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RESEARCH ARTICLE

Corticospinal excitability for flexor carpi radialis decreases with baroreceptor unloading during intentional co-contraction with opposing forearm muscles

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Abstract
Concurrent activation of antagonistic muscles (co-contraction) is used for stiffening a joint, whereas its neural control under hemodynamic stress (e.g., posture change, high gravity, and hemorrhage) is unknown. Corticospinal excitability during co-contraction may be altered with baroreceptor unloading due to potential modulations in spinal and/or inhibitory pathways (e.g., disynaptic group I inhibition and GABA-mediated intracortical inhibition). The purpose of this study was to understand the effect of baroreceptor unloading on corticospinal excitability during co-contraction in humans. Motor evoked potential and cortical silent period in a wrist flexor muscle were examined using transcranial magnetic stimulation in two groups of healthy young adults. All subjects performed isometric contraction of the wrist flexors (flexion) and co-contraction of the wrist flexors and extensors (co-contraction). Spinal disynaptic inhibition was also assessed with the ratio of H-reflex responses to unconditioned and conditioned electrical stimulations of the peripheral nerves for the muscles. In one of the groups, baroreflex unloading was induced by applying lower body negative pressure. There was no significant effect of baroreflex unloading on cortical silent period or H-reflex measure of disynaptic inhibition. With baroreflex unloading, motor evoked potential area in the flexor carpi radialis was decreased during co-contraction but not during flexion. The results indicated that baroreceptor unloading decreases corticospinal excitability during co-contraction of antagonistic muscles, apparently by influencing neural pathways that were not probed with cortical silent period or spinal disynaptic inhibition.

Keywords Transcranial magnetic stimulation · Motor cortex · Orthostatic stress · Baroreflex

Introduction

Concurrent activation of antagonistic muscles (co-contraction) is executed when stiffening a joint, intentionally or unintentionally, in controlling the body posture and interacting with objects. Co-contraction is often altered in individuals with impaired movements (e.g., stroke survivors) as well as otherwise healthy older adults, resulting in degraded motor control (Burnett et al. 2000; Dewald et al. 2001; Gibo et al. 2013). Even in healthy young adults, co-contraction can be altered when exposed to psychological stress. For example, co-contraction of leg muscles is exacerbated when encountering postural threat (Carpenter et al. 2001). The magnitude of co-contraction is greater in individuals with Type A personality (Glasscock et al. 1999), who also show greater autonomic nerve responses to psychological stress compared with Type B personality (Lee and Watanuki 2007). Hence, co-contraction can be affected by psychological stress that leads to autonomic nerve responses. With the involvement of stress-related common neural pathways that synthesize neuromodulators (i.e., noradrenaline and adrenaline in the nucleus of the solitary tract) (Pacak et al. 1995; Dayas et al. 2001), physiological stress leading to autonomic nerve responses may also have a modulatory effect on the neuromotor system in the execution of co-contraction. In a resting muscle, we have found that baroreceptor unloading by means of orthostatic stress acutely heightens corticospinal excitability and decreases intracortical inhibition (i.e., disinhibition) of the motor cortex in healthy young

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adults (Buharin et al. 2013, 2014). It is imperative to clarify whether baroreceptor unloading modulates neuromotor excitability during co-contraction as well.

Adjustment of co-contraction under baroreceptor unloading is relevant to various situations. For example, when an individual stands up from a sitting or lying position, causing baroreceptor unloading, appropriate adjustment of co-contraction is essential in controlling joint stiffness for balancing the body and maintaining a handheld object (e.g., cane, filled cup). In an air fighter or a racing-car driver, altered adjustment of co-contraction due to baroreceptor unloading under a high-G situation can be fatal in holding a control stick or a steering wheel, respectively. In wounded soldiers, adjustment of co-contraction for holding a weapon toward a target and maintaining the body posture may be affected by baroreceptor unloading due to internal or external hemorrhage. In response to baroreceptor unloading, degraded baroreceptor sensitivity is associated with increased arterial stiffness, as shown in older adults (Okada et al. 2012). Control of a handheld object or body balance may be affected in individuals with autonomic dysfunction or increased arterial stiffness, including older adults, type 2 diabetes, and idiopathic subjective tinnitus (Avolio et al. 1983; Kimoto et al. 2003; Bayraktar and Tasolar 2017). Hence, motor control requiring co-contraction may be affected depending on the amount of and sensitivity to baroreceptor unloading in various individuals and conditions.

Chronic reduction in corticospinal excitability is often accompanied with degraded motor capability due to neurological impairments, including stroke and spinal cord injury (Davey et al. 1999; Liepert et al. 2005). As a form of neuromuscular training, repetitions of maximal voluntary cocontration lead to neuromuscular adaptations, including an increase in muscle mass, activation, and strength in healthy young adults (Maeo et al. 2014a, b). To help understand degraded or improved control of co-contraction with baroreceptor unloading in various populations and conditions, it is imperative to have its basic understanding in healthy young adults. The primary purpose of this study was to understand the effect of baroreceptor unloading on corticospinal excitability during co-contraction in healthy young adults. According to heightened corticospinal excitability with baroreceptor unloading in the resting muscle (Buharin et al. 2013, 2014), we hypothesized that corticospinal excitability during muscle co-contraction would be heightened with baroreceptor unloading.

Corticospinal excitability represents neural excitability of the corticospinal tract, which is influenced by various excitatory and inhibitory inputs at the cortical and spinal levels. There are a couple of studies that examined relevant neural pathways for corticospinal excitability during co-contraction of the wrist muscles. Corticospinal excitability was lower while intracortical inhibition in the motor cortex was indifferent in the extensor carpi radialis (ECR) muscle during co-contraction compared with agonist contraction (Aimonetti and Nielsen 2002). In contrast, spinal disynaptic group I inhibition between the wrist flexor and extensor muscles (Wargon et al. 2006) was greater during co-contraction compared with agonist contraction (Aimonetti et al. 2000). If disynaptic group I inhibition in the spinal cord and/or intracortical inhibition in the motor cortex during co-contraction is reduced due to baroreflex unloading, it would lead to the heightening of corticospinal excitability. Hence, to additionally shed light on the possible underlying pathways for the potential effect of baroreceptor unloading on corticospinal excitability during co-contraction, we also explored the effect of baroreceptor unloading on a measure of disynaptic group I inhibition in the spinal cord as well as a measure of intracortical inhibition in the motor cortex.

Methods

Subjects

Twenty-two healthy young adults (22.2 ± 4.4 years of age, 7 women) participated in the study. All subjects were right-handed, as confirmed with the Edinburgh handedness inventory (Table 1) (Oldfield 1971). Participants did not present any signs of heightened autonomic nervous activity [e.g., diabetes, cardiovascular problems, brain or nerve disorder, obesity, hypertension, or hypotension (Landsberg 1986)]. Subjects did not take any medication that may affect motor control or brain and nerve function. In addition, subjects were not allowed to participate if they had a family history of seizure or epilepsy, skin allergies, were pregnant, were prone to severe headaches, or had metal in their head, besides dental fillings (Keel et al. 2001). To minimize the variability in the basal physiologic level and responsiveness of sympathetic nerve activity to baroreceptor unloading across

Table 1 Baseline subject characteristics of each group

	Test group	Control group
Number (women)	12 (4)	10 (3)
Age (years)	22.67 ± 5.45	21.70 ± 2.98
L.Q. value	0.76 ± 0.22	0.68 ± 0.19
EMG_{max} (mV)	0.31 ± 0.28	0.39 ± 0.27
Heart rate (bpm)	57.3 ± 10.35	61.0 ± 5.46
MAP (mmHg)	85.4 ± 9.75	83.5 ± 7.82
RMT (%)	51.00 ± 10.39	50.10 ± 7.84

No significant difference between groups

L.Q. laterality quotient for right handedness, EMG_{max} electromyogram amplitude during maximal voluntary contraction, *bpm* beats per minute, *MAP* mean arterial blood pressure, *RMT* resting motor threshold, % percentage relative to maximal stimulator output

subjects, all experiments were conducted at 8 am; participants abstained from food and drink, with the exception of water, for 10 h prior to the experiment (Berne et al. 1989) and from all forms of exercise for 12 h prior to the experiment. To avoid potential confounding effects of estrogen and progesterone on sympathetic nerve activity, women were tested during their follicular phase (Minson et al. 2000). Informed consent was obtained from all individual participants included in the study. The Central Institutional Review Board of Georgia Institute of Technology approved the study (H10174).

Experimental approach

Corticospinal excitability was examined when subjects were asked to concurrently activate opposing forearm muscles intentionally (co-contraction) by imagining the stiffening of their wrist joint. Forearm muscles were chosen because our previous findings were on an upper-limb muscle (Buharin et al. 2013, 2014), and individuals with motor impairment often have difficulties in dealing with coactivation of forearm muscles (Hu et al. 2006). The experiment was conducted in an electrically shielded room. We employed a group-comparison research design, rather than a crossover design, due to the difficulty of scheduling and testing female volunteers two times in early morning during the follicular phase within our capacity. Subjects were randomly assigned to either the test ($n = 12$) or control ($n = 10$) group. In both groups, subjects performed two isometric motor tasks: joint-stiffening co-contraction of the wrist flexor and extensor muscles (co-contraction) and simple wrist flexion (flexion) in the right arm. The muscle of our interest was the flexor carpi radialis (FCR). In both groups, motor evoked potential (MEP, a measure of corticospinal excitability) and cortical silent period (CSP, a measure of GABA-B receptor-mediated inhibition) (Siebner et al. 1998; Werhahn et al. 1999) were measured in FCR in response to TMS over the motor hot spot during the motor tasks. CSP was chosen because it can be assessed using the same recordings for MEP without additional experimental procedures. While there are other measures of intracortical inhibition, we did not employ them in the current study because of the duration and complexity of the experiment, which includes central and peripheral stimulations in multiple conditions and trials. To assess possible variability of electrical response at or distal to the neuromuscular junction, supramaximal compound muscle action potential (M_{max}) was measured in FCR at rest. To assess potential changes in disynaptic group I inhibition in the spinal cord, conditioned H-reflex was recorded in FCR during co-contraction.

In the test group, an intervention of baroreceptor unloading was included by applying lower body negative pressure of 40 mmHg. In this group, measurements were made without this intervention (basal condition) in Trial 1 and with lower body negative pressure (condition with unloaded baroreceptors) in Trial 2. An ordered protocol was followed to avoid interference of possible residual effects of the lower body negative pressure. To account for potential effects of repetition and time, a control group, which was tested at basal condition in both trials 1 and 2, was included in the study design. Effects of lower body negative pressure on corticospinal excitability during co-contraction and flexion were assessed from the MEP area during Trial 1 and Trial 2 for each task, compared between the two groups.

Data collection sequence was as follows. In Trial 1, data were collected at ambient pressure (0 mmHg lower body pressure) in both groups. In Trial 2, data were collected again at ambient pressure in the control group and with lower body negative pressure of 40 mmHg in the test group. In both trials 1 and 2, data for Mmax at rest were collected first, followed by corticospinal excitability during flexion, corticospinal excitability during co-contraction, and disynaptic reciprocal inhibition during co-contraction in random order.

Motor tasks

Subjects were positioned supine on a bed, and their head was oriented in neutral position on a pillow. The right shoulder was abducted approximately 30° and the forearm was secured midway between pronation and supination in a brace. Subjects were instructed to perform isometric contraction to either flex their wrist (flexion) or co-contract their wrist flexor and extensor muscles in a joint-stiffening fashion (co-contraction), depending on the motor task being assessed. The orientation of the right hand was monitored throughout the experiment to ensure consistency. Bipolar surface electromyogram (EMG) was recorded from the right FCR and ECR muscles using pairs of Ag–AgCl electrodes (E224A, IVM, Healdsburg, CA, USA) placed on the skin over the muscle bellies. On each muscle, the inter-electrodes distance was 2 cm. A disposable electrode (Telectrode/T716, Bio Protech, Wonju si, Gangwon-do, Korea) was placed on the medial epicondyle of the right arm to serve as the reference. EMG was differentially amplified (300×) and band-pass-filtered (15–2000 Hz) using a battery-powered amplifier (Y03-000, Motion Lab Systems Inc., Baton Rouge, LA, USA) to minimize the contamination of electrical noise.

Maximal voluntary isometric contraction of the wrist flexors was performed to obtain the maximal EMG amplitude of FCR for determining the contraction intensity in the subsequent flexion and co-contraction tasks. With their right hand fixed between two boards with C-clamps in the neutral wrist position, subjects increased their EMG amplitude of FCR to maximum in a ramp fashion over 3 s, and maintained it at maximum for 2 s with visual feedback. Subjects were

instructed to contract only their wrist flexors without trying to handgrip, and to relax other muscles. Verbal instruction and encouragement were provided while the arm and hand were visually monitored. A rectified running average EMG with an averaging window of 0.175 s was used to provide visual feedback to subjects and to calculate the maximal EMG amplitude of FCR. An averaging window of 0.175 s was used because, during the pilot study, this window reduced the distracting high-frequency signals for judging the level of muscle activity but did not lose the responsiveness of detecting the changes in muscle activity.

Flexion and co-contraction tasks were performed using the same visual feedback of EMG. The right hand of each subject was secured in a neutral wrist position midway between pronation and supination in a hand brace, with a dowel inside the palm at the level of the metacarpophalangeal joints. The fingers were freely curved around the dowel. Subjects were provided visual feedback of EMGs for FCR and ECR. The subjects were instructed to either contract their wrist flexor muscles (flexion) or co-contract their wrist flexor and extensor muscles (co-contraction, Fig. 1) while maintaining FCR activity no greater than 10% of maximal EMG amplitude. Subjects were repeatedly asked of their fatigue perception and breaks were given in between TMS blocks as necessary. During flexion, subjects were told to flex their wrist isometrically against the dowel. During co-contraction, subjects were instructed to stiffen the wrist joint, and not to squeeze the fingers or radially deviate the wrist. Instructions with regard to a specific target level of ECR activity were not provided because of the difficulty in adjusting the amount of ECR activity to reach the same level across subjects. Instead, subjects were instructed to maintain the achieved level of ECR activity throughout the co-contraction task. Subjects were instructed to maintain the contractions at the same levels even after receiving TMS or peripheral nerve stimulation. One subject in the test group was unable to complete the experiment during co-contraction of Trial 2.

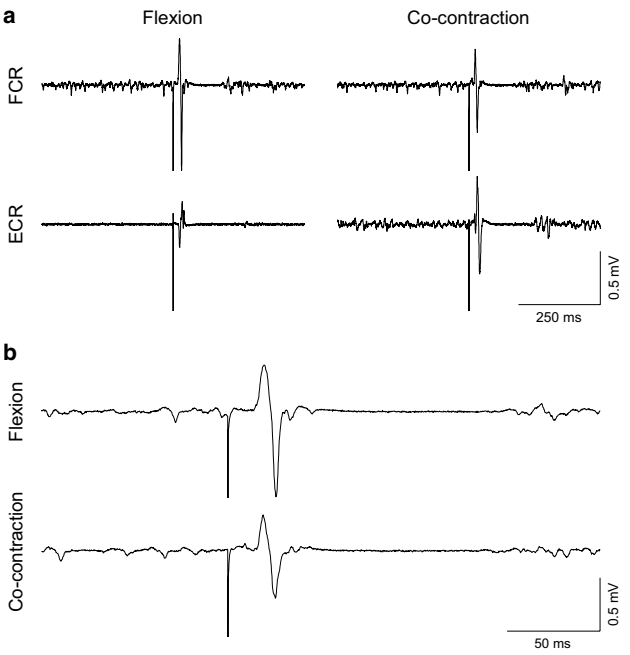

Fig. 1 Representative recordings of interference electromyogram with transcranial magnetic stimulation (TMS) during flexion (left column) and co-contraction (right column) in Trial 1. The top and bottom rows show recordings from the flexor carpi radialis (FCR) and the extensor carpi radialis (ECR), respectively (**a**). Recordings in ECR demonstrate the absence and presence of activity in flexion and co-contraction, respectively. Pre-stimulation activity, a large artifact, motor evoked potential (MEP), and silent period are observed in FCR. The FCR traces are also shown for a shorter period for MEP visibility (**b**)

Lower body negative pressure

Lower body negative pressure was used to unload the baroreceptors, similar to our previous studies (Buharin et al. 2013, 2014). The lower body of the subjects was sealed inside an airtight chamber at the level of the iliac crest. A bicycle seat inside the chamber insured the subject remained in a stable position. The pressure inside the chamber was controlled with the aid of a valve and a commercial vacuum (Dayton Industrial, Dayton, OH, USA). In Trial 2 of the test group, the pressure in the chamber was gradually reduced to − 40 mmHg relative to ambient pressure and maintained at this value during data collection. Lower body negative pressure of 40 mmHg is known to unload the baroreceptors and increase sympathetic nerve activity, as evidenced by increased muscle sympathetic nerve discharges (Sundlöf and Wallin 1978; Taylor et al. 1992; Davy et al. 1998), increased concentration of noradrenaline in plasma (Hinghofer-Szalkay et al. 1996), and increased heart rate with little changes in blood pressure (Serrador et al. 2000; Buharin et al. 2013, 2014). During Trial 1 for the test group and trials 1 and 2 for the control group (i.e., all trials besides Trial 2 in the test group), data collection was performed with the lower body pressure set to ambient (0 mmHg) and the vacuum turned on. Blood pressure at the brachial artery of the left arm and heart rate (averaged over 5–7 s) from the electrocardiogram (ECG) were monitored noninvasively (Cardiocap/5, General Electric Co., Giles, UK) and recorded in between TMS blocks. ECG was recorded at 100 samples/s with a 16-bit analog-to-digital converter (Power 1401, Cambridge Electronic Design Ltd., Cambridge, UK) and data acquisition software (Spike 2 ver. 7, Cambridge Electronic Design Ltd., Cambridge, UK) for offline analysis.

TMS

Corticospinal excitability was assessed with single-pulse TMS (Magstim 200^2, by way of BiStim module, Magstim Co, Wales, UK) of the left primary motor cortex. A figure-of-eight coil (Magstim second-generation double 70-mm remote coil, Magstim Co, Wales, UK) was held over the left primary motor cortex at the optimum position (i.e., hot spot) for eliciting an MEP in the resting FCR of the right forearm. The coil was held with the handle pointing posteriorly at an angle of approximately 45º to the sagittal plane yielding an E-field perpendicular to the central sulcus (Brasil-Neto et al. 1992). A coil navigation system (NDI TMS Manager, Northern Digital Inc., Waterloo, Ontario, Canada) was used to maintain the coil position in three-dimensional space relative to the head. EMG was recorded at 5000 samples/s with a 16-bit analog-to-digital converter (Power 1401, Cambridge Electronic Design, Cambridge Ltd., UK) and data acquisition software (Signal ver. 5, Cambridge Electronic Design, Cambridge Ltd., UK) for online monitoring, storage, and offline analysis.

The resting motor threshold (RMT) for FCR was determined as the smallest TMS intensity needed to elicit an MEP with peak-to-peak amplitude greater than 50 μV in five out of ten consecutive stimulations (Butler et al. 2005; Darling et al. 2006) in the resting FCR. RMT was measured in percentage of maximal stimulator output for each subject. MEPs were collected at TMS intensity of 110% of RMT and greater in a stepwise fashion at 10% RMT increments. TMS was delivered every 6 s. Measurements were made in blocks, with 12 MEP responses per block (i.e., per TMS intensity), and the order of the TMS intensity blocks was randomized. Breaks were given in between blocks as needed to prevent fatigue. Surface interference EMG in responses to TMS was collected during flexion and co-contraction tasks (Fig. 1). Appropriate assessment of corticospinal excitability was not possible in one subject in each group due to technical issues.

Peripheral nerve stimulation

Maximal amplitude of M-wave (M_{max}) of FCR was measured to assess potential variations in the peripheral electrical response with time or intervention. Disynaptic group I inhibition of FCR was measured, using conditioned H-reflex, to assess its potential involvement of the spinal inhibitory pathway in the modulation of corticospinal excitability due to baroreflex unloading during co-contraction. M-wave and H-reflex were evoked using transcutaneous bipolar electrical stimulation of the median nerve and the radial nerve. The electrical stimulation was delivered via pairs of spherical stimulating electrodes, separated by 2 cm, connected to a constant current stimulator (S44 and S88-SIU5-CCU1, Grass Products, Natus Neurology Inc., Warwick, RI, USA). The stimulating electrodes were attached 5 cm above the elbow to the medial and lateral aspects of the arm for median and radial nerve stimulation, respectively (Nielsen and Kagamihara 1992). M_{max} and disynaptic group I inhibition were assessed only in those subjects who did not perceive the electrical stimulation as painful because potential increase in sympathetic nerve activity due to stimulation-induced pain sensation would present a confounding variable to an increase in sympathetic nerve activity with lower body negative pressure (Sundlöf and Wallin 1978; Taylor et al. 1992; Davy et al. 1998). In other words, subjects who declared that the supramaximal stimulation was too painful to be repeated were excluded (3 and 2 in the test and control group, respectively). M_{max} of FCR was induced by a 1-ms square-wave electrical stimulation delivered to the median nerve at supramaximal intensity: 150% of intensity that elicited maximum compound muscle action potential. Twelve M_{max} responses in surface interference EMG were recorded in the resting FCR, while electrical stimulation was delivered every 10 s. M_{max} was obtained from nine and eight subjects from the Test and Control groups, respectively. In our previous study in a resting muscle, M-wave or H-reflex was not influenced by various maneuvers that heighten sympathetic nerve activity including mental arithmetic, handgrip, post-handgrip ischemia, and cold stimulation (Kamibayashi et al. 2009).

Disynaptic group I inhibition during co-contraction was assessed as the reduction of the H-reflex in FCR due to conditioning stimulation of the radial nerve (Nielsen and Kagamihara 1992). The H-reflex in the resting FCR was induced by the test electrical stimulation of the median nerve at an intensity on the ascending limb of the recruitment curve for the H-reflex. Between trials 1 and 2, intensity of stimulation was adjusted as necessary to maintain an H-reflex of comparable size. The radial nerve was conditionally stimulated at motor threshold, as judged by the appearance of a muscle compound action potential in the EMG of the resting ECR. Pilot experiments showed that the H-reflex amplitude of FCR was prominently reduced when the conditioning stimulation of the radial nerve preceded the test stimulation of the median nerve by 0 or 1 ms. In the main experiment, unconditioned H-reflex was first measured in the resting FCR muscle. Then, the reduction in the resting FCR H-reflex was compared due to conditioning stimulation of the radial nerve preceding the test stimulation by 0 and 1 ms. The interval that gave the greater reduction in the resting FCR H-reflex was subsequently used to assess disynaptic inhibition during co-contraction. Surface interference EMG in response to 12 unconditioned and 12 conditioned stimulations delivered every 6 s was recorded from FCR (Fig. 2). Both nerves were stimulated with a 1-ms square-wave pulse. H-reflexes were successfully obtained in eight and six subjects from the test and control groups, respectively.

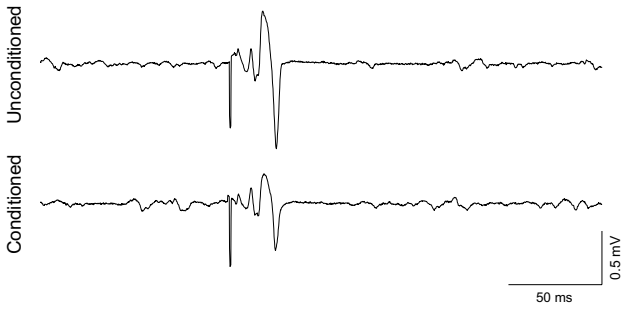

Fig. 2 Representative recordings of interference electromyogram for obtaining H-reflex responses in FCR during co-contraction. A large artifact followed by a large H-reflex response is observed due to unconditioned (top trace) and conditioned (bottom trace) electrical stimulation

Data reduction

In the data for corticospinal excitability, the first two MEP responses in each block were discarded to control for startle. Additionally, recordings that showed obvious pre-stimulus activity in ECR during the flexion task were discarded. Remaining EMG recordings were rectified and trigger-averaged in reference to TMS within stimulation blocks. To assess the pre-stimulus activity, the mean pre-stimulus EMG amplitude was calculated from FCR and ECR data 100 ms preceding the application of TMS. To verify that FCR was activated no greater than 10% of maximal EMG amplitude as instructed, the pre-stimulus EMG amplitude in FCR was expressed relative to maximal EMG amplitude. As a measure of corticospinal excitability, MEP area was calculated to match the area analysis for H-reflex and M_{max}. MEP area was calculated between 12 and 50 ms post-TMS, which covers the whole MEP response based on our pilot data and confirmed in the current recordings.

As a probe of motor cortical inhibition, CSP induced in the FCR by TMS was computed using the automated cumulative sum method (King et al. 2006) as in our previous study (Buharin et al. 2014). The start and end of CSP were defined as the times, following the MEP, from when EMG fell below and increased back up to the pre-stimulus EMG level, respectively.

In the EMG recordings for M_{max} in the resting FCR, data that showed obvious pre-stimulus EMG activity in FCR were discarded. Remaining recordings were rectified and trigger-averaged in reference to electrical stimulation of the median nerve. To examine the excitability at and distal to the neuromuscular junction, M_{max} area was determined for the supramaximal M-wave response that was identified from the rectified and trigger-averaged EMG.

H-reflex areas in FCR with unconditioned and conditioned stimulations were determined during co-contraction. The first two recordings in each H-reflex stimulation block were discarded. Remaining EMG recordings were rectified and trigger-averaged in reference to peripheral electrical stimulation within stimulation blocks. H-reflex area was determined for the H-reflex response that was identified from the rectified and trigger-averaged EMG. For assessing disynaptic inhibition in the spinal cord, the ratio of the H-reflex area during conditioned stimulation to the area during unconditioned stimulation was calculated as H-reflex ratio.

To examine the autonomic responses to lower body negative pressure, heart rate variability was assessed from the ECG recordings taken during the measurement of corticospinal excitability in the motor tasks. All ECG recordings used in calculation of heart rate variability were greater than 3 mins in duration. From the ECG recording, all R-wave peaks were identified, marked, and visually inspected. Then the power spectrum of the R-to-R interval was calculated. Low-frequency (0.05–0.15 Hz) power was expressed relative to the power in total frequencies (0.05–0.50 Hz) and was used as a measure of sympathetic nerve activity (HRV_{LF}) (Cardiology and Electrophysiology 1996; Buharin et al. 2014).

Statistical analysis

Subject characteristics include the age, handedness index, baseline heart rate, baseline mean arterial blood pressure (MAP), and RMT that was measured with the vacuum turned off before Trial 1. These variables were compared between the two groups with a Student's independent-sample *t* test. Analysis of variance (ANOVA) was performed to examine the effect of lower body negative pressure on various dependent variables. The levels of factors for ANOVAs were: test and control for the group factor, Trial 1 and Trial 2 for the trial factor, and flexion and co-contraction for the task factor. Effects of lower body negative pressure on M_{max}, unconditioned H-reflex, and H-reflex ratio were assessed with a two-factor (Group × Trial) ANOVA with repeated measures for trial. Effects of lower body negative pressure on MEP response, CSP, pre-stimulus EMG amplitude, heart rate, HRV_{LF}, and MAP were assessed using a three-factor (Group × Trial × Task) ANOVA with repeated measures for trial and task. TMS intensity was not included as a factor because it did not influence the effect of lower body negative pressure on MEP response or CSP in the initial analysis. Effects of lower body negative pressure were judged from within-group effects of Trial. Inclusion of the control group in the ANOVAs ensured that any differences seen between trials 1 and 2 in the experimental group were not due to order effect. When a three-factor interaction was found, to clarify whether task affected the variables without the influence of lower body negative pressure, the variables in Trial 1 were assessed with a two-factor (Group × Task)

ANOVA with repeated measures for task. An alpha level of 0.05 was used for all significance testing, and $P < 0.05$ and $P < 0.01$ were noted where appropriate. Tukey post hoc test was used when appropriate. Statistical analyses were performed using Statistica 9.0 (StatSoft Inc., Tulsa, OK, USA). Unless stated otherwise, the data are presented as mean ± SD in the text and tables and as mean ± standard error of mean in the figures.

Results

Subject characteristics

Basic subject characteristics, including age, handedness index (laterality quotient), maximal EMG amplitude, heart rate, mean arterial blood pressure, and RMT were not significantly different between groups (Table 1).

Background contraction

Subjects were asked to produce a steady contraction with their FCR no greater than 10% of maximal EMG amplitude during the motor tasks. As a result, pre-stimulus EMG amplitude in FCR was 6.9 ± 2.8% and 5.3 ± 2.2% of maximal EMG amplitude in the test and control groups, respectively, across tasks with a main effect of group ($P < 0.05$). There was no significant effect or interaction of task or trial on pre-stimulus EMG amplitude in FCR.

For ECR, pre-stimulus EMG amplitude of ECR increased to approximately eightfold from 3.2 ± 0.6 µV during flexion (when ECR was not supposed to be involved) to 24.0 ± 19.2 µV during co-contraction, with a main effect of task ($P < 0.01$). There was no significant effect or interaction of group or trial on pre-stimulus EMG amplitude of ECR.

Corticospinal excitability

As a measure of corticospinal excitability, MEP area in FCR was assessed during flexion and co-contraction. Figure 3 shows the average MEP response of FCR across subjects during flexion and co-contraction in trials 1 and 2. The left and right panels show the test and control groups, respectively. In Trial 2, subjects in the test group, *i.e.*, with the application of 40 mmHg lower body negative pressure, appeared to show increased MEP area during flexion and, conversely, decreased MEP area during co-contraction, compared with Trial 1.

These observations were statistically tested with an ANOVA. There were a main effect of Task ($P < 0.01$) and Group × Task ($P < 0.01$), Group × Trial ($P < 0.05$), Trial × Task ($P < 0.01$), and Group × Trial × Task ($P < 0.01$) interactions on MEP area. Post hoc analysis revealed that, in the test group, MEP area during co-contraction was decreased by 22% in Trial 2 compared with Trial 1 ($P < 0.01$, Fig. 4). In contrast, there was no significant difference between Trial 1 and Trial 2 during flexion in the test group. In the control group, MEP area was not significantly different across tasks and trials. When the effect of task on MEP area without lower body negative pressure was further examined by testing Trial 1 data only, both groups presented lower MEP area during co-contraction (4.90 ± 2.83 mV ms) by 8.6% compared with flexion (5.36 ± 3.25 mV ms), with a main effect of task ($P < 0.05$).

Large variability in pre-stimulus EMG amplitude of ECR during co-contraction was noted above (background

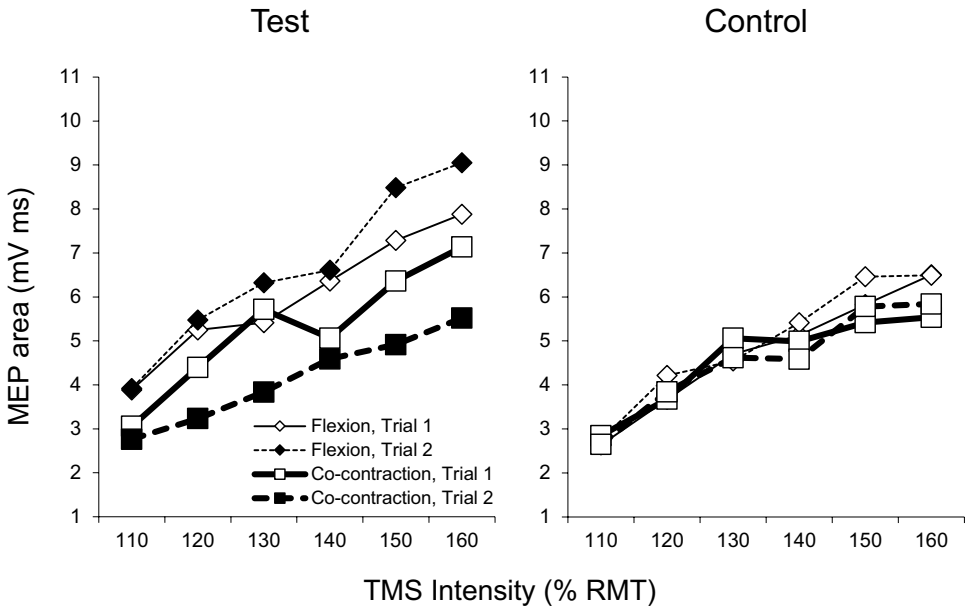

Fig. 3 Average MEP response of FCR in test and control subjects at each TMS intensity. Solid lines indicate responses during Trial 1; broken lines indicate responses during Trial 2; square symbols denote responses during wrist flexion; diamonds denote responses during wrist co-contraction; filled symbols indicate when baroreceptors were unloaded (Trial 2 of Test group, only). MEP, motor evoked potential; RMT, resting motor threshold

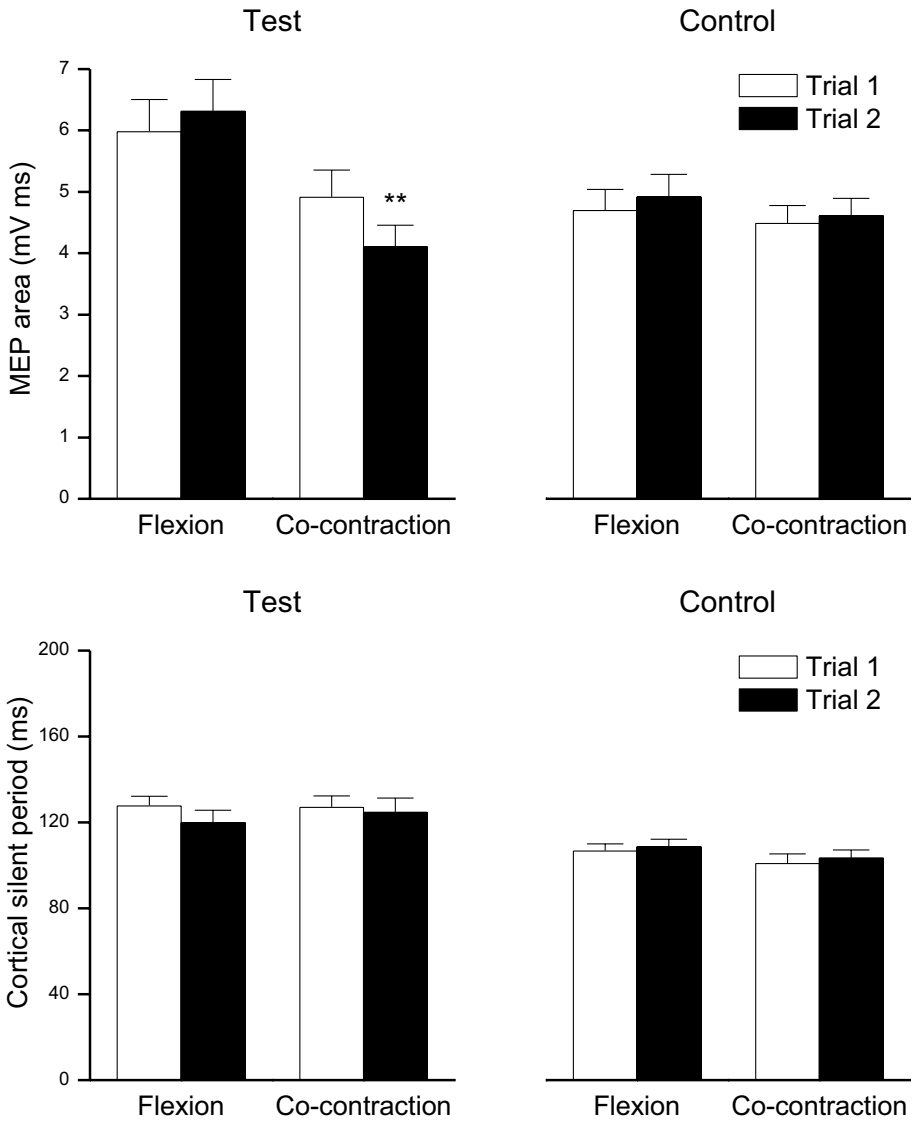

Fig. 4 Corticospinal excitability (**a**) and cortical silent period (**b**) for FCR during flexion and co-contraction. Response of test group and control group subjects during flexion and co-contraction tasks in trials 1 and 2. MEP, motor evoked potential. $^{**}P < 0.01$ between trials for the specified task in the group. In each group, there was no significant difference in cortical silent period between trials

contraction). To examine a potential relationship between variability of background ECR activity and individual changes in corticospinal excitability of FCR from Trial 1 to Trial 2, Pearson correlation coefficient (r) between their individual values during co-contraction was calculated across groups. There was no significant correlation between the change in MEP area of FCR and pre-stimulus EMG amplitude of ECR in Trial 1 ($r = -0.130$, $P = 0.184$) or Trial 2 ($r = -0.124$, $P = 0.205$).

Cortical silent period

CSP in FCR was assessed as a probe of motor cortical inhibition. There was a main effect of group ($P < 0.01$) and a Group × Trial interaction ($P < 0.05$) on CSP. While CSP was longer in the test group (125 ± 42 ms) compared with the control group (105 ± 27 ms), there were no significant within-group effects of trial (Fig. 4).

H-reflex and M_{max}

To examine the amount of disynapatic inhibition in FCR, H-reflex ratio between unconditioned and conditioned stimulation was obtained with the peripheral stimulation intensity that was expected to yield the comparable unconditioned H-reflex in FCR across trials. The unconditioned H-reflex was not significantly different between trials or groups (3.81 ± 2.73 mV ms, on average). H-reflex ratio in test group (0.89 ± 0.18) was greater compared with the control group (0.64 ± 0.25) across trials (Table 2) with a main effect of group ($P < 0.05$). There was no significant main effect of trial or interaction on H-reflex ratio.

Table 2 H-reflex ratio and maximal amplitude of M-wave in the flexor carpi radialis in each group

	Test group	Control group
H-reflex ratio		
Trial 1	0.86 ± 0.11	0.61 ± 0.23
Trial 2	0.92 ± 0.23	0.67 ± 0.29
	(n = 8)	(n = 6)
M_{max} (mV ms)		
Trial 1	25.5 ± 16.5	25.1 ± 13.1
Trial 2	26.1 ± 15.9	24.5 ± 13.0
	(n = 9)	(n = 8)

Lower body negative pressure of 40 mmHg was applied during Trial 2 in the test group, only. M_{max}, compound muscle action potential in response to supramaximal electrical stimulation. There was a main effect of group ($P < 0.05$) on the H-reflex ratio, but no interaction

To examine the excitability in the periphery, M_{max} in FCR was obtained with supramaximal peripheral stimulation. There was no significant main effect or interaction of group or trial on M_{max} (Table 2).

Cardiovascular measurements

Heart rate and HRV_{LF} were tested for assessing changes in sympathetic nerve activity. For heart rate, there were a main effect of trial ($P < 0.01$), task ($P < 0.01$), an interaction of Group × Trial ($P < 0.01$), and an interaction of Group × Trial × Task ($P < 0.05$). As a within-group effect, heart rate in Trial 2 (i.e., 40 mmHg lower body negative pressure) was greater compared with Trial 1 by 15.9 bpm ($P < 0.01$) in the test group across tasks (Table 3). A significant effect of trial was not found in the control group. During Trial 1 (i.e., no lower body negative pressure), heart rate was found to be affected by the Task ($P < 0.01$). In Trial 1, heart rate during co-contraction (61.2 ± 8.79 bpm) was slightly greater compared with flexion (58.3 ± 8.28 bpm) by 2.9 bpm, on average, across groups.

For HRV_{LF}, there were a main effect of Trial ($P < 0.01$) and an interaction of Group × Trial ($P < 0.01$), but not a significant interaction of Group × Trial × Task. In the test group, HRV_{LF} increased from Trial 1 to Trial 2 by 47.4% ($P < 0.01$, Table 3), but not in the control group.

Mean arterial blood pressure was 84.1 ± 8.5 mmHg, on average, throughout the experiment. There was no significant effect or interaction of group, trial, or task on mean arterial blood pressure.

Table 3 Heart rate and heart rate variability during flexion and co-contraction in each group

	Test group	Control group
Heart rate (bpm)		
Flexion		
Trial 1	58.5 ± 10.5	58.0 ± 4.9
Trial 2	73.3 ± 10.1**	61.3 ± 5.7
Co-contraction		
Trial 1	60.2 ± 11.0	62.3 ± 5.4
Trial 2	77.3 ± 12.0**	60.6 ± 9.4
HRV_{LF} (a.u.)		
Flexion		
Trial 1	0.47 ± 0.18	0.43 ± 0.17
Trial 2	0.68 ± 0.21**	0.45 ± 0.19
Co-contraction		
Trial 1	0.47 ± 0.17	0.45 ± 0.18
Trial 2	0.71 ± 0.20**	0.46 ± 0.19

Lower body negative pressure of 40 mmHg was applied during Trial 2 in the test group, only. HRV_{LF}, low-frequency content of heart rate variability (0.05–0.15 Hz power fraction of heart rate variability relative to the total power of the R-to-R interval spectrum), a.u., arbitrary units

**$P < 0.01$ between trials in test group

Discussion

The major findings of this study are the decrease in MEP during co-contraction with the application of lower body negative pressure (Trial 2 in the test group) and no significant effect of trial or task on CSP (i.e., measure of intracortical inhibition) or H-reflex ratio (i.e., measure of spinal disynaptic group I inhibition) in each group.

Before interpreting the neuromotor results, the efficacy of the employed intervention for baroreceptor unloading needs to be discussed in reference to the cardiovascular results. Lower body negative pressure of 40 mmHg is known to unload the baroreceptors and heighten sympathetic nerve activity as evidenced by increases in muscle sympathetic nerve discharges (Sundlöf and Wallin 1978; Taylor et al. 1992; Davy et al. 1998), noradrenaline concentration in plasma (Taylor et al. 1992; Hinghofer-Szalkay et al. 1996), heart rate (Sundlöf and Wallin 1978; Taylor et al. 1992; Davy et al. 1998; Buharin et al. 2013, 2014), and HRV_{LF} (Lee et al. 2004; Buharin et al. 2014). In the current study, increased heart rate and HRV_{LF} were confirmed, while mean arterial blood pressure was maintained, due to lower body negative pressure of 40 mmHg in Trial 2 of the test group. These cardiovascular responses are comparable to previous studies employing lower body negative pressure (Sundlöf and Wallin 1978; Taylor et al. 1992; Davy et al. 1998; Lee et al. 2004; Buharin et al. 2013). In the control group, there were no significant differences in these cardiovascular

measures between trials, indicating no significant effect of repeated trials. Thus, the cardiovascular results support substantial baroreceptor unloading with the application of lower body negative pressure in the current protocol.

Due to this baroreceptor unloading, a reduction in corticospinal excitability during co-contraction is indicated by the decrease in MEP during co-contraction in Trial 2 (i.e., with lower body negative pressure) compared with Trial 1 (i.e., without negative pressure) in the test group. This reduction is contrary to our hypothesis. For interpreting this result, it is imperative to examine the potential effect of major extraneous factors. No significant difference in M_{max} across groups and tasks is consistent with the absence of significant effect of lower body negative pressure in our previous study (Buharin et al. 2013). It confirms that baroreceptor unloading does not influence the efferent pathways at and distal to the neuromuscular junction, but within corticospinal pathways. Within each group, subjects maintained comparable contraction intensity across trials and tasks as shown by the indifferent pre-stimulus EMG amplitude. The very small difference in pre-stimulus EMG amplitude between groups (1.6% of maximal EMG amplitude) is not related to baroreceptor unloading because there was no significant interaction of group and trial. Comparable pre-stimulus EMG amplitude in FCR between flexion and co-contraction confirms comparable voluntary activation of spinal motor neurons between the two tasks. Hence, a potential alteration in the excitability of the motor neurons due to different levels of neural excitation (Nielsen 1998; Aimonetti and Nielsen 2002) is not likely to be involved in the obtained decline in MEP.

The findings on MEP demonstrate that the effect of baroreceptor unloading on corticospinal excitability depends on the type of muscle contraction in the forearm: agonist contraction or co-contraction. During agonist contraction, no influence of baroreceptor unloading on corticospinal excitability is indicated by the absence of significant effect of trial on MEP in FCR during flexion in the test group. It is unknown why there is a difference between agonist contraction and antagonist co-contraction in the effect of baroreceptor unloading. The current study examined a couple of candidates that would help identify the neural pathways that may contribute to the effect of baroreceptor unloading on corticospinal excitability during co-contraction. At the spinal level, the inhibition of alpha motor neurons by Ia inhibitory interneurons (Nielsen and Kagamihara 1992; Nielsen 1998; Wargon et al. 2006) (i.e., spinal disynaptic inhibition) may be involved between antagonistic muscles. For the FCR muscle, the ECR-coupled Ia inhibitory interneurons (i.e., the ones that inhibit the FCR motor neurons) can be recruited by group I afferents of the FCR and ECR (Wargon et al. 2006) and can be modulated by corticospinal neurons of the ECR (Fetz and Cheney 1987). In the current study, however, the invariable H-reflex ratio between trials in the test group does not support a modulation of spinal disynaptic group I inhibition by baroreceptor unloading, while it is unknown whether it is specific to co-contraction. Within the motor cortex, the current findings of invariant CSP in FCR across trials and tasks indicate that baroreceptor unloading does not affect intracortical inhibition that is probed by CSP, i.e., GABA-B receptor-mediated inhibition (Siebner et al. 1998; Werhahn et al. 1999). Collectively, the decrease in MEP of FCR due to baroreceptor unloading during co-contraction is thus likely to be mediated by other intracortical mechanisms that are modulated or additionally recruited with the wrist co-contraction. Potential pathways include GABA-A receptor-mediated intracortical inhibition, cortical reciprocal inhibition (Bertolasi et al. 1998; Capaday et al. 1998; Hortobagyi et al. 2006), and corticospinal neurons that are recruited specifically during co-contraction (Fetz and Cheney 1987). Additionally, intrinsic input to the primary motor cortex from other brain areas (e.g., sensory cortex and motor-related areas) may be altered. The current study was not designed to examine all these potential underlying mechanisms, and thus further research is warranted to delineate the involvement of these potential pathways by examining short-interval intracortical inhibition (SICI) and facilitation (SICF), for example.

The potential functional significance of the findings can be discussed by understanding that decreased corticospinal excitability implies decreased responsiveness of the corticospinal neurons in response to the motor cortical command. During a motor task involving co-contraction, when baroreceptors are unloaded (e.g., during sudden postural change), a decrease in corticospinal excitability would result in smaller modulation of muscle activity per given amount of intracortical input to the corticospinal neurons. Put another way, greater amount of intracortical input would be needed for achieving the same amount of modulation of muscle activity. This consequence may be beneficial to maintaining a steady co-contraction (e.g., stabilizing a load in space) without perturbation because the effect of involuntary fluctuations in intracortical input on fluctuations in muscle activity would be attenuated. In contrast, it may be detrimental to situations that require modulation of co-contraction (e.g., stability against perturbation). The latter effect might produce greater impact in older adults because they have reduced capability in modifying their joint stiffness against perturbation compared with young adults (Gibo et al. 2013). When speculated collectively with previous findings, baroreceptor unloading might potentially (1) facilitate the induction of (co-)contraction due to heightened excitability in the resting state (Buharin et al. 2013, 2014) and (2) impede a modulation of co-contraction due to diminished excitability in the co-contraction state. This speculation is in line with so-called fight, flight, or freeze response when exposed to acute stress.

There are some limitations to be mentioned of this study. Since the study focused on our principal interest in corticospinal excitability but did not assess mechanical output, the actual impact of baroreceptor unloading on motor control via way of altered corticospinal excitability is unknown. Since ECR and FCR can also work as synergists in radial deviation, the extension of the results on this particular muscle pair to other pairs is not guaranteed. We employed a group-comparison research design due to our limited capacity, but a crossover design would have been ideal, if possible. Nonetheless, we believe this first study produced intriguing findings on the effect of baroreceptor unloading during co-contraction on neural excitability, which will motivate the clarification of the listed uncertainties as the logical next steps in future studies.

In conclusion, baroreceptor unloading by means of 40 mmHg lower body negative pressure did not influence corticospinal excitability or motor cortex inhibition during wrist flexion but diminished corticospinal excitability during forearm co-contraction.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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