The Effects of Passive Heat Stress on Muscle Fatigue and Intracortical Excitability of the Wrist Flexors

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# Table of Contents

- Project Summary 5
- Relevance/Lay Audience Summary 7
- Introduction 8
  - Justification 11
  - Assumptions and Limitations 13
- Review of the Literature 14
  - Effect of Heat Stress on Human Physiologic Responses 14
  - Paired-Pulse Transcranial Magnetic Stimulation 17
- Research Question and Approach 20
  - Purpose 20
- Materials and Methods 21
  - Thermal Conditions and Measurement of Temperature and Cardiovascular Outcomes 22
  - Muscle and Nerve Function Methods and Outcome Measures 22
- Result 28
- Discussion 30
  - Future Directions 34
- Bibliography 35
- Figures 39
- Appendix A: Institutional Review Board Approval Document 50
- Appendix B: Informed Consent Page 51
- Appendix C: Accepted *Ergonomics* Manuscript 56
PROJECT SUMMARY

Individuals who are exposed to extreme heat or work in hot environments are at an increased risk for the development of heat illnesses and have increased incidences of work-place accidents and injuries (NIOSH 2009). Heat stress has been strongly associated with decreases in exercise performance (Galloway and Maughan 1997; Gonzalez-Alonso, Teller et al. 1999; Drust, Rasmussen et al. 2005; Thomas, Cheung et al. 2006; Ely, Cheuvront et al. 2007; Altareki, Drust et al. 2009). Comparative studies have observed similar decreases in the drive to ambulate with large increases in internal temperature (Fuller, Carter et al. 1998; Walters, Ryan et al. 2000). Workers, however, rarely perform sustained maximal efforts or increase internal temperatures to the extent of endurance athletes. Many governments have labor codes that limit internal temperature increases to ~1.0 °C above resting values (Jay and Kenny 2010). Certain occupations such as firefighting, foundry work, and industrial baking can expose workers to high ambient temperatures and induce moderate heat stress, but it is less clear what effect this moderate heat stress has on neuromuscular fatigue and performance. Accordingly, this study evaluated the effect of passive-heat stress on the neuromuscular properties of the wrist flexor muscles, which are commonly used in manual labor hand tasks. We utilized a combination of techniques involving nerve stimulation and paired-pulse transcranial magnetic stimulation to assess changes in muscle strength, contractile properties, fatigue-resistance, and central activation as well as indices of intracortical excitability in 10 healthy humans who were exposed to a passive heat stress protocol as well as a normothermia control protocol. Passive heat stress increased core body temperature ~1 °C (37.2±0.4 to 38.2±0.4 °C; p<0.01), mean skin temperature (34.5±0.7 °C to 37.3±1.1 °C; p<0.01), and heart rate (79.5±20.0 to 110.0±23.0 beats/min; p=0.04). No effect was observed on muscle strength, contractile properties, muscle
fatigability, central activation, or indices of intracortical excitability (p>0.05). These findings suggest that a passive heat stress that raises the core body temperature 1 °C (to ~ 38.2 °C) does not impair muscle function, central activation or motor cortical excitability of the wrist flexor muscles as can occur in severe exercise-heat stress of larger, more proximal muscles. Thus, neuromuscular performance of smaller, more distal muscle groups involved in hand and wrist flexion tasks utilized in many occupational tasks should not be affected by moderate heat stress.
RELEVANCE/LAY AUDIENCE SUMMARY

Increases in core body temperature associated with exercise are known to result in impairments of physical and physiologic function. However, to date the specific effects of increased core body temperature per se (in the absence of exercise) is poorly understood. In this project, I sought to determine the effect of passive-heat stress on the physical work capacity and muscle and nerve physiology in healthy humans. I found no effects of passive-heat stress on muscle performance or intracortical physiological variables.
INTRODUCTION

Individuals who are exposed to extreme heat or work in hot environments such as firefighters, military personnel, and construction and industry workers are at an increased risk for the development of heat stress related illnesses including: heat stroke, heat exhaustion, heat syncope, heat cramps, and heat rash (NIOSH 2009). These heat stress illnesses provide not only a direct risk to the health of the worker, but also decrease the ability to perform common tasks (e.g. driving, gripping materials, walking). These heat stress related impairments result in an increased risk for a number of work-place accidents and injuries (NIOSH 2009). While much research has been conducted to investigate the physiological effects of heat stress, a great deal more work is needed to truly isolate the causes of impaired human performance. By understanding the effects of environmental stressors on human performance this research will help create safer and more efficient conditions for work in extreme environments.

Heat stress has been strongly associated with decreases in work and exercise performance (Ely et al.; Galloway and Maughan 1997; Gonzalez-Alonso et al. 1999; Kay et al. 2001; Drust et al. 2005; Thomas et al. 2006; Ely et al. 2007; Altareki et al. 2009). Comparative studies observe similar decreases in task performance with increases in internal temperatures (Fuller et al. 1998; Walters et al. 2000). The proposed mechanisms for the observation that exercise-related heat stress accelerates muscle fatigue may be related to neuromuscular, metabolic, or cardiovascular changes associated with heat stress (Cheuvront et al.; Cheung and Sleivert 2004; Gonzalez-Alonso et al. 2008; Nybo 2008).

Muscle fatigue—defined here as an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force (Enoka and Stuart 1992)—during heat stress could arise from: i. neurological
(central) and ii. skeletal muscle (peripheral) factors, as it is well known that the output from these sources controls force production (Duchateau and Enoka 2002; Clark and Manini 2008). Many studies have shown heat stress induced muscle fatigue in both the presence and absence of exercise (studies described below in literature review). Collectively, these findings have led to the hypothesis that the site for central activation failure associated with heat stress is at the cortical level (Morrison et al. 2004; Cheung 2007; Nybo 2008).

To my knowledge, only one study has directly tested the effects of hyperthermia on indices of motor cortical excitability (Todd et al. 2005). In this insightful study, Todd and colleagues used single-pulse transcranial (brain) magnetic stimulation (TMS) to examine changes in motor evoked potential (MEP) amplitude and silent period duration, along with measures of central activation, muscle fatigue, and evoked muscle force properties following passive-heat stress. They observed that passive-heat stress resulted in impairments in central activation and faster muscle contractile relaxation rates, without a concomitant change in MEP amplitude or silent period duration. Despite the insight obtained from the above-mentioned study, there are several limitations to this work (described below in literature review). Additional work with both a refined heating technique and a more sophisticated evaluation of intracortical properties may obtain more definitive and valuable conclusions.

Almost all comparative studies observe decreases in the drive to ambulate with large increases in internal temperature (Fuller, Carter et al. 1998; Walters, Ryan et al. 2000). Workers, however, rarely perform sustained maximal efforts or increase internal temperatures to the extent of endurance athletes. Many governments have labor codes that limit internal temperature increases to ~1.0 °C above resting values (Jay and Kenny 2010). Certain occupations such as firefighting, foundry work, and industrial baking can expose workers to high ambient
temperatures and induce moderate heat stress, but it is less clear what effect this moderate heat stress has on neuromuscular fatigue and performance. This study will use a more moderate passive heat stress model in an effort to have results that may be more applicable from an ergonomic standpoint.

Accordingly, in the present study I used a classical heat stress model (i.e., water-perfused suit) with well-known cardiovascular effects such as decreases in cerebral blood flow to increase skin and internal temperature (Wilson et al. 2006; Wilson et al. 2007; Crandall et al. 2008; Lucas et al. 2008). I also used paired-pulse TMS to more directly measure cortico-cortical excitability serially over time. I additionally assessed the effects of passive heat stress on voluntary muscle strength, muscle fatigue, impairments in central activation, and skeletal muscle contractile properties of the wrist flexor muscles. I hypothesized that the passive heat stress will result in accelerated muscle fatigue and impairments in central activation, along with a concomitant decrease in intracortical excitability.
JUSTIFICATION

Thousands of people are exposed to environments that can be considered extreme. Firefighters, military personnel, industry workers, and athletes all frequently work and perform in environments which not only limit their potential production, but also provide risks to their health in the form of direct heating damage (i.e. heat stroke, fatigue, cramps, rash) and workplace accidents caused by impaired performance. While we have the knowledge to help limit potential negative effects of heat-stress through preventative measures (proper hydration; cool, breathable clothing), there is still much to be explored regarding the physiological mechanisms by which heat-stress causes fatigue. By increasing our knowledge, we can work to further prevent unwanted damage and accidents.

Much of the current knowledge on this subject has been obtained through observations of exercise-induced heat-stress. Relatively little work has been done to investigate passive heat-stress, which can remove many of the confounding variables associated with exercise (accumulation of metabolic products, additional cardiovascular stress). Even less work has been done to investigate neurological variables associated with passive heat-stress at a cortical level. Most of the existing work has also been performed exclusively on the lower limb (knee extensor muscles). Little has been done to investigate the effects of heat-stress on small muscle groups and muscles in the upper limb. This experiment is novel because it uses a sophisticated technique to measure cortical excitability in subjects who have undergone a passive heat-stress protocol with known cardiovascular effects. It will also look at the effects of passive heat-stress in a muscle group which has not been previously explored.

The information found in this experiment could be crucial in determining how heat-stress results in muscle fatigue and physical impairment. By helping to identify if and how passive-
heat stress affects humans at the cortical level, this experiment will help in the development of the appropriate countermeasures and treatments to limit damage caused by environmental heat-stress.
ASSUMPTION AND LIMITATIONS

In order to conduct this study the following assumptions must be made:

1. Equipment employed will be in proper working condition, and all data collected from such equipment will be accurate.

The following is a limitation of this study:

1. There are several physiological variables that could be altered with heating that will not be measured (e.g. motor unit discharge rate, muscle metabolism). Thus, while this study has been designed to provide comprehensive insight into the neuromuscular system, it is still limited to a certain degree. The reasons that other variables have not been assessed are primarily due to either financial constraints or technical/equipment capability.

The following are de-limitations of the study:

1. Subjects will volunteer for the study instead of being selected via random sampling; therefore conclusions cannot be generalized for the entire population.

2. Subjects will be young, healthy, and free of diseases, therefore conclusions cannot be generalized for the entire population.
REVIEW OF THE LITERATURE

Effect of Heat Stress on Human Physiologic Responses. Past research has shown heat stress to be strongly associated with decreases in work and exercise performance. For example, Ely et al. and Galloway et al., in similar experiments, found that the capacity for cycling performance is limited by environmental temperatures and that as environmental temperature increases, the time to task failure (point at which a rate of exercise cannot be maintained) decreases (Ely et al.; Galloway and Maughan 1997). In 2001, Kay et al. also contributed to the idea that heat stress negatively impacts work and exercise performance by observing signs of neuromuscular fatigue in subjects who performed a sustained cycling task in a warm, humid environment (Kay et al. 2001). In 2005, Drust et al. observed that power output of repeated sprint performances on a cycle ergometer is significantly impaired in a warm (40°C) environment compared to a cool environment (20°C) (Drust et al. 2005). Ely et al., in a 2007 study, compared data from past marathons which took place in dramatically different climates (temperatures ranging from 5-25°C). They found that marathon performance of both men and women was limited in warmer climates, especially in slower runners (Ely et al. 2007). Altareki et al. in 2009 again confirmed the idea of heat stress limiting exercise performance as they observed that cyclists exhibit impaired power output and inferior times during a 4 kilometer time trial in a simulated warm environment (Ely et al.; Galloway and Maughan 1997; Gonzalez-Alonso et al. 1999; Kay et al. 2001; Drust et al. 2005; Thomas et al. 2006; Ely et al. 2007; Altareki et al. 2009). Collectively, these studies provide a foundation of knowledge that leads to the conclusion that environmental heat stress impairs exercise and work performance.

Comparative studies observe similar decreases in task performance with increases in internal temperature. This can be seen in the work done by Fuller et al. in 1998 which observed
that despite varying initial body and environmental temperatures, rats consistently reached a point of voluntary activity failure when reaching a certain abdominal and hypothalamic temperature (~40°C) (Fuller et al. 1998). Gonzalez-Alonzo observed similar evidence in a 1999 study involving humans. Here, subjects exercised to fatigue on a cycle ergometer with varied initial core body temperatures and rates of heat acclimatization (controlled via a water conditioning garment). They found that regardless of initial temperature or rate of heat acclimatization, subjects reached a point of fatigue at a consistent esophageal temperature (~40°C) (Gonzalez-Alonso et al. 1999). In a 2000 study, Walters et al. observed that rats reached a point of exercise fatigue at a consistent rectal temperature that is independent of initial core temperature. They also found that the time to task failure was indirectly proportional to the initial core temperature (Walters et al 2000). These studies each provide insight that allows us to conclude that internal temperature is directly linked to the effects of heat stress-induced fatigue.

Several studies began to measure specific degrees of muscle failure due to heat stress. Muscle fatigue and central (voluntary) activation were both evaluated in an effort to determine whether the site of fatigue was at the neurological (central) or muscular (peripheral) level. Nybo and Nielsen (2001) observed dramatic impairments in central (voluntary) activation of the knee extensor (thigh) muscles, assessed by superimposing electrical stimulation during a maximal contraction, following extensive cycling in a warm environment (exercise-heat stress) (Nybo and Nielsen 2001). More recently, Morrison and colleagues demonstrated that an increase in core body temperature even in the absence of exercise (passive-heat stress) also impaired central activation of the knee extensor muscles (Morrison et al. 2004). Collectively, these findings have led to the hypothesis that the site for central activation failure associated with heat stress is at the cortical level (Nybo and Nielsen 2001; Cheung 2007).
To my knowledge, only one study has directly tested the effects of hyperthermia on indices of cortical excitability (Todd et al. 2005). In this insightful study, Todd and colleagues used single-pulse transcranial magnetic stimulation (TMS) as their primary means of assessment (note: TMS is discussed in detail in the next section). This technique uses electromagnetic induction, created through the production of a weak electrical current through a series of coils, to stimulate the neurons of the brain with minimum discomfort. A diagram of TMS can be seen in figure 1. Todd et al. used TMS to examine changes in motor evoked potential (MEP) amplitude and silent period duration (variables of cortical excitability), along with measures of central activation, muscle fatigue, and evoked muscle force properties following passive-heat stress. They observed that passive-heat stress resulted in impairments in central activation as well as faster muscle contractile relaxation rates, without a concomitant change in MEP amplitude or silent period duration.

Despite the insight obtained from the above-mentioned study, there are several limitations to this work. First, the hyperthermia stimulus was induced via head-out hot water immersion followed by a period where subjects dried themselves, ambulated to another laboratory space, and put on warm clothing prior to testing. This lack of continuous heating and less clarity as to the extent of the metabolic and cardiovascular strain make generalizations more difficult. Second, the effects of the passive-heat stress were not measured serially over time (e.g., before and after heat stress) and the control trial did not include thermoneutral water immersion. Lastly, the interpretation of data using single pulse TMS is somewhat limited because the resulting MEPs and silent periods can be mediated at both the cortical and spinal levels (Kobayashi and Pascual-Leone 2003).
Paired-Pulse Transcranial Magnetic Stimulation. The earliest work in brain stimulation techniques was conducted in the late 1800s and early 1900s by scientists such as Fritsch (1870), Ferrier (1876), Bartholow (1874), and Penfield and Jasper (1954) (Terao and Ugawa 2002). These men provided the fundamental understanding of the central nervous system that has allowed us to begin to unravel the complex nature of the brain. Even with ground work provided by these men, our capacity to explore the brain in human research and treat it in a clinical setting was limited until 1980 when Merton and Morton invented the transcranial electrical stimulator (Merton and Morton 1980). This instrument used a high-voltage electric current that was able to penetrate the scalp and evoke responses in the motor cortex. While this technique was a major breakthrough in terms of its investigative potential, the painful nature of the procedure limited its use to unconscious human subjects. Five years later, Barker and colleagues successfully demonstrated that motor cortex responses could be elicited via magnetic stimulation (Barker et al. 1985). This approach shared the noninvasive component of the transcranial electrical stimulator, but resulted in a pain-free stimulation of the cortex which allowed its transition into regular human subject research. Over the past 25 years magnetic brain stimulation has been used in a number of settings to both advance our knowledge of brain physiology and neuroplasticity and to treat a number of psychological disorders in a clinical setting.

Transcranial magnetic stimulation (TMS) is founded on the principal of electromagnetic induction that was discovered in 1838 by Michael Faraday. This principal states that electromagnetic induction is the result of voltage being applied across a conductor situated in a changing magnetic field or a conductor moving across a stationary magnetic field. A TMS unit consists of a wire coil which is capable of producing a high-current pulse which is subsequently
discarded at a rapid pace (~ 1 msec). This electric discharge produces a magnetic field perpendicular to itself that, depending on the coil used, can produce a magnetic field that exceeds 2 Tesla. This rapid magnetic field subsequently induces an eddy current within the brain that excites neurons in the motor cortex (Figure 1).

As stated before, the interpretation of data using single pulse TMS is somewhat limited because the resulting MEPs and silent periods can be mediated at both the cortical and spinal levels (Kobayashi and Pascual-Leone 2003). However, cortico-cortical excitability can be more directly examined by using paired-pulse TMS, which combines a conditioning stimulus with a test stimulus at different interstimulus intervals (Ziemann et al. 1995; Ziemann et al. 1996; Ziemann 2003; Ziemann 2004) (Figure 2). For example, when a subthreshold conditioning pulse (i.e. 5% less than motor threshold) precedes a suprathreshold test pulse (i.e. 30% above MT) by 15 msec the MEP amplitude associated with the test pulse is greater than that of a single unconditioned pulse of the same intensity (intracortical facilitation [ICF]). Conversely, when the interstimulus interval is 3 msec the test motor response is reduced by the conditioning pulse (short-interval intracortical inhibition [SICI]), and the test motor response is also inhibited when two suprathreshold pulses are separated by 100 msec (long-interval intracortical inhibition [LICI]). It is generally thought that SICI is mediated by gamma-aminobutyric acid (GABA) type A receptors (GABA_A) (Ziemann 2003; Florian et al. 2008), LICI is mediated by GABA type B receptors (GABA_B) (McDonnell et al. 2006; Florian et al. 2008), and ICF is mediated by excitatory glutamatergic interneurons and N-methyl-D-aspartate (NMDA) receptors (Ziemann et al. 1995; Ziemann 2003; Ziemann 2004; Reis et al. 2008). In general, SICI and ICF are considered to be mediated locally within the primary motor cortex (M1). LICI is also commonly
suggested to be mediated within M1 (Nakamura et al. 1997; Reis et al. 2008), although recent evidence suggests that it can also be influenced by spinal mechanisms (McNeil et al. 2009).
RESEARCH QUESTION AND APPROACH

PURPOSE

The purpose of this study is to advance the knowledge of the physiological effects of heat-stress and to help identify potential causes of heat-stress induced fatigue. I used a classical heat stress model (water-perfused suit) with well-established cardiovascular effects such as decreases in cerebral blood flow and increases in skin and internal temperature (Wilson et al. 2006; Wilson et al. 2007; Crandall et al. 2008; Lucas et al. 2008) to induce a passive-heat stress and measure its affects on neurological, muscular, and intracortical properties. By using a well-established passive heat-stress model, I was able to more specifically examine its effects on human performance and better control for confounding variables (e.g. metabolic exercise products, unknown cardiovascular changes). This study investigated the effects of passive heat-stress on voluntary muscle strength, muscle fatigue, impairments in central activation, and skeletal muscle contractile properties of the wrist flexor muscles. The wrist flexors have been chosen for two reasons. They are a very feasible muscle group to work well with TMS. They are innervated by an easily identified section of the brain and provide more consistent findings than the muscles of the lower limb. The wrist flexors are also a distal muscle group which can be easily removed from the heating suit to prevent unwanted elevations in muscle temperature. This study seeks to only examine the effects associated with elevations in core temperature as muscle temperature may affect the contractile properties of the muscle fibers and add an additional confounding variable. This study also used paired-pulse TMS to more directly measure cortico-cortical excitability serially over time. I hypothesized that the passive-heat stress would result in accelerated muscle fatigue and impairments in central activation along with concomitant decrease in intracortical excitability.
MATERIALS AND METHODS

General Overview of the Study Design. Ten healthy subjects participated in two testing sessions on different days separated by at least one week. During one of these sessions, the subjects underwent a passive-heat stress, and during the other visit, the subjects participated in a normothermia (control) protocol. The order of the visits was randomized. Each visit was conducted at the same time of day, and subjects were asked to report to the laboratory in a well-hydrated state and to avoid caffeine and alcohol for 24 hours before the experimental sessions. Baseline testing consisted of measurements of muscle strength, central activation, fatigue-resistance of the wrist flexor muscles, and paired-pulse TMS to assess cortical properties. Throughout baseline testing, heart rate, arterial blood pressure, skin temperature, and core temperature were continuously monitored. Upon completion of the baseline testing, subjects began the thermal protocol (passive-heat stress or normothermia). When the subject’s core body temperature increases 0.5°C above baseline (or ~ 30 minutes into the normothermia condition), a muscle strength analysis was performed to allow for a mid-testing assessment. After the subjects core body temperature had increased 1.0°C above baseline (or ~ 1-hour into the normothermia condition), the initial testing session was again repeated. The study design and timeline is illustrated in Figure 3 and specific details of the study protocol are described below.

Subjects. Ten healthy subjects participated in this study. Subjects were excluded if they were taking any medications or supplements, had any known neurologic or orthopedic limitations, or had a BMI greater than 30.0 kg/m². The Ohio University Biomedical Institution Review Board has approved this study, and all subjects were provided written informed consent prior to participation.
Thermal Conditions and Measurement of Temperature and Cardiovascular Outcomes

**Hyperthermia and Normothermia.** Each subject performed both a passive-heat stress and normothermia protocol. During normothermia, subjects were kept at a thermoneutral temperature by perfusing 35°C water through a high-density tube lined suit (Med-Eng Systems, Ottawa, ON, Canada). This water ran through the suit during the entire protocol. During the heat stress protocol, whole body heating was performed until the body’s core temperature was raised to ~1°C about baseline temperature. Passive-heat stress was accomplished by running 46°C water through the tube-lined suit. The forearm of the tested arm was not covered by the tube lined suit and thus wrist flexors of the tested arm were not directly heated. Testing was completed in the sitting position, but between testing sessions, subjects were reclined to a supine position.

**Skin and Core Body Temperature.** Throughout each protocol, continuous measurements of skin temperature and core temperature were obtained to monitor and track progress of heating. Mean skin temperature was measured using 4 thermocouples (chest, upper arm, thigh, and calf) and weighted according to the Ramanathan (Ramanathan 1964) formula. Core body temperature was measured by an ingestible pill telemetry system (HTI Technologies, Palmetto, FL).

**Arterial Blood Pressure and Heart Rate.** Blood pressure and heart rate were monitored throughout the experiment at the finger using the Penaz method (Finapres Ohmeda, Englewood, CO).

Muscle and Nerve Function Methods and Outcome Measures

**Electrical and Mechanical Recordings.** Electromyographic (EMG) signals were recorded from the dominant flexor carpi radialis (FCR) muscle using bipolar surface electrodes.
located longitudinally over the muscle on shaved and abraded skin with a reference electrode just distal to the medial epicondyle (Ag–AgCl, potential sensitive area of 22-mm, 25-mm center-to-center interelectrode distance; 2015 Nikomed Trace1, Hudson Valley, PA). The EMG signals were amplified (500–1,000x), bandpass-filtered (10–500 HZ), and sampled at 5,000 HZ (MP150, Biopac Systems). To quantify wrist flexion forces, subjects were seated on a Biodex System 4 with the arm extended parallel to the ground, the hand pronated, and the forearm supported (figure 4). The wrist joint was aligned to the rotational axis of a torque motor to which a constant-length lever arm was attached. The signal was scaled to maximize its resolution (208.7 mV/N•m; Biodex Researchers Tool Kit Software), smoothed over a 10-point running average, and sampled at 625 HZ (MP150 Biopac Systems). Subjects received visual feedback of all exerted forces on a 53-cm computer monitor located 1-meter directly in front of them.

Muscle Strength and Central Activation. To assess maximal wrist flexion strength, subjects performed a minimum of three maximal voluntary isometric contractions (MVC) with a 1–2-min rest period between each contraction. If subjects continually record more force with increasing trials, or if the two highest trials are not within 5% of each other, additional trials were performed until a plateau is reached. Verbal encouragement was provided during testing, and visual feedback of the exerted forces was displayed on a computer monitor located 1-m in front of the subject. The highest value was considered the MVC.

To determine what percentage of the total force generating capacity of the wrist flexors can be produced voluntarily, a combination of voluntary and electrically stimulated contractions were performed. Transcutaneous electrical stimulation was delivered to the median nerve in the bicipital groove via stimulating electrodes (Ag–AgCl, 2015 Nikomed Trace1, Hudson Valley, PA). The electrical stimuli consisted of 0.5-msec pulses (Digitimer DS7; Digitimer, Welwyn...
Garden City, Hertfordshire, UK). Stimuli were administered at increasing stimulation intensities until the FCR peak-to-peak (p-p) EMG amplitude reached a plateau ($M_{max}$), and for central activation testing the intensity was subsequently increased 20% above that eliciting $M_{max}$. Next, to assess central activation a supramaximal electrical doublet (100 Hz) was delivered while the subject performed a 4–5 s MVC. The increase in force immediately following the stimulation was expressed relative to a potentiated response evoked 1–2 s after the MVC, and central activation was calculated as follows:

\[
\% \text{ central activation} = \left[1 - \left( \frac{\text{evoked force during MVC}}{\text{evoked force following MVC}} \right) \right] \times 100.
\]

During the assessment of central activation verbal encouragement and visual feedback of the exerted force was provided. A sample central activation trace can be seen in figure 5

**Muscle Contractile Properties.** To identify changes in the functional properties of the wrist flexor muscles, I evaluated the force-time curves evoked from an electrical doublet (100 Hz) delivered 1 s following a 5-s MVC (post activation potentiated doublet). Two trials were performed and averaged for calculating peak force, the relative rate of evoked force development between 10 and 90% of peak force ($+\text{dF/dt}$), and the relative rate of force relaxation between 90 and 50% of peak force ($-\text{dF/dt}$).

**Fatigue Task.** To determine fatigue-resistance, subjects performed a sustained wrist flexion MVC for 60-secs. Subjects were given a 2-min rest before the start of the fatigue task, and they were instructed to contract as hard as possible for 60-secs. Verbal encouragement was provided during the first 5-secs of the contraction, and then verbal encouragement was ceased. Subjects were provided feedback of the force level, but they will not be aware of the time remaining in the task. One to two seconds prior to the end of the task, central activation was again assessed as described above. Muscle fatigue was quantified as the percent reduction in
MVC force over the last 5-seconds of the fatigue task (prior to the measurement of central activation).

**Transcranial Magnetic Stimulation.** TMS pulses were delivered using two connected Magstim (Wales, UK) 200² stimulators through a 70-mm figure-eight coil (figure 6). The coil was positioned tangential to the scalp and 45° to the midline so that the induced current flows in a lateral-posterior to medial-anterior direction (Brasil-Neto et al. 1992), which predominantly activates corticospinal neurons transsynaptically (Werhahn et al. 1994). The stimulation location that elicited the largest p-p amplitude of the FCR MEP was identified and marked on a Lycra cap for coil placement. Next, resting motor threshold (MT) was determined while subjects were seated in the dynamometer by delivering single pulses at gradually increasing stimulation intensities. MT was determined and expressed as a percent of the maximum stimulator output. MTs were determined using a TMS intensity well below MT, and gradually increasing the intensity in 2% increments until MEPs are observed. Resting MT was defined as the stimulation intensity that elicited MEPs with a p-p amplitude of >50 µV in at least four of eight trials. During this assessment, the muscle was completely relaxed as monitored by the EMG signal.

Paired pulse transcranial magnetic stimulation was used to measure variables of intracortical excitability. This combines a conditioning stimulus with a test stimulus at different interstimulus intervals (Ziemann et al. 1995; Ziemann et al. 1996; Ziemann 2003; Ziemann 2004) (figure 2), and allows for a more direct measurement of cortico-cortical excitability. For example, when a subthreshold conditioning pulse (i.e. 5% less than motor threshold) precedes a suprathreshold test pulse (i.e. 30% above MT) by 15-msec the MEP amplitude associated with the test pulse is greater than that of a single unconditioned pulse of the same intensity (intracortical facilitation; ICF). Conversely, when the interstimulus interval is 3-msec the
conditioning pulse reduces the test motor response (short-interval intracortical inhibition; SICI), and the test motor response is also inhibited when two suprathreshold pulses are separated by 100-msec (long-interval intracortical inhibition; LICI). It is generally thought that SICI is mediated by gamma-aminobutyric acid (GABA) type A receptors (GABA\textsubscript{A}) (Ziemann 2003; Florian et al. 2008), LICI is mediated by GABA type B receptors (GABA\textsubscript{B}) (McDonnell et al. 2006; Florian et al. 2008), and ICF is mediated by excitatory glutamatergic interneurons and N-methyl-D-aspartate (NMDA) receptors (Ziemann et al. 1995; Ziemann 2003; Ziemann 2004; Reis et al. 2008). In general, SICI and ICF are mediated locally within the primary motor cortex (M1). LICI is commonly suggested to be mediated within M1 (Nakamura et al. 1997; Reis et al. 2008), although recent evidence suggests that it can also be influenced by spinal mechanisms (McNeil et al. 2009). SICI, ICF, and LICI were evaluated using paired magnetic pulses under resting conditions as has been previously described (Clark et al.; McGinley et al.). To quantify SICI, ICF, and LICI at rest the test pulse (second pulse) were set at an intensity that, when it is given alone, evokes an MEP of ~0.5 to 1.0 mV p-p amplitude. For SICI and ICF quantification the intensity of the first (conditioning) stimulus was set to 70% of MT, and for LICI quantification the first (conditioning) stimulus was set at the intensity used for the aforementioned test pulses. The interstimulus intervals for assessing SICI, ICF, and LICI were 3, 15, and 100 ms, respectively. A total of eight trials of each of these three conditions were randomly performed in blocks and averaged. SICI, ICF, and LICI were operationally defined by expressing the mean p-p amplitude of the conditioned MEP at each interstimulus interval as a percentage of the mean p-p amplitude of the unconditioned test pulse.

**Statistics.** Repeated-measures analysis of variance procedures followed by Sidak post-hoc tests to control for multiple comparisons were utilized to determine changes over time.
between the two conditions (Within subjects factor: time and thermal condition). For all analyses, a two-tailed preset α-level of significance equal to 0.05 was required for statistical significance. Additionally, to further aid in interpretation, effect size (ES; partial eta-squared) was also reported. The SPSS statistical package (v. 17.0, Chicago, Illinois) was used for data analysis.
RESULTS

3.1 Core Body and Skin Temperature. We observed a significant condition by time interaction for the change in core body temperature (p<0.01, ES=0.90). Further examination of the data indicated that core body temperature increased in the passive-heat stress condition (37.26±0.4 to 38.23±0.4 °C; p<0.01, ES=0.84), whereas a slight decrease in core body temperature was observed in the normothermic condition (37.45±0.5 to 37.12±0.8 °C; p=0.06, ES=0.37). Similarly, we observed a significant condition by time interaction for the change in mean skin temperature (p<0.01, ES=0.91). Mean skin temperature increased in the passive-heat stress condition (34.5±0.7 to 37.2±1.0 °C; p<0.01, ES=0.87), but did not change in the normothermic condition (33.7±0.9 to 33.9±0.9 °C; p=0.42, ES=0.09) (Figure 7).

3.2 Heart Rate and Blood Pressure. We observed a significant condition by time interaction for the change in heart rate (P=0.050, ES=0.78) from baseline to post testing. Heart rate increased in the passive-heat stress condition (79.5±20 to 110.0±23 beats/min; p=0.04 ES=0.81), while no change was observed in heart rate during the normothermic condition (84±22 to 80±17 beats/min; p=0.09 ES=0.50). No significant condition by time interaction was observed for changes in mean arterial blood pressure (Hyperthermia: 94±10 to 91±21 mm Hg, Normothermia: 99±6 to 101±9 mm Hg; p=0.60, ES=0.12).

3.3 Muscle Strength, Fatigue, and Central Activation. Passive-heat stress did not alter muscle strength, muscle fatigue or central activation. Specifically, we did not observe a condition by time interaction for wrist flexor muscle strength during brief MVCs (p=0.40, ES=0.10) (Figure 8), nor did we observe a condition by time interaction for muscle fatigue during the 60 s sustained maximal contraction (p=0.91, ES<0.01) (Figure 9). Similarly, we did
not observe a condition by time interaction for central activation during brief MVCs (p=0.50, ES=0.08) (Figure 8) or following the 60 s fatigue task (p=0.15, ES=0.31) (Figure 9).

3.4 Muscle Contractile Properties. Passive-heat stress did not alter the muscle contractile properties. Specifically, we did not observe a condition by time interaction for evoked peak torque (p=0.85, ES<0.01), the rate of peak torque development (p=0.70, ES=0.02), or the rate of peak torque relaxation (p=0.80, ES=0.01) (Figure 10).

3.5 Intracortical Properties. Passive-heat stress did not alter intracortical excitability. Specifically, we did not observe a condition by time ICF (p=0.17, ES=0.20), SICI (p=0.10, ES=0.28), or LICI (p=0.17, ES=0.29) (Figure 11).
DISCUSSION

Numerous investigations have reported that exercise-heat stress reduces human performance and exacerbates muscle fatigue (Galloway and Maughan 1997; Gonzalez-Alonso, Teller et al. 1999; Drust, Rasmussen et al. 2005; Thomas, Cheung et al. 2006; Ely, Cheuvront et al. 2007; Altareki, Drust et al. 2009). However, much less is currently known about the independent effects of heat stress in the absence of exercise and in more moderate heat stresses such as those more typically experienced in occupational settings. Accordingly, the purpose of this work was to determine the effect of moderate passive-heat stress on muscle function (e.g., fatigability, contractile properties) and central nervous system properties (e.g., central activation, intracortical excitability). The rationale for this experiment was to further examine the postulate that the site for central activation failure associated with heat stress is at the cortical level (Cheung 2007; Nybo 2008). We hypothesized that the passive-heat stress would result in accelerated muscle fatigue and impairments in central activation, along with a concomitant decrease in intracortical excitability. While our experimental protocol resulted in the expected elevations in core body and mean skin temperature, we did not observe an effect of the passive-heat stress on any of our indices of skeletal muscle or nervous system function. This may indicate that workers performing hand tasks should not be adversely affected by neuromuscular fatigue issues if their body temperature is maintained within 1.0 °C.

In this study, we did not observe a heat stress induced change in ICF, SICI, or LICI, indicating a lack of change in intracortical excitability. A previous single pulse TMS study by Todd et al. (2005), observed decreases in elbow flexor central activation and corticospinal excitability (as evidenced by a prolonged silent period duration) during a sustained 2-min MVC fatigue task after an increase in internal temperature of ~1.3 °C; however, no changes were
observed in subjects under resting conditions in which they were not actively contracting. Thus, our resting paired pulse TMS data appear to corroborate their single pulse TMS data. There may be experimental reasons why our fatigue task data show different results. First, their hyperthermia stimulus was induced via head-out hot water immersion followed by a period where subjects dried themselves, ambulated to another laboratory space, and put on warm clothing prior to testing. This lack of continuous heating and less clarity as to the extent of the cardiovascular strain from their mode of whole-body heating make comparisons and interpretations more difficult. Additionally, direct heating of the muscle—which had an effect on contractile properties—occurred with their heating protocol, which was substantially different than our protocol whereby the limb being tested was not heated. Second, the effects of the passive-heat stress were not measured serially over time (e.g., before and after heat stress) and the control trial did not include thermoneutral water immersion. Third, our observations were in wrist flexors vs. their observations in elbow flexors. Lastly, the interpretation of data using single pulse TMS is somewhat limited because the resulting MEPs and silent periods can be mediated at both the cortical and spinal levels (Kobayashi and Pascual-Leone 2003), rather than solely at the cortical level. Hence, it appears that intracortical excitability is not altered in moderate well-controlled thermal stresses, but this could be limited to wrist flexor muscles.

In this study, we did not observe changes in muscle contractile properties, muscle strength, muscle fatigue, or central activation. This is in contrast to some previous studies utilizing severe heat stresses (Brazaitis and Skurvydas 2010; Morrison, Sleivert et al. 2004; Thomas, Cheung et al. 2006). Highlighting this, Morrison et al. (2004) observed that passive-heat stress resulting in an elevation of core body temperature to 39.4 °C resulted in a 13% reduction in knee extensor strength and a similar (11%) reduction in central activation (Morrison,
Sleivert et al. 2004). Hence, it appears that severe heat stress may decrease neuromuscular function but more mild heat stresses do not affect muscle function. This is interesting because the current study did result in significant changes in cardiovascular function (increase in heart rate of ~30 bpm) and blood volume redistribution (Crandall, Wilson et al. 2008) and decreases in cerebral blood flow (Wilson, Cui et al. 2002; Wilson, Cui et al. 2006) occur during mild heat stress, but these cardiovascular changes must not significantly contribute to neuromuscular fatigue.

In the current study we selected wrist flexor muscles because these small distal muscles are used heavily in hand related work tasks. Previous reports suggest that severe passive heat stress results in impairments in central activation in large appendicular muscle groups, namely the knee extensors. Interestingly, exercise performance models that have identified decreases in exercise performance are often reported in cycling or running which utilize the knee extensors (Brazaitis and Skurvydas 2010; Nybo and Nielsen 2001; Morrison, Sleivert et al. 2004; Thomas, Cheung et al. 2006), rather than focusing on muscle groups more involved in work tasks such as the wrist flexors. Intermuscle differences in levels of central activation have previously been observed—with impairments being particularly pronounced in the knee extensors (Behm, Whittle et al. 2002). Additionally, fatigue-induced impairments in central activation are suggested to be muscle group dependent with the knee extensors exhibiting a pronounced decrement in central activation (Enoka and Duchateau 2008). Thus, it is possible that the smaller, weaker and more distal wrist flexor muscles are less prone to the effects of passive-heat stress. This hypothesis is consistent with observations of Saboisky et al. (2003) who observed that exercise-heat stress induced central activation failure in the exercised knee extensors, but not the unexercised elbow flexors (Saboisky, Marino et al. 2003). This indicates that heat stress may
not be robust enough to globally alter central activation of all skeletal muscles or is more selective to specific muscle groups and/or task-dependent differences.

There are again several limitations associated with this study. The subjects of this study were volunteers and not taken from random sampling. This limits our ability to apply the results of this study to the general population. The subject population of this study also consisted of young and healthy individuals. This again limits our ability to apply these results to a general population in which the individuals are not all young and healthy. While our goal was to see the effects of an elevated core temperature on physiological impairment in what is likely to be an occupational elevated temperature, we are only able to estimate what a likely elevated core temperature would be in certain occupation settings. The actual elevations in core temperature would vary between individuals, environments, and tasks being performed. Accordingly, these results cannot be applied to any one specific task or profession.

In summary, severe exercise-heat stress is well known to reduce human performance, exacerbate skeletal muscle fatigue, and impair central activation (Cheung 2007; Nybo 2008). Heat stress can also decrease both cognitive and manual occupational related tasks (Jay and Kenny 2010). This study utilized paired-pulse TMS to measure cortico-cortical excitability serially over time during passive heat stress, and quantified the effects on voluntary muscle strength, muscle fatigue, impairments in central activation, and skeletal muscle contractile properties of the wrist flexor muscles. Elevations in heart rate, and core body and mean skin temperature were observed, but we did not observe an effect of the passive heat-stress on any of our indices of skeletal muscle or nervous system function in the wrist flexors. These findings suggest that a passive heat stress that raises the core body temperature 1 °C (~ 38.2 °C) does not impair muscle function, central activation or motor cortical excitability of the wrist flexor
muscles as can occur in severe exercise-heat stress of larger, more proximal muscles. Thus, neuromuscular performance of smaller, more distal muscle groups involved in hand and wrist flexion tasks utilized in many occupational tasks should not be affected by moderate heat stress.

FUTURE DIRECTIONS

This study found no association with elevation in core temperature and changes in muscular and intracortical physiological performance; however, it is possible that certain limitations of our study may have prevented us from finding significance. The study could be repeated with both a larger subject pool and a more diverse population. It has been shown that there are differences in intracortical activity among different groups, such as between young and elderly individuals, so it is possible that different groups may respond differently in the study. Our results are also contrary to existing research which has found impairments in physiological performance associated both during exercise and at rest with slightly higher elevated core body temperatures (~40 °C). If physiological inhibition is associated with a specific core body temperature, the exact temperature should be identified so that safe working conditions can be mandated to prevent core temperature elevations from reaching this level. Studies may also be performed examining the changes in physiological performances associated specific occupational tasks (e.g. common tasks performed by firefighters, industrial workers, and soldiers) in specific occupational environmental conditions. This will provide a more insightful look at each of the individual conditions and occupations.
BIBLIOGRAPHY


McGinley, M., R. L. Hoffman, et al. "Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults." _Exp Gerontol._


**Figure 1: The basic mechanism of TMS.** The TMS coil induces a magnetic field, which penetrates the scalp and induces an Eddy current within the motor cortex. This eddy current is then able to stimulate neurons within the brain.

Figure 2. The change of motor evoked potential (MEP) sizes obtained with paired pulse TMS. **A:** Measurement of short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). The intensity of the conditioning pulse (CP) was set 5% below active motor threshold, and the test pulse (TP) was set to evoke MEP’s between 0.5-1 mV. At short interstimulus intervals (e.g., 3-msec) the CP inhibits the MEP in comparison to the TP only (SICI), whereas at longer interstimulus intervals (e.g., 15-msec) it facilitates the MEP (ICF). **B:** Measurement of long-interval intracortical inhibition (LICI). To quantify LICI two TP were delivered at an interstimulus interval of 100-msec. This results in the second MEP being inhibited in comparison to the first MEP. 

Hyperthermia: Core temperature increased 1 °C above baseline
Normothermia: Core temperature maintained at baseline for 1 hour

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<th>Baseline Testing</th>
<th>Thermal Condition (Hyperthermia or Normothermia)</th>
<th>Post Testing</th>
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</thead>
<tbody>
<tr>
<td>Muscle Strength</td>
<td>Mid-Testing</td>
<td>Muscle Strength</td>
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<tr>
<td>Central Activation</td>
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<td>Muscle Fatigue</td>
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<td>Paired Pulse TMS</td>
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Figure 3. Study design and timeline.
Figure 4. Experimental set-up for testing muscle strength and fatigue-resistance.
Figure 5. Sample Central Activation Trace.
Figure 6. Illustration of transcranial magnetic stimulation.
Figure 7. **Passive-heat stress increased core body and skin temperature.** Passive-heat stress (closed symbol) resulted in a significant increase in core body temperature (A) and mean skin temperature (B) in comparison to baseline at both the mid-testing and post-testing time points. No effect was observed in the normothermic condition (open symbol).

*p ≤ 0.05 relative to baseline.
Figure 8. Passive-heat stress did not significantly influence wrist flexor muscle strength or central activation. **A.** The effect of passive-heat stress and normothermic control conditions on voluntary muscle strength. **B.** The effect of passive-heat stress and normothermic control conditions on wrist flexor central activation.
Figure 9. Passive-heat stress did not influence wrist flexor muscle fatigue, or the central activation at the end of a 60-second maximal contraction fatigue task. Prior to the thermal condition (baseline) and following the thermal condition (post-testing) the passive-heat stress and normothermic control groups exhibited a similar reduction in maximal voluntary contraction (MVC) torque (A) and central activation (B) at the end of a sustained maximal 60-s contraction.
Figure 10. Passive-heat stress did not influence the wrist flexor muscle contractile properties. Prior to (baseline) and following (post-testing) the thermal conditions the passive-heat stress and normothermic control groups did not exhibit changes in peak doublet torque (A), or the associated rates of evoked torque development (+dF/dt; panel B) or relaxation (-dF/dt; panel C).
Figure 11. Passive-heat stress did not influence intracortical properties as assessed using paired-pulse TMS. Prior to (baseline) and following (post-testing) the thermal conditions the passive-heat stress and normothermic control groups did not exhibit changes in short-interval intracortical inhibition (SICI; panel A), intracortical facilitation (ICF; panel B), or long-interval intracortical inhibition (LICI; panel C).
The following research study has been approved by the Institutional Review Board at Ohio University for the period listed below.

**Effect of Passive Heating on Cortical Excitability and Muscle Function**

**Researcher(s):** Brian Clark
Thad Wilson

**Advisor:**
(if applicable)

**Department:** Biomedical Sciences

[Signature]
Robert Staron, Ph.D., Interim Chair
Institutional Review Board

**Approval Date:** Dec. 16, 2009

**Expiration Date:** Dec. 2, 2010

This approval is valid until expiration date listed above. If you wish to continue beyond expiration date, you must submit a periodic review application and obtain approval prior to continuation.

The approval remains in effect provided the study is conducted exactly as described in your application for review. Any additions or modifications to the project must be approved by the IRB (as an amendment) prior to implementation.

Adverse events must be reported to the IRB promptly, within 5 working days of the occurrence.
Ohio University Consent Form

Title of Research: Effect of Passive Heating on Cortical Excitability and Muscle Function

Researchers: Brian Clark, PhD. and Thad Wilson, Ph.D.

You are being asked to participate in a research study. For you to be able to decide whether you want to participate in this project, you should understand what the project is about, as well as the possible risks and benefits in order to make an informed decision. This process is known as informed consent. This form describes the purpose, procedures, possible benefits, and risks. It also explains how your personal information will be used and protected. Once you have read this form and your questions about the study are answered, you will be asked to sign it. This will allow your participation in this study. You should receive a copy of this document to take with you.

Explanation of Study
The purpose of this study is to determine the effects of increased body temperature on the function of the nervous system. By determining whether or not an increase in body temperature has an effect on nervous system function, we may be able to gain further insight into the effects of increased body temperature on muscle fatigue and the role that the brain plays in muscle fatigue.

You should not participate in this study if you have: any cardiovascular problems, a history of blood clotting or sickle cell anemia, high blood pressure (140/90 mmHg), a body mass index greater than 30 kg/m^2 (number calculated from a person's weight and height that is a fairly reliable indicator of body fatness for most people), gastrointestinal problems, a history of smoking, alcohol or drug abuse within the past 6-months, are taking ANY medication or supplements (including contraceptive hormones), have metal implants or devices that could be disrupted by a magnetic field, are pregnant or are planning to become pregnant during the study.

We will be recruiting participants (male and female) between the ages of 18-40 years who meet the above criteria. Participation will require three visits to the lab, including a 1 hour orientation session and 2 testing sessions of approximately 3 hours each. The first visit to the laboratory is an orientation session where we will describe all procedures to you and answer any questions. During this visit, if you decide to participate, you will complete several forms to determine if you are eligible for the study. If you are qualified for the study we will then have you perform two testing sessions to collect data. A minimum of 4 days and a maximum of 14 days will separate these visits.

Both of the testing sessions will require wearing a body suit where we can control body temperature, and all subjects will have their strength and endurance of the forearm muscles assessed as well as the ability of your brain to activate those same muscles. On one visit, your body temperature will remain normal, while during the other your body temperature will be slowly elevated using warm water that is circulated through the body suit. The water will not come in contact with your skin;
it will be contained within the suit itself. To monitor your internal body temperature you will swallow a small device that will allow us to detect and record your body temperature.

The testing sessions are designed to assess your nerve function as well as the strength of your muscles under different conditions of body temperature. The testing session will begin by swallowing a temperature pill and by us shaving the skin on your dominant forearm and cleaning it with alcohol followed by us placing sticky electrodes on your skin. These electrodes will record the electrical activity of your muscles. Then we will place some additional electrodes on your skin to determine your skin temperature and monitor your heart rhythm, and then have you put a body suit on so that we can control your temperature. Next, you will be seated in a machine where your hand will be attached to a device designed to measure the force of your forearm muscles, and we will determine your muscle strength. In doing this we will ask you to contract your forearm muscles (push) as hard as you can against an immovable object. After we know your strength we will then evaluate your muscles responses to electrical and magnetic stimulation. In doing this we will place some small electrodes around your elbow (electric stimulation) or place a magnetic coil over the top of your head. Either through the electrodes on your elbow or through the coil near your head, your nerves will be periodically stimulated and your forearm muscles will contract. During this time you will either be at normal temperature or you will have your body temperature elevated. The intensity of the stimulations will vary, but overall each stimulation pulse will be very short (milliseconds long). During some of the stimulations you will be asked to sit quietly, while during others you will be asked to contract your wrist muscles at certain intensity (i.e. 15% of max strength).

Also at the beginning and the end of each testing session you will be asked to contract your forearm as hard as you can for sixty seconds to assess muscle endurance.

**Risks and Discomforts**

There are inherent risks associated with participation in this research study. The risks associated with the testing will be reviewed below.

- The sticky electrodes that are placed are your arm may cause a skin irritation. This irritation generally subsides after a few days.
- You will experience some pain/discomfort during the testing. For example, when we apply periodic electrical stimulation to your nerves this results in some mild discomfort as it is “shocking” you. This discomfort will be extremely brief (milliseconds long), but there are no lasting effects.
- Muscle strength and fatigue testing: It is possible that muscle soreness may result from the exercise testing. If this does occur it will peak within 24-48 hours following the testing session and then gradually subside.
- The magnetic coil placed over your brain that will induce an electric current and make your muscles contract should not be painful per se, but is frequently described as “weird”. When we do this you will hear a sharp sound that could cause your ears to ring. To minimize this we will give you ear plugs to reduce this noise. More common complaints during or following this procedure are neck pain
or headache. It is unknown if these complaints are due to having to sit still or due to the muscles contracting and creating a tension-type headache. These symptoms will probably appear in around 1 out of 4 subjects tested; however, they typically dissipate within a day, and respond well to acetaminophen (Tylenol). The magnetic coil elicits a magnetic field, so you should not participate in this study if you have any metallic or electrical objects in or on your body (i.e. cardiac pacemakers, metal plates). There is no radiation exposure associated with this. There is a theoretical chance that the magnetic stimulation could cause a seizure, although this has never been known to occur using the device in the manner that we will in healthy people. However, if you have a predisposition to seizures or are taking certain anti-depressant medications you may be susceptible to this. Therefore, if you have a family history of seizures or epilepsy, if you take anti-depressant medications or have experienced a traumatic head injury you should not participate in this study. The magnetic coil makes a 'popping' noise when it is used. You will be asked to insert foam ear plugs during this portion of testing to protect your hearing. Some subjects may report tinnitus or a ringing of the ears but this is transitory in nature and short-lived. The muscles and nerves near the stimulating coil are activated by TMS. Thus, in susceptible individuals TMS may cause persistent muscle tension-type headaches and neck pain. These side effects have been reported to respond well to acetaminophen. It should also be noted that these side effects have been observed in sham-stimulation studies (nine studies have reported this), and it has been speculated that these side effects may be related to the subject having to sit still during this procedure. In general the reported headaches in the literature are "mild"—however, we have had one case of a migraine headache developing after TMS— but it is difficult to know if this was due to TMS per se.

- **Skin temperature:** There are no known risks of measuring skin temperature. There could be skin irritation from the adhesive tape used to connect the probe holder to the skin. To minimize this we will use hypoallergenic tape when possible.

- **Skin blood flow:** There are no known risks of shining a low powered laser light into the skin. There could be skin irritation from the adhesive tape used to connect the probe holder to the skin. To minimize this we will use hypoallergenic tape when possible.

- **Internal temperature:** There are minimal risks associated with measuring temperature with a pill. However, you must not have an MRI performed until the pill is no longer in your body (see below). The risks involved in this measurement are the pill aggravating a gastrointestinal condition, getting caught in an existing blockade, causing a gag reflex, or being swallowed into the lungs. The pill that takes your temperature will pass through the gastrointestinal tract and is usually eliminated from the body as part of normal waste production in approximately 24-72 hours. It is possible that the sensor could get stuck in your gut, thus it is very important to be honest about any gastrointestinal disorders during the medical history. If gastrointestinal discomfort occurs following ingestion of the pill, report it immediately to a health care practitioner and Brian Clark (see below contact information). You will receive a temporary hospital bracelet warning medical personnel that you should not have an MRI within the time indicated on the bracelet. You will also be asked to return to the laboratory 2 days after the experiments to allow us to confirm that the probe has been eliminated (this can
be checked via the telemetry monitoring system and will take less than 1 minute. If the probe is still detected you will be asked to return to the laboratory daily until we confirm it has been eliminated.

- Whole-body heating and cooling: There are minimal risks for a person to perform whole-body heating. You may feel uncomfortably hot when we are pumping the water through the suit. It is also possible that heating could make small bumps appear on your skin. This happens if your sweat glands get clogged, if you notice this please let us know immediately. If you do get these bumps during heating it is not serious and they will decrease over the next few days.

- In the event that these risks and discomforts occur and are of a serious nature please seek medical care (in the event of a medical emergency call 911), and also please contact Brian Clark (cell phone: 828.447.8732). Examples of serious events would be a headache lasting more than 24 hours after the end of a testing session or a seizure.

**Benefits**

Although there are no direct benefits to you as a subject, this study will greatly enhance the scientific understanding of the neural alterations that occur as a result of increases in body temperature. At the present there is very little known on this topic, and because increased body temperature often results in fatigue and loss of physical function, it is imperative that the basic physiologic adaptations are understood.

**Confidentiality and Records**

Only the investigators in the study will have access to the data from the individual subjects. Published or presented data will not identify subjects in any way. Subjects will not be audiotaped or videotaped. All medical history files will be kept in a locked file cabinet located in our office facilities (room 211 or 221 Irvine Hall). If anything is discovered about any subjects for whom medical attention would be appropriate, we will suggest to the subject that they see a physician about it. Once this research has been completed the files will be kept for an additional five years and then destroyed.

Additionally, while every effort will be made to keep your study-related information confidential, there may be circumstances where this information must be shared with:

- Federal agencies, for example the Office of Human Research Protections, whose responsibility is to protect human subjects in research;
- Representatives of Ohio University (OU), including the Institutional Review Board, a committee that oversees the research at OU;

**Compensation**

Participants will receive a total of $100 for participating in the entire study. Subjects will receive a prorated portion of that money for each session of testing that they participate in (i.e. $50 per session completed).
Contact Information
If you have any questions regarding this study, please contact Brian Clark, Ph.D. at 740-593-2354 or email at clarkb2@ohio.edu. If this is an urgent matter Brian Clark can be reached on his cell at 828.447.8732. In the event of a medical emergency please call 911. Additionally, if symptoms exist following completion of the study please contact Brian Clark.

If you have any questions regarding your rights as a research participant, please contact Jo Ellen Sherow, Director of Research Compliance, Ohio University, (740)593-0664.

By signing below, you are agreeing that:
• you have read this consent form (or it has been read to you) and have been given the opportunity to ask questions
• known risks to you have been explained to your satisfaction.
• you understand Ohio University has no policy or plan to pay for any injuries you might receive as a result of participating in this research protocol
• you are 18 years of age or older
• your participation in this research is given voluntarily
• you may change your mind and stop participation at any time without penalty or loss of any benefits to which you may otherwise be entitled.

Signature________________________________________ Date________________

Printed Name____________________________________

Version Date: [12/15/09]
Passive-heat stress does not induce muscle fatigue, central activation failure or changes in intracortical properties of wrist flexors

Robert W. Bendera, Thad E. Wilsona,b,c, Richard L. Hoffmana and Brian C. Clarka,b*

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This study evaluated the effect of passive-heat stress on the neuromuscular properties of the wrist flexor muscles, which are commonly used in manual labour hand tasks. A combination of techniques were utilised, involving nerve stimulation and paired-pulse transcranial magnetic stimulation to assess changes in muscle strength, contractile properties, fatigue-resistance and central activation as well as indices of intracortical excitability in 10 healthy humans who were exposed to a passive heat stress protocol as well as a normothermia control protocol. Passive-heat stress increased core body temperature ∼1°C (37.2 ± 0.4 to 38.2 ± 0.4°C; p < 0.01), mean skin temperature (34.5 ± 0.7°C to 37.3 ± 1.1°C; p < 0.01), and heart rate (79.5 ± 20.0 to 110.0 ± 23.0 beats/min; p = 0.04). No effect was observed on muscle strength, contractile properties, muscle fatigability, central activation or indices of intracortical excitability (p > 0.05). These data indicate that allowing internal temperatures of workers to increase ≤1.0°C does not affect neuromuscular properties of the wrist flexors.

Exercise-heat stress has been shown to reduce human performance and exacerbate muscle fatigue. However, less is known about passive-heat stress, especially during milder heat stress encountered in many occupational settings. Accordingly, the effect of occupationally relevant passive-heat stress on the neuromuscular properties of the wrist flexors was examined.

Keywords: central activation; heating; transcranial magnetic stimulation

1. Introduction

Individuals who are exposed to extreme heat or work in hot environments are at increased risk for the development of heat illnesses and have increased incidences of workplace accidents and injuries (National Institute for Occupational Safety and Health 2009). Heat stress has been strongly associated with decreases in exercise performance (Galloway and Maughan 1997, Gonzalez-Alonso et al. 1999, Drust et al. 2005, Thomas et al. 2006, Ely et al. 2007, Altareki et al. 2009). Comparative studies observe similar decreases in the drive to ambulate with large increases in internal temperature (Fuller et al. 1998, Walters et al. 2000). Workers, however, rarely perform sustained maximal efforts or increase internal temperatures to the extent of endurance athletes. Many governments have labour codes that limit internal temperature increases to ∼1.0°C above resting values (Jay and Kenny 2010). Certain occupations such as firefighting, foundry work and industrial baking can expose workers to high ambient temperatures and induce moderate heat stress, but it is less clear what effect this moderate heat stress has on neuromuscular fatigue and performance.

Muscle fatigue – defined here as an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force (Enoka and Stuart 1992) – during heat stress could arise from: i) neurological (central); ii) skeletal muscle (peripheral) factors, as it is well known that the output from these sources controls force production (Duchateau and Enoka 2002, Clark and Manini 2008). Nybo and Nielsen (2001) observed dramatic impairments in central activation of the knee extensor muscles – assessed by superimposing electrical stimulation during a maximal contraction—following exercise-heat stress that elevated core body temperature to 40°C (Nybo and Nielsen 2001). Morrison et al. (2004) demonstrated that an increase in core body temperature to 39.4°C even in the absence of exercise (passive-heat stress) also impaired central activation of the knee extensor muscles. Collectively, these findings have led to the hypothesis that the site for central activation failure associated with heat stress might be at the cortical level (Cheung 2007, Nybo 2008). To the present authors’ knowledge, only one study has directly tested the effects of hyperthermia...
on indices of motor cortical excitability (Todd et al. 2005). In this insightful study, Todd and colleagues used single-pulse transcranial magnetic stimulation (TMS) to examine changes in motor evoked potential (MEP) amplitude and silent period duration, together with measures of central activation, muscle fatigue and evoked muscle force properties of the biceps muscles following passive-heat stress. They observed that passive-heat stress resulted in impairments in central activation and faster muscle contractile relaxation rates, without a concomitant change in MEP amplitude or silent period duration. The more moderate heat stress (core body temperature raised to 38.5°C) imposed in this study indicated that cortico-spinal excitability may be decreased in work-related tasks involving the arms. However, because the passive-heat stress was not tightly controlled (e.g. subjects were not continuously heated) and because single pulse TMS results can be mediated at both the cortical and spinal levels (Kobayashi and Pascual-Leone 2003), this research question related to intracortical excitability remains unanswered.

Accordingly, the present study sought to determine the effect of passive-heat stress on the neuromuscular properties and intracortical excitability of the wrist flexor muscles using a classical heat stress model (i.e. water-perfused suit) with well-known cardiovascular effects that could affect neuromuscular function such as decreases in cerebral blood flow (Wilson et al. 2002, 2006) and increases in muscle sympathetic nerve activity (Cui et al. 2004, 2009). Because many government labour codes limit internal temperature increases to ~1.0°C above resting values (Jay and Kenny 2010), it was decided to use a moderate heat stress of this nature. Paired-pulse TMS was used to more directly measure cortico-cortical excitability serially over time. In addition, the effects of passive-heat stress on voluntary muscle strength, muscle fatigue, impairments in central activation and skeletal muscle contractile properties of the wrist flexor muscles were assessed. It was hypothesised that passive-heat stress would result in accelerated muscle fatigue and impairments in central activation, together with a concomitant decrease in intracortical excitability. The wrist flexor muscle group was chosen for study because it is heavily used in work tasks and because upper limb muscles are ideal for comprehensively examining intracortical properties and central activation.

2. Materials and methods

2.1. Ethical information

The Ohio University Biomedical Institution Review Board approved this study and all subjects provided written informed consent prior to participation.

2.2. Subjects

In total, 10 healthy subjects participated in this study (eight men and two women; mean age 22 ± 4 years; mean weight 71.82 ± 10.62 kg). Data were collected during the winter months in a temperate climate. Subjects were recreationally active and none reported being exposed to hot environments in the recent months prior to enrolment in the study. Subjects were excluded if they were taking any medications or supplements, had any known neurological or orthopaedic limitations or had a BMI > 30.0 kg/m².

2.3. General overview of the study design

Altogether, 10 healthy subjects participated in two testing sessions on different days separated by at least 1 week. During one of these sessions, the subjects underwent a passive-heat stress, and during the other visit the subjects underwent a normothermia (control) protocol. The order of the visits was randomised. Each visit was conducted at the same time of day during the winter and spring months of a temperate climate and subjects were asked to report to the laboratory in a well-hydrated state and to avoid caffeine and alcohol for 24 h before the experimental sessions. Subjects maintained their regular routines in the days leading up to the experiment and were asked to perform no or only moderate intensity exercise in the 48 h prior to testing. Water was not given to subjects during the experiment as this may have confounded core temperature data, but subjects were provided with water immediately following the completion of the protocol. Baseline testing consisted of an assessment of muscle strength, central activation and fatigue-resistance of the wrist flexor muscles of the dominant arm and paired-pulse TMS was performed to assess cortical properties. Throughout baseline testing, heart rate, arterial blood pressure, skin temperature and core temperature were continuously monitored. Upon completion of the baseline testing, subjects began the thermal protocol (passive-heat stress or normothermia). After the subject’s core body temperature had increased 1.0°C above baseline (or ~1 h into the normothermia condition), the initial testing session was again repeated. The study design and timeline is illustrated in Figure 1 and specific details of the study protocol are described below.

2.4. Thermal conditions and measurement of temperature and cardiovascular outcomes

2.4.1. Hyperthermia and normothermia

Each subject performed both a passive-heat stress and normothermia protocol. During normothermia,
subjects were kept at a thermoneutral temperature by perfusing 35°C water through a high-density tube lined suit (Med-Eng Systems, Ottawa, ON, Canada). This water ran through the suit through the entire protocol. During the heat stress protocol, whole body heating was performed until the body’s core temperature was raised to about 1°C above baseline temperature. Passive-heat stress was accomplished by running 46°C water through the tube-lined suit. After the internal temperature goal was obtained, water temperature was decreased to attenuate the increase in internal temperature. This mode of heat stress increases both internal and skin temperatures, which, in combination, have been identified to accentuate fatigue in experimental conditions (Cheuvront et al. 2010). The tube-lined suit did not cover the forearm of the tested arm and thus wrist flexors of the tested arm were not directly heated. This was by design to facilitate neuromuscular measurements and because previous observations indicate that internal, not local muscle, temperature is the primary determinant of voluntary activation (Thomas et al. 2006). Despite not directly heating the forearm, sweating was observed in this local area. The researchers purposefully attempted to keep the forearm skin relatively dry to minimise changes in skin conductance. Testing was completed in the sitting position required for the data acquisition equipment, but between testing sessions, subjects were reclined to a supine position. Subjects were in the seated position for ~40 min for each testing period.

2.4.3. Arterial blood pressure and heart rate
Blood pressure and heart rate were monitored throughout the experiment at the finger via photoplethysmography using the Penaz method (Finapres Medical Systems, Amsterdam, The Netherlands).

2.5. Muscle and nerve function methods and outcome measures

2.5.1. Electrical and mechanical recordings
Electromyographic (EMG) signals were recorded from the dominant flexor carpi radialis (FCR) muscle using bipolar surface electrodes located longitudinally over the muscle on shaved and abraded skin with a reference electrode just distal to the medial epicondyle (Ag–AgCl, potential sensitive area of 22 mm, 25 mm centre-to-centre interelectrode distance; 2015 Nikomed Trace1, Hudson Valley, PA, USA). The EMG signals were amplified (500–1000x), bandpass-filtered (10–500 Hz) and sampled at 5000 Hz (MP150; Biopac Systems Inc., Goleta, CA, USA). To quantify wrist flexion torques, subjects were seated on a Biodex System 4 with the arm extended parallel to the ground, the hand pronated, and the forearm supported (Figure 2). The wrist joint was aligned to the rotational axis of a torque motor, to which a constant-length lever arm was attached. The signal was scaled to maximise its resolution (208.7 mV/N; Biodex Researchers Tool Kit Software, New York, USA), smoothed over a 10-point running average and sampled at 625 Hz (MP150 Biopac Systems). Subjects received visual feedback of all exerted torques on a 53-cm computer monitor located 1 m directly in front of them.

2.5.2. Muscle strength and central activation
To assess maximal wrist flexion strength, subjects performed a minimum of three 3–5 s long maximal voluntary isometric contractions (MVC) with a 1–2-min rest period between each contraction. If subjects continually recorded more torque with...
increasing trials, or if the two highest trials were not within 5% of each other, additional trials were performed until a plateau was reached. Verbal encouragement was provided during testing. The highest value was considered the MVC.

To determine what percentage of the total torque generating capacity of the wrist flexors can be produced voluntarily, a combination of voluntary and electrically stimulated contractions was performed. Transcutaneous electrical stimulation was delivered to the median nerve in the bicipital groove via stimulating electrodes (Ag–AgCl, 2015 Nikomed Trace1). The electrical stimuli consisted of 0.5 ms pulses (Digitimer DS7; Digitimer, Welwyn Garden City, Hertfordshire, UK). Stimuli were administered at increasing stimulation intensities until the FCR peak-to-peak (p-p) EMG amplitude reached a plateau (Mmax) and for central activation testing the intensity was subsequently increased 20% above that eliciting Mmax. Next, to assess central activation a supramaximal electrical doublet (100 Hz) was delivered while the subject performed a 4–5 s MVC. The increase in torque immediately following the stimulation was expressed relative to a potentiated response evoked 1–2 s after the MVC and central activation was calculated as follows:

\[
\% \text{ central activation} = \left[1 - \frac{\text{evoked torque during MVC}}{\text{evoked torque following MVC}}\right] \times 100.
\]

During the assessment of central activation, verbal encouragement and visual feedback of the exerted torque were provided.

2.5.3. Muscle contractile properties

To identify changes in the functional properties of the wrist flexor muscles, the torque-time curves evoked from an electrical doublet (100 Hz) delivered 1 s following a 5-s MVC (post activation potentiated doublet) were evaluated. Two trials were performed and averaged for calculating peak torque, the relative rate of evoked torque development between 10 and
90% of peak torque (+dF/dt), and the relative rate of torque relaxation between 90 and 50% of peak torque (−dF/dt).

2.5.4. Fatigue task
To determine fatigue-resistance, subjects performed a sustained wrist flexion MVC for 60 s. Subjects were given a 2-min rest before the start of the fatigue task and they were instructed to contract as hard as possible for 60 s. Verbal encouragement was provided during the first 5 s of the contraction and then ceased. Subjects were provided feedback of the torque level, but they were not aware of the time remaining in the task. For 1–2 s prior to the end of the task central activation was again assessed as described above. Muscle fatigue was quantified as the percent reduction in MVC torque over the last 5 s of the fatigue task compared with the highest recorded MVC (prior to the measurement of central activation).

2.5.5. Transcranial magnetic stimulation
TMS pulses were delivered using two connected Magstim (Whitland, Carmarthenshire, Wales, UK) 200° stimulators through a 70-mm figure-eight coil. The coil was positioned tangential to the scalp and 45° to the midline so that the induced current flows in a lateral-posterior to medial-anterior direction (Brasil-Neto et al. 1992), which predominantly activates corticospinal neurons trans-synaptically (Werhahn et al. 1994). The stimulation location that elicited the largest p-p amplitude of the FCR MEP was identified and marked on a lycra cap for coil placement. Next, resting motor threshold (MT) was determined while subjects were seated in the dynamometer by delivering single pulses at gradually increasing stimulation intensities. MT was determined and expressed as a percent of the maximum stimulator output. MTs were determined using a TMS intensity well below MT and gradually increasing the intensity in 2% increments until MEPs were observed. Resting MT was defined as the stimulation intensity that elicited MEPs with a p-p amplitude of >50 μV in at least four of eight trials. During this assessment the muscle was completely relaxed, as monitored by the EMG signal.

Paired-pulse TMS was used to measure variables of intracortical excitability. This combines a conditioning stimulus with a test stimulus at different interstimulus intervals (Ziemann 2003, 2004) (Figure 3) and allows for a more direct measurement of cortico-cortical excitability. For example, when a subthreshold conditioning pulse (i.e. 5% less than MT) precedes a suprathreshold test pulse (i.e. 30% above MT) by 15 ms the MEP amplitude associated with the test pulse is greater than that of a single unconditioned pulse of the same intensity (intracortical facilitation; ICF). Conversely, when the interstimulus interval is 3 ms, the conditioning pulse reduces the test motor response (short-interval intracortical inhibition; SICI) and the test motor response is also inhibited when two suprathreshold pulses are separated by 100 ms (long-interval intracortical inhibition; LICI). It is generally thought that SICI is mediated by gamma-aminobutyric acid (GABA) type A receptors (GABA_A) (Ziemann 2003, Florian et al. 2008), LICI is mediated by GABA type B receptors (GABA_B) (McDonnell et al. 2006, Florian et al. 2008) and ICF is mediated by excitatory glutamatergic interneurons and N-methyl-D-aspartate receptors (Ziemann 2003, 2004, Reis et al. 2008). In general, SICI and ICF are mediated locally within the primary motor cortex (M1). LICI is commonly suggested to be mediated within M1 (Nakamura et al. 1997, Reis et al. 2008), although recent evidence suggests that it can also be influenced by spinal mechanisms (McNeil et al. 2009). SICI, ICF and LICI were evaluated using paired magnetic pulses under resting conditions as has been previously described (Clark et al. 2010, McGinley et al. 2010). To quantify SICI, ICF and LICI at rest, the test pulse (second pulse) was set at an intensity that, when it was given alone, evoked an MEP of ~0.5 to 1.0 mV p-p amplitude. For SICI and ICF quantification, the intensity of the first (conditioning) stimulus was set to 70% of MT, and for LICI quantification the first (conditioning) stimulus was set at the intensity used for the aforementioned test pulses. The interstimulus intervals for assessing SICI, ICF and LICI were 3, 15 and 100 ms, respectively. A total of eight trials of each of these three conditions were randomly performed in blocks and averaged. SICI, ICF and LICI are operationally defined by expressing the mean p-p amplitude of the conditioned MEP at each interstimulus interval as a percentage of the mean p-p amplitude of the unconditioned test pulse.

2.6. Statistics
Repeated-measures ANOVA procedures followed by Sidak post-hoc tests to control for multiple comparisons were utilised to determine changes over time between the two conditions (within subjects factor: time and thermal condition). For all analyses, a preset z-level of significance equal to 0.05 was required for statistical significance. Additionally, to further aid in interpretation, the effect size (ES; partial eta-squared) was also reported. The SPSS statistical package (v. 17.0; SPSS Inc., Chicago, IL, USA) was used for data analysis. Data are presented as means ± SEM.
3. Results

3.1. Core body and skin temperature

A significant condition by time interaction for the change in core body temperature \((p < 0.01, \text{ES} = 0.90)\) was observed. Further examination of the data indicated that core body temperature increased in the passive-heat stress condition \((37.26 \pm 0.4 \text{ to } 38.23 \pm 0.4^\circ C; \ p < 0.01, \ \text{ES} = 0.84)\), whereas a slight decrease in core body temperature was observed in the normothermic condition \((37.45 \pm 0.5 \text{ to } 37.12 \pm 0.8^\circ C; \ p = 0.06, \ \text{ES} = 0.37)\). Similarly, a significant condition by time interaction for the change in mean skin temperature \((p < 0.01, \text{ES} = 0.91)\) was observed. Mean skin temperature increased in the passive-heat stress condition \((34.5 \pm 0.7 \text{ to } 37.2 \pm 1.0^\circ C; \ p < 0.01, \ \text{ES} = 0.87)\), but did not change in the normothermic condition \((33.7 \pm 0.9 \text{ to } 33.9 \pm 0.9^\circ C; \ p = 0.42, \ \text{ES} = 0.09)\).

3.2. Heart rate and blood pressure

A significant condition by time interaction for the change in heart rate \((p = 0.050, \ \text{ES} = 0.78)\) from
baseline to post testing was observed. Heart rate increased in the passive-heat stress condition (79.5 ± 20 to 110.0 ± 23 beats/min; \( p = 0.04 \) ES = 0.81), while no change was observed in heart rate during the normothermic condition (84 ± 22 to 80 ± 17 beats/min; \( p = 0.09 \) ES = 0.50). No significant condition by time interaction was observed for changes in mean arterial blood pressure (hyperthermia: 94 ± 10 to 91 ± 21 mm Hg; normothermia: 99 ± 6 to 101 ± 9 mm Hg; \( p = 0.60 \), ES = 0.12).

3.3. Muscle strength, fatigue, and central activation
Passive-heat stress did not alter muscle strength, muscle fatigue or central activation. Specifically, no condition by time interaction for wrist flexor muscle strength during brief MVCs (\( p = 0.40 \), ES = 0.10) (Figure 4) was observed, nor was a condition by time interaction for muscle fatigue during the 60-s sustained maximal contraction (\( p = 0.91 \), ES < 0.01) (Figure 5) observed. Similarly, a condition by time interaction for central activation during brief MVCs (\( p = 0.50 \), ES = 0.08) (Figure 4) or following the 60-s fatigue task (\( p = 0.15 \), ES = 0.31) (Figure 5) was not observed.

3.4. Muscle contractile properties
Passive-heat stress did not alter the muscle contractile properties. Specifically, a condition by time interaction for evoked peak torque (\( p = 0.85 \), ES < 0.01), the rate of peak torque development (\( p = 0.70 \), ES = 0.02) or the rate of peak torque relaxation (\( p = 0.80 \), ES = 0.01) (Figure 6) was not observed.

![Figure 4](image1.png)

**Figure 4.** Passive-heat stress did not significantly influence wrist flexor muscle strength or central activation. (a) The effect of passive-heat stress and normothermic control conditions on voluntary muscle strength; (b) the effect of passive-heat stress and normothermic control conditions on wrist flexor central activation.

![Figure 5](image2.png)

**Figure 5.** Passive-heat stress did not influence wrist flexor muscle fatigue, or the central activation at the end of a 60-s maximal contraction fatigue task. Prior to the thermal condition (baseline) and following the thermal condition (post-testing) the passive-heat stress and normothermic control groups exhibited a similar reduction in maximal voluntary contraction (MVC) torque (a) and central activation (b) at the end of a sustained maximal 60-s contraction.
3.5. Intracortical properties

Passive-heat stress did not alter intracortical excitability. Specifically, a condition by time ICF ($p = 0.17$, ES = 0.20), SICI ($p = 0.10$, ES = 0.28), or LICI ($p = 0.17$, ES = 0.29) (Figure 7) was not observed.

4. Discussion

Numerous investigations have reported that exercise-heat stress reduces human performance and exacerbates muscle fatigue (Galloway and Maughan 1997, Gonzalez-Alonso et al. 1999, Drust et al. 2005, Thomas et al. 2006, Ely et al. 2007, Altareki et al. 2009). However, much less is currently known about the independent effects of heat stress in the absence of exercise and in more moderate heat stresses, such as those more typically experienced in occupational settings. Accordingly, the purpose of this work was to determine the effect of moderate passive-heat stress on muscle function (e.g. fatigability, contractile properties) and central nervous system properties (e.g. central activation, intracortical excitability).
The rationale for this experiment was to further examine the postulate that the site for central activation failure associated with heat stress is at the cortical level (Cheung 2007, Nybo 2008). It was hypothesised that the passive-heat stress would result in accelerated muscle fatigue and impairments in central activation, together with a concomitant decrease in intracortical excitability. While the experimental protocol resulted in expected elevations in core body and mean skin temperature, an effect of the passive-heat stress was not observed on any of the indices of skeletal muscle or nervous system function. This may indicate that workers performing hand tasks should not be adversely affected by neuromuscular fatigue issues if their body temperature is maintained within 1.0°C.

In this study, a heat stress-induced change was not observed in ICF, SICI or LICI, indicating a lack of change in intracortical excitability. A previous single pulse TMS study, by Todd et al. (2005), observed decreases in elbow flexor central activation and corticospinal excitability (as evidenced by a prolonged silent period duration) during a sustained 2-min MVC fatigue task after an increase in internal temperature of ~1.3°C. However, no changes were observed in subjects under resting conditions in which they were not actively contracting. Thus, the resting paired pulse TMS data of the present study appear to corroborate their single pulse TMS data. There may be experimental reasons why these fatigue task data show different results. First, their hyperthermia stimulus was induced via head-out hot water immersion followed by a period where subjects dried themselves, ambulated to another laboratory space and put on warm clothing prior to testing. This lack of continuous heating and less clarity as to the extent of the cardiovascular strain from their mode of whole-body heating make comparisons and interpretations more difficult. Additionally, direct heating of the muscle – which had an effect on contractile properties – occurred with their heating protocol, which was substantially different from the present protocol, whereby the limb being tested was not directly heated. With this stated, sweating in this area was observed, which likely decreased forearm skin temperature and increased forearm skin conductance. However, it seems unlikely that these local forearm changes significantly altered muscle contractile properties, electrical stimulation or EMG measurement between conditions. Second, the effects of the passive-heat stress were not measured serially over time (e.g. before and after heat stress) and the control trial did not include thermoneutral water immersion. Third, the present observations were in wrist flexors vs. their observations in elbow flexors. Finally, the interpretation of data using single pulse TMS is somewhat limited because the resulting MEPs and silent periods can be mediated at both the cortical and spinal levels (Kobayashi and Pascual-Leone 2003), rather than solely at the cortical level. Hence, it appears that intracortical excitability is not altered in moderate well-controlled thermal stresses, but this could be limited to wrist flexor muscles.

In this study, no changes were observed in muscle contractile properties, muscle strength, muscle fatigue or central activation. This is in contrast to some previous studies utilising severe heat stresses (Morrison et al. 2004, Thomas et al. 2006, Brazaitis and Skurvydas 2010). Highlighting this, Morrison et al. (2004) observed that passive-heat stress resulting in an elevation of core body temperature to 39.4°C resulted in a 13% reduction in knee extensor strength and a similar (11%) reduction in central activation (Morrison et al. 2004). Hence, it appears that severe heat stress may decrease neuromuscular function but more mild heat stresses do not affect muscle function. This is interesting because the current study did result in significant changes in cardiovascular function (increase in heart rate of ~30 beats/min) and blood volume redistribution (Crandall et al. 2008) and decreases in cerebral blood flow (Wilson et al. 2002, 2006) occur during mild heat stress, but these cardiovascular changes must not significantly contribute to neuromuscular fatigue.

In the current study, wrist flexor muscles were selected because these small distal muscles are used heavily in hand-related work tasks. Previous reports suggest that severe passive heat stress results in impairments in central activation in large appendicular muscle groups, namely, the knee extensors. Interestingly, exercise performance models that have identified decreases in exercise performance are often reported in cycling or running, which utilise the knee extensors (Nybo and Nielsen 2001, Morrison et al. 2004, Thomas et al. 2006, Brazaitis and Skurvydas 2010), rather than focusing on muscle groups that are more involved in work tasks, such as the wrist flexors. Intermuscle differences in levels of central activation have previously been observed – with impairments being particularly pronounced in the knee extensors (Behm et al. 2002). Additionally, fatigue-induced impairments in central activation are suggested to be muscle group dependent, with the knee extensors exhibiting a pronounced decrement in central activation (Enoka and Duchateau 2008). Thus, it is possible that the smaller, weaker and more distal wrist flexor muscles are less prone to the effects of passive-heat stress. This hypothesis is consistent with results of Saboisky et al. (2003), who observed that exercise heat stress induced central activation failure in the exercised knee extensors, but not the unexercised
elbow flexors. This indicates that heat stress may not be robust enough to globally alter central activation of all skeletal muscles or is more selective to specific muscle groups and/or task-dependent differences.

In summary, severe exercise-heat stress is well known to reduce human performance, exacerbate skeletal muscle fatigue and impair central activation (Cheung 2007, Nybo 2008). Heat stress can also decrease both cognitive and manual occupational-related tasks (Jay and Kenny 2010). This study utilised paired-pulse TMS to measure cortico-cortical excitability serially over time during passive heat stress and quantified the effects on voluntary muscle strength, muscle fatigue, impairments in central activation and skeletal muscle contractile properties of the wrist flexor muscles. Elevations in heart rate and core body and mean skin temperature were observed, but an effect of the passive heat-stress was not observed on any of the indices of skeletal muscle or nervous system function in the wrist flexors. These findings suggest that a passive heat stress that raises the core body temperature 1°C (to ~38.2°C) does not impair muscle function, central activation or motor cortical excitability of the wrist flexor muscles as can occur in severe exercise-heat stress of larger, more proximal muscles. Thus, neuromuscular performance of smaller, more distal muscle groups involved in hand and wrist flexion tasks, utilised in many occupational tasks, should not be affected by moderate heat stress.

References


