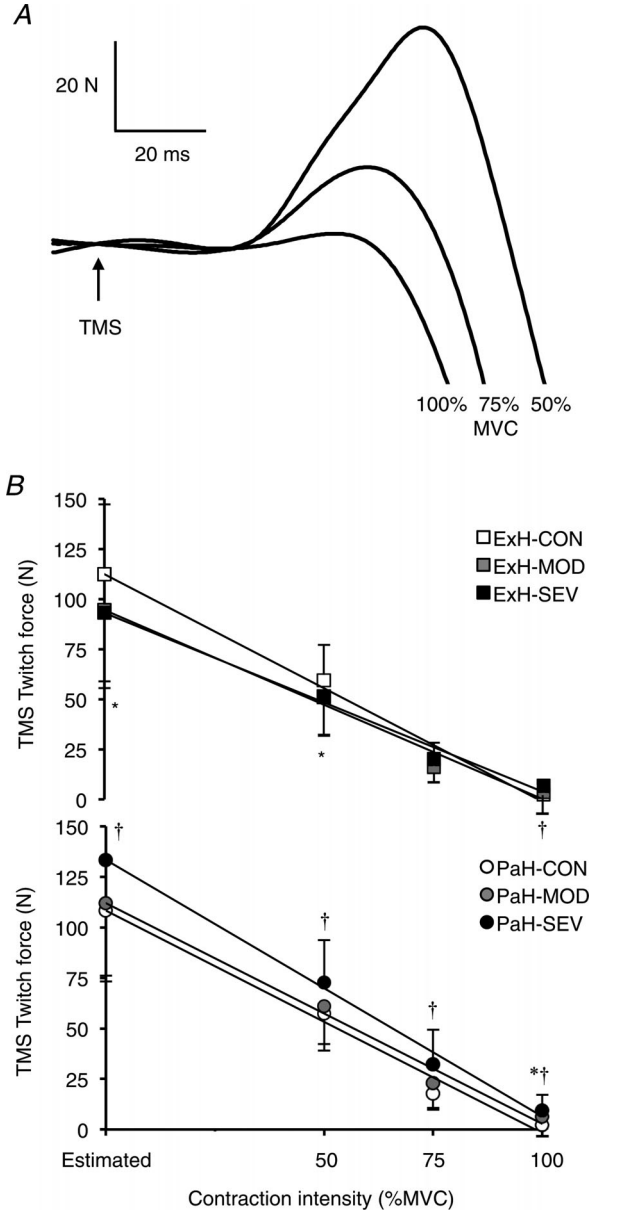

Figure 2. Estimated resting twitch force
A, representative data of force production evoked by TMS during knee extension at 50, 75, and 100% MVC at baseline (CON) and during moderate (MOD) and severe (SEV) exercise-induced hyperthermia (ExH) and passively induced (PaH) hyperthermia. *B*, resting twitch force estimated using the force production evoked via TMS at 50, 75, and 100% MVC. Mean $r^2 \geq 0.98 \pm 0.01$ in both ExH and PaH conditions. *Significant difference between CON and MOD ($P < 0.05$). †Significant difference between CON and SEV ($P < 0.05$).

Neuromuscular function

Force production during the brief MVC decreased significantly on reaching SEV-ExH and SEV-PaH, compared with CON and MOD hyperthermia (Table 2; $P < 0.05$). However, no difference in force production was observed between conditions. The RMS activity of the vastus lateralis was unaffected on reaching MOD-ExH (0.43 ± 0.12 mV), MOD-PaH (0.41 ± 0.13 mV), SEV-ExH (0.39 ± 0.13 mV) and SEV-PaH (0.35 ± 0.10 mV) relative to CON (0.38 ± 0.12 and 0.38 ± 0.12 mV for ExH and PaH, respectively), or when expressed as a function of M_{max} (RMS/M; Table 2). Voluntary muscle activation measured via MNS was depressed during SEV-ExH and SEV-PaH, relative to CON and MOD hyperthermia ($P < 0.05$). Cortical activation measured using TMS was lower in both the ExH and PaH trials during MOD and SEV hyperthermia, relative to CON ($P < 0.05$).

Mean force production throughout the sustained MVC was decreased during MOD-ExH (−9.7%), SEV-ExH (−12.9%) and SEV-PaH (−7.2%) compared with CON (Fig. 4; $P < 0.01$). The decrease in mean sustained force production observed during MOD-ExH and SEV-ExH was significantly greater than during MOD-PAH and SEV-PaH ($P < 0.01$). Normalized force production decreased progressively during all sustained MVCs ($P < 0.005$). The decline in normalized force was 9% greater during SEV-ExH compared with CON ($P < 0.05$). The RMS activity remained stable throughout the sustained MVCs, although mean RMS activity decreased significantly during MOD-ExH (0.29 ± 0.07 mV) and MOD-PaH (0.25 ± 0.08 mV), as well as SEV-ExH (0.27 ± 0.07 mV) and SEV-PaH (0.24 ± 0.07 mV), relative to CON (0.31 ± 0.10 and 0.31 ± 0.10 mV for ExH and PaH, respectively; $P < 0.01$). In each of the conditions, RMS/M remained unchanged (Fig. 4). Voluntary activation measured using both MNS and TMS demonstrated no effect of condition during the sustained MVC (Fig. 5). However, a significant decline in voluntary muscle activation was observed with the use of MNS on reaching SEV-ExH and SEV-PaH compared with CON ($P < 0.01$). Motor cortical activation measured via TMS decreased on reaching MOD-ExH and SEV-ExH, as well as MOD-PaH and SEV-PaH, relative to CON ($P < 0.001$).

Motor cortical stimulation responses

Estimated resting twitch force via TMS was significantly greater during MOD-PaH and SEV-PaH compared with MOD-ExH and SEV-ExH ($P < 0.05$; Fig. 2). The additional force produced during TMS at 50, 75 and 100% MVC was also greater during MOD-PaH, whereas it was higher during the 50% contraction only in SEV-PaH, relative to ExH ($P < 0.05$). Peak muscle relaxation rate during the brief MVCs increased on reaching

MOD-ExH and SEV-ExH, as well as MOD-PaH and SEV-PaH compared with CON ($P < 0.05$; Table 2). A further increase in muscle relaxation was observed when increasing from MOD-PaH to SEV-PaH ($P < 0.01$). During the sustained MVCs, peak relaxation rate increased on reaching MOD-ExH and SEV-ExH, as well as MOD-PaH and SEV-PaH, compared with CON ($P < 0.01$; Fig. 6). An increase in muscle relaxation from MOD-PaH to SEV-PaH was also observed during the sustained MVC ($P < 0.001$). As a result, a significant increase in muscle relaxation rate was noted in SEV-PaH, relative to SEV-ExH ($P < 0.002$). During the sustained MVCs, the rate of muscle relaxation slowed on reaching the 28 s stimulation interval, relative to 2 and 15 s ($P < 0.02$). The MEP/*M* during the contractions at 50, 75 and 100% MVC did not differ between or within hyperthermic conditions (Fig. 3).

Motor nerve stimulation responses

Peak twitch force remained similar to CON on reaching MOD-PaH and SEV-PaH (Table 3). In contrast, peak twitch force decreased significantly from CON to MOD-ExH and SEV-ExH ($P < 0.05$). As such, peak twitch force was higher during MOD-PaH and SEV-PaH compared with ExH ($P < 0.01$). Contraction time was depressed on reaching SEV-ExH and SEV-PaH compared with CON ($P < 0.01$). Half-relaxation time also decreased significantly during MOD-ExH and SEV-ExH, as well as MOD-PaH and SEV-PaH, relative to CON ($P < 0.05$). A greater reduction in half-relaxation time was observed during MOD-ExH and SEV-ExH compared with MOD-PaH and SEV-PaH ($P < 0.05$). The M-amplitude during the resting twitch and contractions at 50, 75 and 100% MVC decreased significantly on reaching both SEV-ExH and SEV-PaH, relative to CON ($P < 0.05$; Fig. 3).

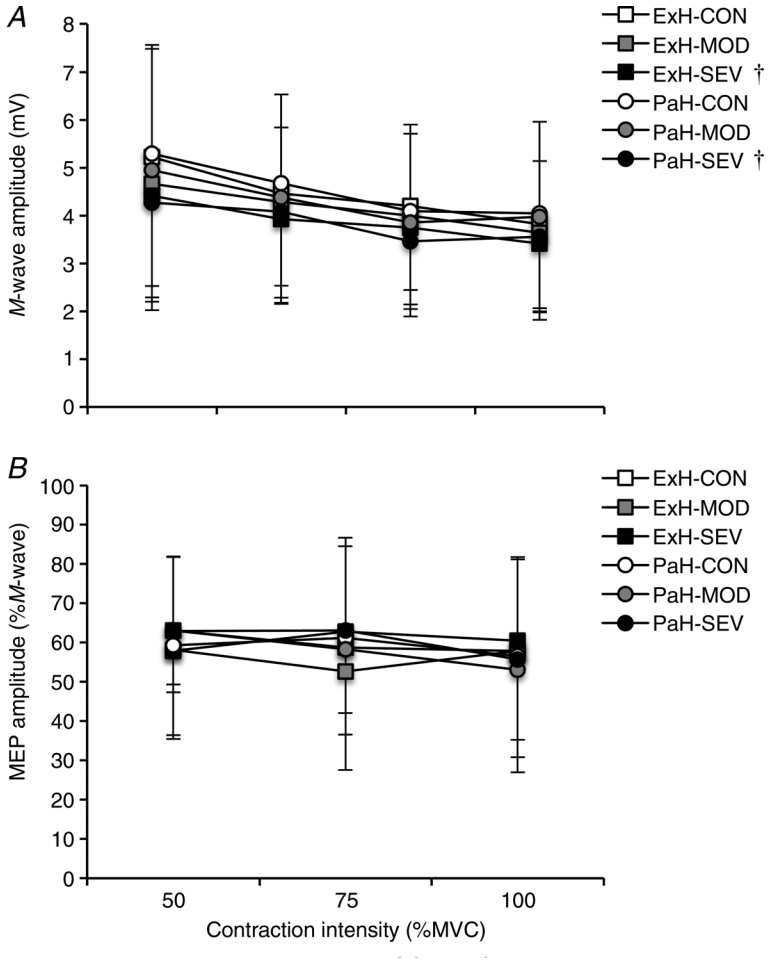

Figure 3. Amplitude of the M-wave (*A*) and normalized motor evoked potentials (MEPs; *B*) during isometric knee extensions at 50, 75 and 100% MVC
†Significant difference between CON and SEV ($P < 0.05$).

Table 1. Temperature, thermal comfort and heart rate responses at baseline (CON) and during moderate (MOD) and severe (SEV) exercise-induced hyperthermia (ExH) and passively induced hyperthermia (PaH)

	CON		MOD		SEV	
Parameter	ExH	PaH	ExH	PaH	ExH	PaH
T_{re} (°C)	37.1 ± 0.3	37.1 ± 0.4	38.5 ± 0.2*	38.5 ± 0.1*	39.4 ± 0.1*†	39.5 ± 0.1*†
T_{mu} (°C)	35.3 ± 0.7	35.7 ± 0.9	38.7 ± 0.6*	38.5 ± 0.2*	39.3 ± 0.4*†	39.4 ± 0.3*†
T_{sk} (°C)	30.6 ± 1.0	30.6 ± 1.1	37.7 ± 0.7*	39.9 ± 0.6*‡	38.2 ± 0.7*	40.5 ± 0.7*†‡
Thermal comfort	2.6 ± 0.8	3.0 ± 0.8	5.9 ± 0.6*	6.3 ± 0.8*	6.1 ± 0.6*†	6.7 ± 0.5*†
Heart rate (beats min^{-1})	59.7 ± 7.4	60.6 ± 7.3	160.7 ± 13.4*	103.7 ± 8.5*‡	169.3 ± 8.3*†	109.2 ± 8.2*†‡

Abbreviations: T_{mu}, muscle temperature; T_{re}, rectal temperature; and T_{sk}, skin temperature. *Significantly different from CON ($P < 0.05$); †significantly different from MOD ($P < 0.05$); and ‡significant difference between ExH and PaH ($P < 0.01$).

Table 2. Force production capacity, voluntary muscle and cortical activation, maximal rate of force relaxation and RMS/*M* during brief MVCs performed at baseline and during moderate and severe exercise-induced hyperthermia and passively induced hyperthermia

	CON		MOD		SEV	
Parameter	ExH	PaH	ExH	PaH	ExH	PaH
Force (N)	641.5 ± 179.6	643.0 ± 177.7	608.1 ± 176.3	639.1 ± 181.0	587.7 ± 174.3*†	607.5 ± 178.2*†
VA-MNS (%)	95.4 ± 4.2	96.0 ± 3.3	94.0 ± 4.8	95.3 ± 4.2	91.9 ± 3.2*†	91.8 ± 5.5*†
VA-TMS (%)	97.4 ± 3.3	97.9 ± 2.0	94.9 ± 3.2*	93.1 ± 5.9*	92.5 ± 4.6*	93.2 ± 5.0*
PRMR (%Po ms^{-1})	−1.4 ± 0.3	−1.4 ± 0.3	−1.7 ± 0.3*	−1.6 ± 0.3*	−1.7 ± 0.2*	−1.8 ± 0.3*†‡
RMS/*M* (%)	10.9 ± 5.1	13.6 ± 7.8	13.6 ± 6.7	10.9 ± 5.1	12.0 ± 5.4	11.5 ± 6.2

Abbreviations: MNS, motor nerve stimulation; PRMR, Peak rate of muscle relaxation; MVC, maximal voluntary contraction; RMS/*M*, root mean square of electromyography signal from the vastus lateralis normalized to M_{max}; TMS, transcranial magnetic stimulation; and VA, voluntary activation. For other abbreviations, see Table 1. *Significantly different from CON ($P < 0.05$); †significantly different from MOD ($P < 0.05$); and ‡significant difference between ExH and PaH ($P < 0.01$).

Discussion

To our knowledge, this is the first study to examine the effects of both progressive passive and exercise-induced hyperthermia on motor nerve and cortical activation during brief and sustained maximal voluntary contractions. The aim of the study was to determine whether hyperthermia-induced adjustments in contractile function mediate an additional failure in maintaining voluntary muscle and motor cortical activation. Our data indicate that maximal force production capacity was reduced to a similar extent during the brief MVCs upon reaching SEV-ExH and SEV-PaH. In contrast, force production was lower during MOD-ExH and SEV-ExH compared with MOD-PaH and SEV-PaH when performing the sustained contractions. Moreover, the rate of decline in force production was exacerbated during SEV-ExH, compared with SEV-PaH. However, regardless of contraction length, voluntary muscle and motor cortical activation were reduced to similar extents during ExH and PaH.

The novel findings of this study are that peak muscle relaxation rate increased during both ExH and PaH when performing brief and sustained MVCs and that the increase in relaxation rate was greatest during SEV-PaH; however, the additional increase did not exacerbate central fatigue relative to ExH. The increase in peak muscle relaxation supports previous observations made during brief (Ross *et al.* 2012) and sustained MVCs (Todd *et al.* 2005) performed during passive hyperthermia. Our results extend these observations to indicate that despite the development of peripheral fatigue as a result of exercise, the rate of muscle relaxation also increases during ExH in response to a rise in whole-body temperature. In addition, the increase in muscle relaxation during SEV-PaH does not translate into greater central fatigue development.

Brief contractions

The decline in force production capacity and voluntary activation noted during the brief MVCs on reaching SEV-ExH and SEV-PaH (Table 2) supports previous observations (Morrison *et al.* 2004; Thomas *et al.* 2006; Racinais *et al.* 2008; Périard *et al.* 2011*a*,*b*; Ross *et al.* 2012). It was anticipated that a larger decline in brief MVC force output would occur during MOD-ExH compared with MOD-PaH due to development of peripheral muscle fatigue. Although a significantly larger decline was not observed, a slight reduction in force was observed. Evidence of peripheral fatigue was demonstrated by a reduction in peak twitch force (MNS) and estimated twitch force (TMS) during MOD-ExH and SEV-ExH relative to PaH (Fig. 2 and Table 3). Conversely, voluntary muscle and cortical activation during ExH and PaH were decreased to similar levels, indicating a similar level of hyperthermia-induced central activation failure.

The decrement in voluntary activation may also be associated with a failure in the peripheral transmission of the neural drive. Racinais *et al.* (2008) suggested that a passive hyperthermia-induced decrease in M_{max} may indicate that for a given level of neural drive, an equivalent sarcolemmal action potential is not achieved. Our data displayed a significant decrease in M-amplitude during the 50, 75 and 100% MVCs in both the SEV-ExH and SEV-PaH trials (Fig. 3). This corroborates observations of a passive reduction in M_{max} during localized warming of the leg (Dewhurst *et al.* 2005) and extends these observations to include reductions in M-amplitude during submaximal and maximal contractions in association with SEV-ExH. Based on the modelling of compound action potentials of peripheral nerves *in situ* (Stegeman & De Weerd, 1982), it appears that the reduction may stem from a temperature-induced decrease in depolarization time and a consequent attenuation of cellular Na^+ influx (Rutkove, 2001).

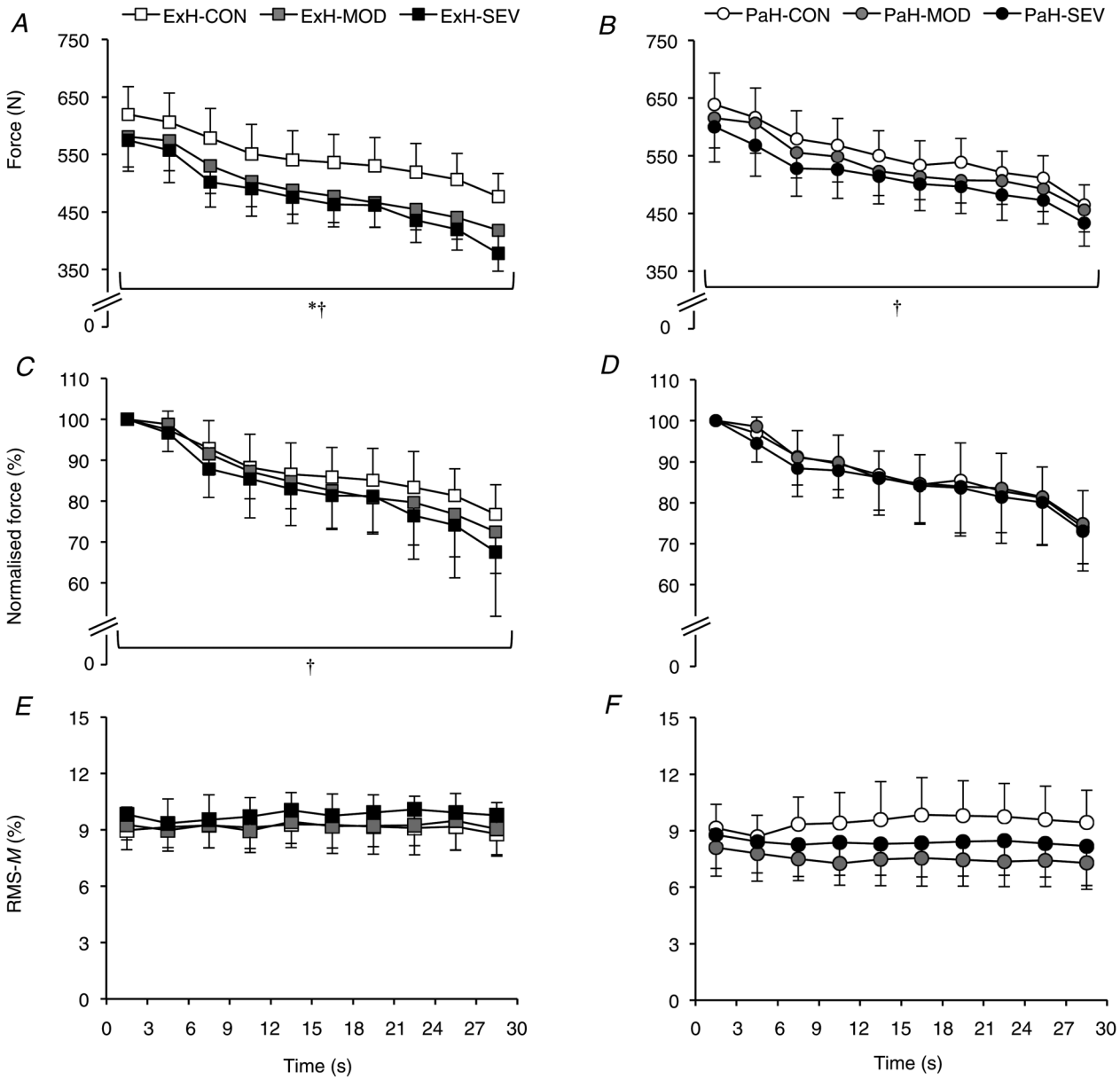

Figure 4. Force production and RMS activity
Capacity for force production during a 30 s MVC at baseline (CON) and during moderate (MOD) and severe (SEV) exercise-induced hyperthermia (ExH; *A*) and passively induced hyperthermia (PaH; *B*). Force output normalized to peak force production (*C* and *D*) and RMS activity normalized to the maximal amplitude of the M-wave (RMS/*M*; *E* and *F*) in the same conditions. *Significant difference between CON and MOD ($P < 0.01$). †Significant difference between CON and SEV ($P < 0.01$).

Both ExH and PaH also influenced contractile function, as demonstrated by reductions in twitch contraction time and half-relaxation time (Table 3). Adjustments in contractile function were further evidenced by an increase in the peak muscle relaxation rate during brief MVCs on reaching MOD and SEV hyperthermia (Table 2). This increase was further enhanced during SEV-PaH. Others have noted such increases in muscle relaxation (Todd *et al.* 2005; Ross *et al.* 2012), which suggests that elevated motor unit firing rates are required to produce maximal force in order to match the increase in contractile speed. During brief MVCs, it appears that firing rates are sufficiently elevated to attain maximal force (Todd *et al.* 2005). Accordingly, whilst instantaneous (i.e. first 100 ms when tension is increasing) rates $\geq$100 Hz have been recorded in human muscles at the onset of an MVC, motor unit discharge rates typically vary between 30 and 60 Hz when maximal force is reached and subsequently decrease during sustained contractions (Grimby *et al.* 1981; Bigland-Ritchie *et al.* 1983*a*). At elevated muscle temperatures, the opening and closing of voltage-gated Na^+ channels is accelerated, which allows less Na^+ to enter the cell. Consequently, a decrease in action potential amplitude, duration and area occurs, leading to a more rapid onset depolarization and faster muscle fibre conduction velocity (Rutkove *et al.* 1997). The increased action potential delivery results in greater Ca^{2+} release and re-uptake from the sarcoplasmic reticulum (Gray *et al.* 2006). This increase in Ca^{2+} handling (i.e.

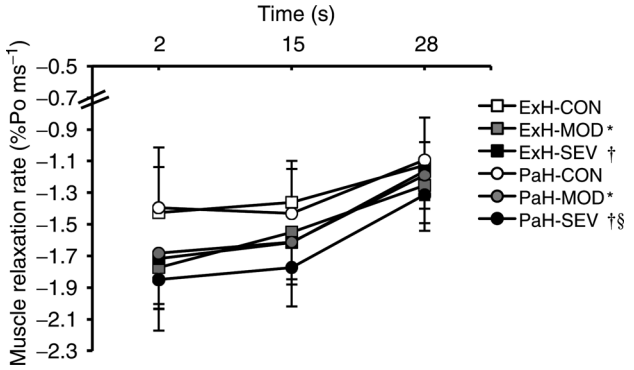

Figure 6. Peak rate of muscle relaxation during the silent period following TMS during a 30 s MVC
The rate was normalized to the total force (i.e. sum of MVC and TMS) evoked prior to the silent period per unit of time (%Po ms^{-1})
*Significant difference between CON and MOD ($P < 0.01$); †significant difference between CON and SEV ($P < 0.01$); and §significant difference between ExH and PaH ($P < 0.002$).

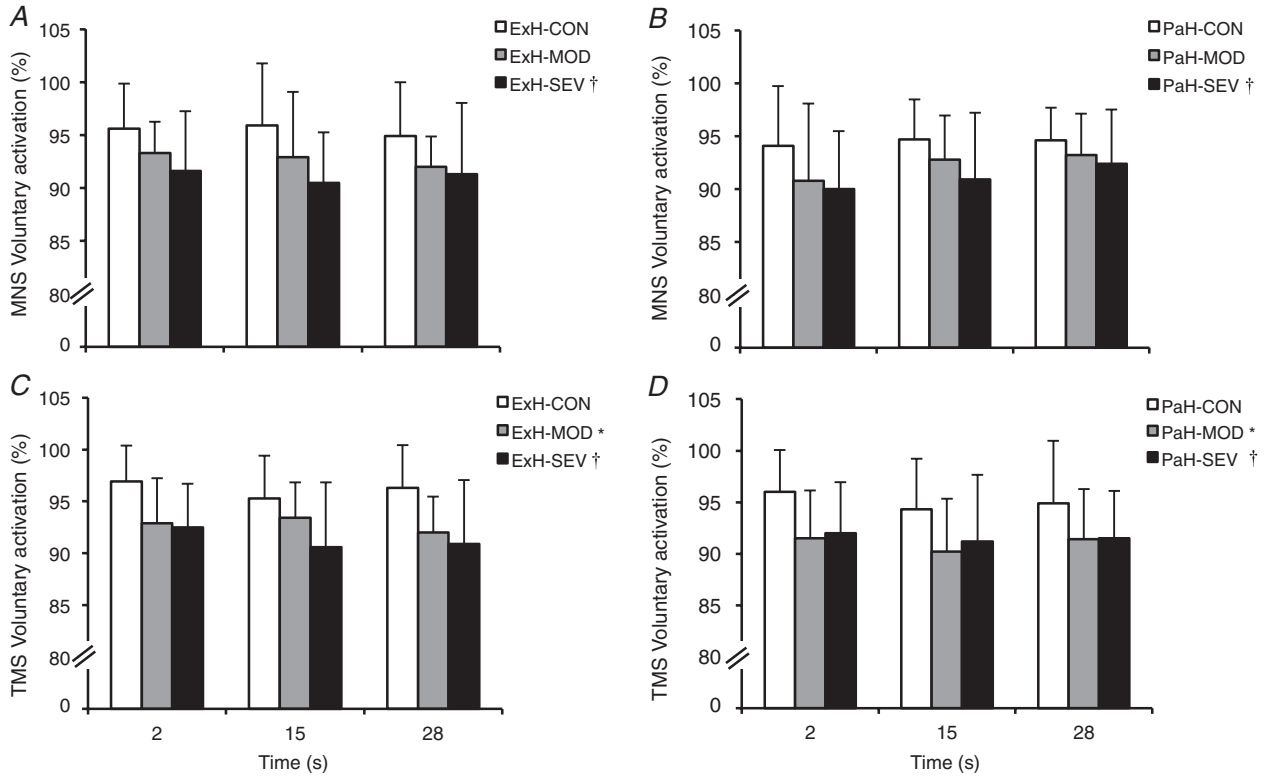

Figure 5. Voluntary activation measured via MNS (*A* and *B*) and TMS (*C* and *D*) during a 30 s MVC during ExH (*A*) and PaH (*B*)
*Significant difference between CON and MOD ($P < 0.01$); and †significant difference between CON and SEV ($P < 0.01$).

Table 3. Twitch properties at baseline and during moderate and severe exercise-induced hyperthermia and passively induced hyperthermia

	CON		MOD		SEV	
Parameter	ExH	PaH	ExH	PaH	ExH	PaH
Peak force (N)	129.1 ± 22.9	132.9 ± 21.2	103.8 ± 21.8*	134.5 ± 23.8†	106.8 ± 12.8*	136.4 ± 20.6†
Contraction time (ms)	72.7 ± 7.5	73.4 ± 7.2	65.8 ± 6.6	67.5 ± 6.8	62.6 ± 5.7*	61.1 ± 8.7*
Half-relaxation time (ms)	62.2 ± 8.9	67.0 ± 12.4	52.7 ± 9.2*	61.5 ± 14.0*†	48.0 ± 3.7*	61.6 ± 12.1*†

For abbreviations, see Table 1. *Significantly different from CON ($P < 0.05$); and †significantly different from ExH ($P < 0.05$).

release and re-uptake) may thus require higher motor unit firing rates to maintain the fusion of maximal force during a sustained MVC.

Sustained contractions

The ability to generate and maintain force was impaired during ExH and PaH (Fig. 4). In the ExH trial, the impairment was more pronounced, as evidenced by a decrease in force production capacity during both MOD-ExH and SEV-ExH compared with PaH, as well as a greater rate of force loss on reaching SEV-ExH, relative to CON. Although central fatigue was observed in both conditions, the greater rate of force loss in the ExH trial was not associated with a larger decrement in voluntary drive. Indeed, voluntary muscle and motor cortical activation failure were similar between the ExH and PaH conditions (Fig. 5). Rather, the greater loss of force observed during ExH appears to have originated from adjustments occurring beyond the neuromuscular junction (i.e. peripheral fatigue) in response to repeated contractile activity (Périard *et al.* 2011*a*). These adjustments were probably associated with an exercise-induced acidification of the contractile milieu and/or changes in sarcoplasmic reticulum Ca^{2+} handling (e.g. release and re-uptake) and cross-bridge cycling (e.g. formation and detachment; Fitts, 1994; Allen *et al.* 2008). Interestingly however, the direct inhibition of force production by acidification of the contractile milieu declines markedly with increasing temperature and does not appear to be a major factor in muscle fatigue at physiological temperatures (Millar & Homsher, 1990; Westerblad *et al.* 1997).

The production of extra force via MNS during an MVC demonstrates the potential for additional α-motoneurones to discharge. When TMS evokes an increase in force production, it indicates a supraspinal component to central fatigue, signifying that motor cortical output is insufficient to activate the motoneurone pool maximally (Gandevia, 2001). Our data indicate similar impairments in voluntary muscle and motor cortical activation during the sustained MVCs, thus supporting evidence that additional failure at the supraspinal level may impair motor drive in the heat. Todd *et al.* (2005) suggested that additional central fatigue is not related to differences in motor cortical excitability, because changes in MEP and silent period duration are influenced in a similar manner during sustained MVCs performed in hyperthermic and normothermic individuals. Rather, they proposed that a sustained increase (∼20%) in peak muscle relaxation rate during PaH, compared with normothermia, would require higher motor unit firing rates to cause fully fused muscle contraction. Although these rates may be attained transiently during brief MVCs, it would appear that they cannot be sustained during prolonged maximal contractions. Data from the present study support part of these observations, in that an increase in muscle relaxation rate was noted during the sustained MVCs (Fig. 6). However, the magnitude of increase was not consistent throughout the MVC and tended to diminish as the contraction progressed. Closer examination of the data from Todd *et al.* (2005) suggests a similar pattern of decline during the time course (30 s) associated with the MVCs performed in the present study. Our data therefore extend previous observations in that a further increase in whole-body temperature, from 38.5 to 39.5°C, exacerbates the increase in peak muscle relaxation rate during PaH. Furthermore, it appears that ExH also increases the muscle relaxation during sustained MVCs, despite the development of peripheral fatigue, which is known to reduce contractile speed (Bigland-Ritchie *et al.* 1983*b*; Fuglevand *et al.* 1999; Orizio *et al.* 2004). The additional increase in muscle relaxation during SEV-PaH did not exacerbate the loss of force or central activation failure relative to ExH. This suggests that the central activation level remained sufficiently high to offset faster muscle relaxation during the 30 s MVC in these hot conditions.

Interestingly, it has been suggested that large evoked MEPs, relative to M_{max}, are indicative of the ability of motoneurones to respond adequately to descending synaptic input (Todd *et al.* 2005). In the present study, MEP/*M* was not measured during the sustained MVCs because corresponding M-waves (i.e. condition, temperature, contraction intensity and time point) were not obtained due to doublet stimulations. Nevertheless, data obtained during the resting twitches and the brief submaximal and maximal contractions indicate a decrement in M-amplitude during SEV-ExH and SEV-PaH (Fig. 3). The decrease in M-amplitude may be due, at least in part, to a depressed conduction of the

action potential along the sarcolemma (Metzger & Fitts, 1987). Given this decrement in M-amplitude and the slight reduction in amplitude associated with increasing contraction intensity, along with the maintenance of MEP/*M*, it appears that the ability of motor units to fire in response to the descending stimulus volleys was not compromised. Moreover, we noted that RMS/*M* was maintained during the brief MVCs, whereas M-amplitude was depressed. This is evidence of the ability to maintain a high level of motor unit recruitment. In contrast, mean RMS activity decreased on reaching SEV-ExH and SEV-PaH during the sustained MVC. If it is assumed that M-amplitude remains depressed during the sustained MVC, as it was during the brief MVCs, it may be inferred that a reduction occurred in the number of motor units voluntarily recruited during the sustained contraction. This corroborates previous observations that hyperthermia exacerbates the decrement in sustained force production in the absence of additional alterations in M-amplitude and H reflex, suggesting the occurrence of supraspinal fatigue (Racinais *et al.* 2008).

The reduction in voluntary muscle and cortical activation may also have originated partly from the development of mental, rather than central fatigue (Périard, 2012). Mental fatigue involves tiredness, a limited attention span and an aversion or decreased commitment to continuing a task or activity (Holding, 1983; Hockey, 1997). During activities such as a sustained MVC in hot conditions, these mental fatigue attributes could contribute to decrease voluntary drive to the muscle. Cabanac (2006) suggested that conscious signals originating from central and peripheral afferent pathways could mediate behaviour and reduce motivation in order to minimize discomfort. As a result, this may cause the abandonment or withdrawal from a task in which the energetic demands (i.e. effort) outweigh its perceived benefits (Boksem & Tops, 2008). Accordingly, a lack of motivation may reduce central neural drive to the appropriate motor neurones, leading to a loss of force production (Enoka & Stuart, 1992).

Conclusion

This study has demonstrated that the progressive development of exercise and passive hyperthermia are associated with similar decrements in maximal force production capacity and central activation failure during brief MVCs. Moreover, the results show that the loss of force is exacerbated during sustained MVCs performed during exercise-induced hyperthermia when compared with passive hyperthermia. This occurs despite similar reductions in voluntary muscle and motor cortical activation. We have also provided new evidence that the development of both exercise-induced and passive hyperthermia results in an increase in the peak rate of muscle relaxation during the silent period following TMS during brief and sustained MVCs. Furthermore, we have shown that the increase from moderate to severe passive hyperthermia contributes to enhance the rate of relaxation, but without exacerbating the loss of force or voluntary muscle and cortical activation relative to exercise. This suggests that the centrally mediated rate of activation (i.e. motor unit firing) is sufficient to overcome the increase in peak muscle relaxation rate.

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Additional Information

Competing interests

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