Title: Ischemic Conditioning Increases Strength and Volitional Activation of Paretic Muscle in Chronic Stroke: A Pilot Study

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Abstract

Ischemic conditioning (IC) on the arm or leg has emerged as an intervention to improve strength and performance in healthy populations, but the effects on neurologic populations are unknown. The purpose of this study was to quantify the effects of a single session of IC on knee extensor strength and muscle activation in chronic stroke survivors. Maximal knee extensor torque measurements and surface EMG were quantified in 10 chronic stroke survivors (>1 year post-stroke) with hemiparesis before and after a single session of IC or Sham on the paretic leg. IC consisted of five minutes of compression with a proximal thigh cuff (inflation pressure = 225 mmHg for IC or 25 mmHg for Sham) followed by five minutes of rest. This was repeated five times. Maximal knee extensor strength, EMG magnitude, and motor unit firing behavior were measured before and immediately after IC or Sham. IC increased paretic leg strength by 10.6±8.5 Nm while no difference was observed in the Sham group (change in Sham = 1.3±2.9 Nm; p = 0.001 IC vs. Sham). IC-induced increases in strength were accompanied by a 31±15% increase in the magnitude of muscle EMG during maximal contractions and a 5% decrease in motor unit recruitment thresholds during sub-maximal contractions. Individuals who had the most asymmetry in strength between their paretic and non-paretic legs had the largest increases in strength (r^2 = 0.54). This study provides evidence that a single session of IC can increase strength through improved muscle activation in chronic stroke survivors.

New and Noteworthy: Current rehabilitation strategies for chronic stroke survivors do not optimally activate paretic muscle, and this limits potential strength gains. Ischemic conditioning of a limb has emerged as an effective strategy to improve muscle performance in healthy individuals, but has never been tested in neurologic populations. In this study we show that ischemic conditioning on the paretic leg of chronic stroke survivors can increase leg strength and muscle activation while reducing motor unit recruitment thresholds.

Key Words: Stroke Rehabilitation, Ischemic Conditioning, Muscle Strength, Electromyography

Introduction

The aim of this study was to quantify gains in paretic muscle strength and muscle activation due to ischemic conditioning. Diminished ability to generate paretic muscle force contributes to long term motor deficits and disability in chronic stroke survivors (6, 26, 37). Fundamentally, damage to cortical structures limits a stroke survivor's ability to optimally activate paretic motoneuron pools, thereby reducing force development (21, 27, 28), even during brief maximal efforts. Stroke rehabilitation interventions are currently not optimized because stroke survivors are unable to adequately activate the paretic muscle, and functional gains in response to traditional therapies have been moderate at best (32, 35, 43). Interventions that optimize residual paretic muscle activation and strength are needed to achieve greater functional gains.

In healthy populations, ischemic conditioning (IC) has emerged as a neuroadaptive technique which results in improved motor performance. IC was first described in 1986 as a vascular stimulus to protect vital organs from ischemic injury (36). Subsequent studies in humans have shown that both local IC (performed on tissue of interest) and remote IC (performed on a remote limb) improves motor learning, muscle performance and delays muscle fatigue. Specifically, in healthy individuals, brief, repeated 5 minute bouts of limb ischemia (using a blood pressure cuff inflated to 225 mmHg on the arm or leg) improve stability on a tilted platform balance task (8), task duration during handgrip exercise (4), 5 km running time (3), and maximal power output (10). In these studies, IC was shown to enhance force generation and muscle activation and the authors propose a potential mechanism of engagement of autonomic centers in the brainstem sensitive to ischemia and exercise. Given the positive effects on motor

output in individuals with intact nervous systems and optimal motor function, it is likely that IC may have a larger neuroadaptive effect on clinical populations with impaired neural activation of muscle and diminished motor function. At this time, the effects of ischemic conditioning on motor recovery in patient populations such as stroke are unknown and quantifying the effects may lead to a new treatment strategy to optimize strength gains and function.

In this pilot study, we quantified the effects and tolerance of a single session of IC on paretic leg strength and muscle activation in chronic stroke survivors. We hypothesize that IC will be well-tolerated, increase the magnitude of the maximal voluntary contraction of the knee extensor muscles of the paretic leg, and that this increase will be accompanied by increased *vastus lateralis* activity as measured by electromyography (EMG). Interpretive measures of resting twitch responses were made to understand the effects of IC on muscle contractile properties.

Methods

Subjects

This study was a single-blinded, randomized, controlled trial with paired analysis. All subjects were studied twice with a minimum of one week between study sessions. All activities in this study were approved by the Institutional Review Boards of Marquette University and the Medical College of Wisconsin (PRO19103). All participants gave written informed consent prior to study participation. Ten participants with chronic stroke (≥ 1 year post-stroke) participated in this study (see Table 1 for participant characteristics). Stroke subject inclusion criteria were: 1) history of a single, unilateral

stroke and 2) residual hemiparesis. Stroke subject exclusion criteria: 1) history of multiple strokes, 2) brainstem stroke, 3) any uncontrolled medical condition, 4) lower extremity contractures, 5) uncontrolled hypertension, 6) inability to follow 2-3 step commands, 7) deep vein thrombosis, 8) peripheral arterial grafts in the lower extremity, and 9) any condition in which tissue ischemia is contraindicated.

Torque Measurements

Participants were positioned in a dynamometer chair (Biodex Medical Systems, Inc, Shirley New York) with their test knee and hip at 90° of flexion. Subjects had a belt placed around their trunk and waist to reduce movement during knee extensor contractions. Knee extension torque was sampled at 2048 Hz and acquired by an EMG-USB2+ amplifier (256-channel regular plus 16-auxiliary channels, OT Bioelettronica, Turin, Italy) and acquired using the OT Biolab software.

Surface Electromyography Measurements

Surface EMGs were obtained using a 64 channel 2-D electrode array (13 rows, 5 columns). A double-sided adhesive sticker designed for and compatible with the array was placed over the array. The holes within the adhesive sticker were filled with a conductive electrode paste (Ten20, Weaver and Company, Aurora, Co). The array was placed over the belly of the *vastus lateralis*, midway between the patella and the greater trochanter, after rubbing the subject's skin with an alcohol swab to remove superficial dead skin. The signals for each channel were differentially amplified between 1000 and 5000 v/v (subject dependent) and bandpass filtered between 10 and 500 Hz using the

EMG-USB2+ amplifier. The signals were sampled at 2048 Hz and acquired with the OT Biolab software throughout the duration of the experimental protocol.

Ischemic Conditioning

IC treatments were performed in accordance with other studies which have used IC as an intervention (31, 39, 45). Briefly, in a supine position, a rapid inflation cuff (Hokanson SC12 thigh cuff) was placed around the proximal thigh and inflated to 225 mmHg for five minutes, then released for a five minute recovery period, and five cycles of inflation/recovery were performed. For the IC Sham, the cuff was inflated to 25 mmHg. This level of inflation was chosen because participants still perceive the cuff tightness, however the inflation pressure is not high enough to occlude arterial blood flow or venous return. Subjects were blinded to the purpose of the different cuff inflation pressures. A minimum of one week between test sessions was given, and the order of IC vs. Sham IC was randomized.

Electrical Stimulation

In a subset of six participants, resting twitch torque responses were elicited to quantify the effects of IC on muscle contractile properties as done in other studies (24, 49, 50). Following each MVC, a brief constant-current stimulator (Digitimer DS7AH, Welwyn Garden City, UK) delivered a rectangular pulse of 100 μs duration with maximum amplitude of 400 V, which was used to percutaneously stimulate the quadriceps muscle. The stimulation intensity (200 mA to 500 mA) was set at 20% above the level required to produce a maximal resting twitch amplitude.

Experimental Protocol

Subjects first performed baseline isometric maximum voluntary contractions (MVCs) of the knee extensor muscles (See Fig. 1A for protocol summary). Subjects were given visual and verbal encouragement. MVC efforts were repeated until there was less than a 5% difference in torque between two subsequent MVCs. A minimum of five MVCs were performed. At least 1 min rest was given between subsequent MVCs. Resting twitch responses were elicited following each MVC. Next, subjects performed a submaximal ramp and hold isometric contraction equal to 40% of their MVC (4 second graded contraction, 5 second hold at 40% of MVC, 4 second graded relaxation) with visual feedback. Subjects then underwent either the IC or IC sham protocol. Immediately following completion of the IC or IC-Sham protocol (within 10 minutes), subjects repeated the MVC, resting twitch, and sub-maximal ramp and hold contractions using identical positioning within the dynamometer chair. Surface EMG measurements of the *vastus lateralis* were made continuously throughout the pre and post motor testing. An example of MVC torque traces from a single subject before and after either IC Sham or IC (see below) are shown in Figs. 1B and 1C, respectively.

Data Processing

Knee extensor torque signals were zero phased lowpass filtered at 15 Hz using a 2nd order Butterworth filter prior to analysis and processed using custom Matlab (MathWorks, Natick, MA) scripts. Peak torque was calculated for each MVC trial and the resting twitch responses. To determine how IC affected force steadiness, the knee extensor torque coefficient of variation ((standard deviation torque/mean torque)*100) was determined for a 4 second window during the hold portion of the ramp contraction as previously described (25).

Surface Electromyography

Single motor unit action potential trains during the sub-maximal ramp and hold contractions were detected with a multichannel blind source separation using convolution kernel compensation (CKC) for the high density surface EMG signal decomposition as described and validated previously (22, 38). Individual motor units were tracked between the pre and post measurements and mean firing rates during a 4 second window in the hold phase of the sub-maximal contraction were calculated as well as the torque at which each motor unit was recruited and de-recruited.

For global surface EMG measurements, the mean root mean square of the EMG for each of the channels during the 4 second hold of the MVC and during the 4 second window during the hold portion of the ramp contraction was calculated using a sliding window of 200 ms. To understand how IC effects the variability of the EMG measurement from each channel (48), the mean coefficient of variation (coefficient of variation = standard deviation of RMS/mean RMS*100) was calculated during the 4 second window of the MVC. A decrease in coefficient of variation would indicate that the EMG activity is more consistent (less variable) during the hold portion of the MVC irrespective of magnitude. In order to understand how IC effects the homogeneity of the spatial activation of the muscle, modified entropy was calculated ($Entropy = -\sum_{i=1}^{59} p^2(i) \log_2 p^2(i)$) (where $p^2(i)$ is the square of the RMS value at electrode i normalized by the summation of the squares of all RMS values for each channel). Modified entropy is the normalized power of the EMG signal across the array and reflects the homogeneity of the muscle activity. Higher values occur if the energy were the same across all channels – i.e. if the muscle activity is very homogenous (14,

30). Measures of coefficient of variation and entropy provide insight into how the nervous system is spatially activating the paretic muscle irrespective of magnitude.

Statistical Analyses

Separate, two way repeated measures ANOVAs were performed on the following variables: MVCs and resting twitch responses amplitudes. Main effects of time (Pre, Post) and condition (IC, IC Sham) and interaction effects of time x condition were determined. A Bonferroni post-hoc test was used to test for differences between individual means. Because the coefficient of variation data were not normally distributed, a Friedman's Test was performed. Linear regression and goodness of fit analysis was performed to determine if there was a correlation between the percent increase in paretic leg strength following IC and baseline motor function (assessed as either symmetry of leg strength, walking speed, or Lower Extremity Fugl-Meyer score).

Because there was no detected effect of the Sham IC condition on torque generation, EMG measurements were only evaluated for the IC condition. Separate paired t-tests were performed to detect pre- and post-IC differences on the following EMG variables: coefficient of variation, force recruitment threshold, modified entropy, and magnitude of the RMS. All statistical tests were performed using an alpha level of 0.05 for significance. Data are reported as the mean ± standard deviation.

Results

Knee extensor strength and muscle activation were measured in ten individuals with chronic stroke before and after a single session of IC or IC sham. Consistent with previous studies performed in chronic stroke subjects from our group (13) and others

(34), the paretic leg was weaker than the non-paretic leg (paretic vs. non-paretic MVC: 88.8 ± 50.2 Nm vs. 139.0 ± 78.6 Nm, respectively; p = 0.012, paired t-test). Following IC, 9/10 individuals had increased strength in their paretic leg knee extensor muscles, with an observed mean increase in MVC of 10.6 ± 8.5 Nm (Fig. 2A; p=0.001 vs. pre-IC, two-way repeated measures ANOVA). No difference in knee extensor MVC was observed after the Sham IC treatment (mean difference post Sham IC: 1.3 ± 2.9 Nm; p=0.65; Fig. 2B). Relative to each individual's baseline strength, a 16.1 ± 14.5 % increase in strength was observed in the IC group vs. a relative change in strength of -0.04 ± 11.76 % in the Sham IC group (p = 0.04 IC vs. Sham IC, paired t-test; Fig. 2C). Pre-test MVCs were similar for all subjects between both the Sham and IC treatment groups (p = 0.79, paired t-test), demonstrating the test/re-test reliability of the MVC measurement across multiple sessions.

There was a significant positive correlation between baseline asymmetry in knee extensor strength and percent change in MVC following IC, whereby those individuals whose paretic leg had the greatest difference in strength compared to their non-paretic leg had the greatest relative increase in knee extensor MVC following IC (Fig. 3A; p = 0.014; R^2 = 0.55). Subjects who had the lowest Lower Extremity Fugl Meyer score (a performance-based index to assess the sensorimotor impairment in stroke survivors) also showed the greatest increase in knee extensor strength following IC (Fig. 3B; p = 0.008; R^2 = 0.61). Finally, there was a moderate correlation between baseline self-selected walking speed and improvement following IC whereby subjects who walked the slowest also tended to show the largest IC-induced improvements in knee extensor MVC (Fig 3C, R^2 = 0.33), however this result was not statistically significant (p = 0.08).

With respect to the magnitude of muscle activation, there was a significant increase in the root mean square (RMS) magnitude of vastus lateralis EMG during MVCs following IC (Fig. 4A; p=0.01; paired t-test), which resulted in an overall 30.7±15% increase in total EMG signal. Fig. 4B, shows a single subject example of the change in EMG RMS between pre and post MVCs. Modified entropy increased from 4.19 ± 0.9 to 5.12 ± 0.3 (p=0.02; paired t-test; Fig. 4C) which reflects an increase in the homogeneity of the spatial EMG potential distribution. Consistent with this, the coefficient of variation of the EMG RMS decreased from 19.4 ± 9.5% to 10.6 ± 8.2% (p=0.02; paired t-test; Fig. 4D) which reflects an overall decrease in the variability in individual EMG channels.

During the 40% submaximal ramp and hold contractions, there was a decrease in the motor unit force recruitment thresholds from 25.0 ± 1.7 % to 21.8 ± 1.7 % of the MVC (See single subject example Fig. 5A, Fig. 5B; p <0.01; paired t-test). Sub-maximal torque regulation during the ramp and hold contractions was not diminished by IC as there was no significant change in the coefficient of variation of the torque trace in response to the IC or IC sham (IC pre = 4.6% ± 2.4 % vs post = 2.8 ± 1.5 %; IC sham pre = 4.4 % ± vs post= 3.9 ± 2.4%). The coefficient of variation tended to decrease but the effect was not significant (p = 0.06).

Finally, as shown in Fig. 6, the mean amplitudes of the resting twitch torque responses were not different pre-post for either the IC or IC sham condition (IC pre-post: 37 ± 13 Nm vs. 35 ± 13 Nm, respectively; Sham IC pre-post: 28 ± 14 Nm vs. 31 ± 13 Nm, respectively; p=0.60, two-way RM ANOVA), indicating that IC had no effect on muscle contractile properties.

Discussion

There are three novel findings from this pilot study. First, our data support the hypothesis that a single session of IC is a feasible, well-tolerated intervention that can increase strength in the paretic leg of chronic stroke survivors. Second, increases in EMG magnitude and unchanged resting twitch responses to electrical stimulation of the muscle indicate that the increased strength is due to improved neural activation of the muscle as opposed to changes in muscle contractile properties. Finally, we show a positive relationship between the response to IC and baseline physical function, whereby individuals whose lower extremity motor function is most affected by the stroke show the largest improvement in leg strength following IC. This finding provides insight into which individuals may benefit the most from IC intervention.

Very recently, two studies have shown that repetitive, remote IC performed on the arm prevents recurrence of stroke (33) and that daily remote IC over the course of one year slows cognitive decline in patients with cerebral small-vessel disease–related mild cognitive impairment (47). We present the first study to our knowledge to apply IC as an intervention to improve motor function post-stroke - specifically increased maximal force generating capabilities in the paretic leg. As other groups have shown, IC can improve motor performance by 2.5 – 11.2% in healthy subjects (2, 5, 45), who presumably have optimal neural activation of their skeletal muscle and thus have a ceiling effect when it comes to IC-induced improvements in motor function. In this study we report, on average, an increase in strength of 16% in the paretic leg of chronic stroke survivors. Furthermore, we show that those subjects with the largest degree of motor deficits had the largest improvement (Fig. 3). Together, these findings suggest

that subjects who have the greatest impairments will benefit the most from IC, and that IC has the potential to produce large strength gains in neurologic populations.

Although multifactorial (7), the neural mechanisms of IC have been linked to the engagement of the autonomic nervous system. For example, in animal models, the cardioprotective effects of IC can be abolished with spinal cord section, bilateral vagotomy or blockade of muscarinic cholinergic receptors (12). One mechanism by which IC is believed to act centrally is through stimulation of muscle afferents sensitive to ischemia (group III and IV afferents) which in turn engage brainstem centers that release neuromodulators such as serotonin and norepinephrine (42, 44). Importantly, these neuromodulators are known to increase the excitability of spinal motoneurons (18, 19, 42). Moreover, there is evidence that the group III and IV pathways in the paretic leg are hyperexcitable post stroke (20), which may amplify the potential response to IC in this patient population. Thus, in individuals without stroke, IC enhances the gain of descending excitatory commands by increasing the excitability of motoneuron pools, thereby improving torque output. Our data are consistent with this mechanism, as maximum voluntary contractions post-IC resulted in increased torque generation and global EMG magnitude. Further, the increased homogeneity (48) of the EMG signal is consistent with a more coordinated and consistent activation of the paretic muscle. Finally, the decrease in the force recruitment thresholds of the matched motor units is also consistent with increased excitability of the motoneuron pools (17). Thus, it is plausible that post-stroke the benefits of IC may be larger as compared to neurologically intact individuals given the decreased volitional ability to fully activate paretic muscle.

Volitional engagement of the nervous system during strength training (as opposed to electrical stimulation of the muscle) is important for the neural adaptations that precede muscle hypertrophy and facilitate motor learning (1, 15). Recently, in persons with spinal cord injury, transient hypoxia has been used to increase the excitability of the nervous system and increase affected muscle activation for therapeutic training (9, 16, 29, 46). Similar to IC, investigators attribute the priming effects of hypoxia to engagement of neuromodulatory centers in the brainstem (11, 40) and forebrain (23). Although intermittent hypoxia may be advantageous for some, IC might be a strong alternative because it is non-invasive, cost effective, and easier to implement in the clinic and in the community because it requires only inflation of a cuff similar to a blood pressure cuff.

Study Limitations and Future Directions

We recognize several study limitations and propose future study directions based on our pilot study. First, we recognize the small sample size of 10 subjects as a study limitation, but our data clearly show that IC is well tolerated in stroke subjects and that it caused an improvement in knee extensor strength in 9/10 of our test subjects. A second limitation is that we did not test the effects of IC on the non-paretic leg, or the remote effects of IC, (i.e. to perform IC on the non-paretic limb and test the paretic limb) and recognize these as important future study directions. Third, we did not test how long the positive effects of IC are sustained. Decades of research on the cardioprotective effects of IC indicate there is both a short (0-24 hours) and long (24-48 hours) phase of IC-induced cardioprotection, and these phases are mediated by different mechanisms (41). Future studies examining the time-course of IC-induced

344 improvements on motor function are necessary to determine how long the
345 improvements in strength last, and whether there are different mechanisms mediating
346 the improvements. We also did not test the effects of multiple sessions of IC to
347 determine if there is an additive effect. Finally, we only performed our study in
348 individuals with chronic stroke. Given that, on average, we saw an increase in strength
349 of 16% following IC in subjects who were many years post stroke, future studies
350 examining the effects of IC on subacute stroke patients (days to weeks post-stroke) who
351 are in a highly plastic recovery stage and undergoing physical therapy are warranted.

352 As our data show, IC is effective at increasing paretic muscle activation in stroke
353 survivors. There are several important, non-trivial advantages of IC as an interventional
354 adjunct to stroke rehabilitation: 1) a wide range of patients can benefit because the
355 technique does not require high levels of physical activity or function, 2) IC is non-
356 invasive, well-tolerated, and safe in cardiovascular populations, and 3) IC can be
357 accomplished with inexpensive equipment at home or in the clinic in less than 60
358 minutes. We propose that IC has the potential to be an ideal adjunct to physical therapy
359 in patients with hemiplegia because it “primes” the nervous system to more fully activate
360 the paretic muscle during exercise and is clinically feasible.

361

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Figure Legends

Figure 1. (A) Protocol summary of the ischemic conditioning (IC) protocol. Subjects performed a series of isometric maximum voluntary contractions (MVC) of the knee extensor muscles followed by a submaximal contraction equal to 40% of their maximum using a Biodex dynamometer. After the initial contractions were completed, the subjects moved to a bed where the ischemic conditioning protocol was performed. The subjects laid in the supine position and a blood pressure cuff was placed around the proximal thigh of paretic leg and inflated to either 225 mmHg (IC condition) or 25 mmHg (Sham condition) for 5 minutes. After 5 minutes of inflation, the cuff was deflated for 5 minutes, and this was repeated for 5 cycles. Following the IC or Sham protocol, subjects were placed back in the Biodex dynamometer and knee extensor MVCs and submaximal contractions were repeated. Representative torque traces of an MVC from a single subject before and after the IC and Sham conditions are shown in panels B and C, respectively. Note the increase in MVC magnitude for the IC condition.

Figure 2. Individual knee extensor maximum voluntary contraction (MVC) responses of the paretic leg before and after either Ischemic Conditioning (IC) or Sham treatment. Individuals in the IC group demonstrated an increase in knee extensor MVC following IC (panel A; $p<0.05$; two-way repeated measures ANOVA), and no difference following Sham treatment (panel B; $p>0.05$). On average, individuals in the IC group demonstrated a 16.1 ± 14.5% increase in knee extensor strength following IC (panel C; $p<0.05$).

Figure 3. Changes in knee extensor strength following IC as a function of leg impairment. There was a strong correlation between asymmetry in MVC magnitude

between the paretic and non-paretic leg and percent change in MVC in response to IC (Panel A). Subjects who showed a greater degree of asymmetry in knee extensor strength between their paretic and non-paretic legs showed a greater improvement in paretic leg strength following IC (R^2 = 0.55; p = 0.014). Subjects who had the lowest Lower Extremity Fugl Meyer Score (panel B) also had the largest improvements in knee extensor strength following IC (Panel B, R^2 = 0.61; p = 0.008). There was a moderate correlation between self-selected walking speed and gains in strength following IC whereby subjects who walked the slowest tended to have the largest increases in strength. (Panel C; R^2 = 0.33; p = 0.08).

Figure 4. Changes in vastus lateralis EMG measurements that accompanied IC-induced increases in knee extensor torque. (A) The average root mean square of the EMG signal during MVCs was increased following IC (p = 0.01; paired t-test). (B) A single subject spatial activation map of the change in the RMS of the EMG across the EMG array, pre to post IC during the MVCs. Coloring reflects the degree of change where red indicates the largest increases and blue indicates decreases in the RMS of the EMG. (C) Modified entropy increased following IC (panel C; p = 0.02; paired t-test). This indicates increased homogeneity in the potential distribution across the array. (D) There was an IC-induced decrease in the average coefficient of variation of the EMG signal from each channel in the array (p=0.02, t-test).

Figure 5. Motor unit firing behavior and recruitment during the sub-maximal ramp and hold task. (A) Single subject raster plot of incidences of action potentials superimposed on the torque generated during the ramp and hold pre (left) and post (right) IC. Each row is a separate motor unit matched between time points. (B) Average force

recruitment thresholds decreased following IC reflecting increased excitability of the motoneuron pools ($p<0.01$,paired t-test).

Figure 6. Resting twitch torque values following maximal electrical stimulation of the knee extensor muscles. There was no difference in the knee extensor resting twitch torque in either the IC or Sham group in response to electrical stimulation of the muscle at a level 20% above the threshold required to elicit a maximal twitch response ($p = 0.60$).

Table 1. Characteristics of all Subjects.

Characteristic	***n*=10**
Sex	
Male (*n*)	4
Female (*n*)	6
Age (yrs)	60±12
Height (cm)	168±11
Weight (kg)	78±16
Body Mass Index (kg/m^2)	27±4
Time Since Stroke (yrs)	16±9
Type of Stroke	
Ischemic (*n*)	7
Hemorrhagic (*n*)	3
Affected Side	
Left (*n*)	6
Right (*n*)	4
Lower Extremity Fugl-Meyer Score (0-34)	26±6
Physical Activity (MET-h/week)	14±7
Self-Selected Walking Speed (m/s)	0.81±0.35

All values are expressed as number (*n*) or mean ± SD. MET, Metabolic Equivalent of Task

FIGURE 1

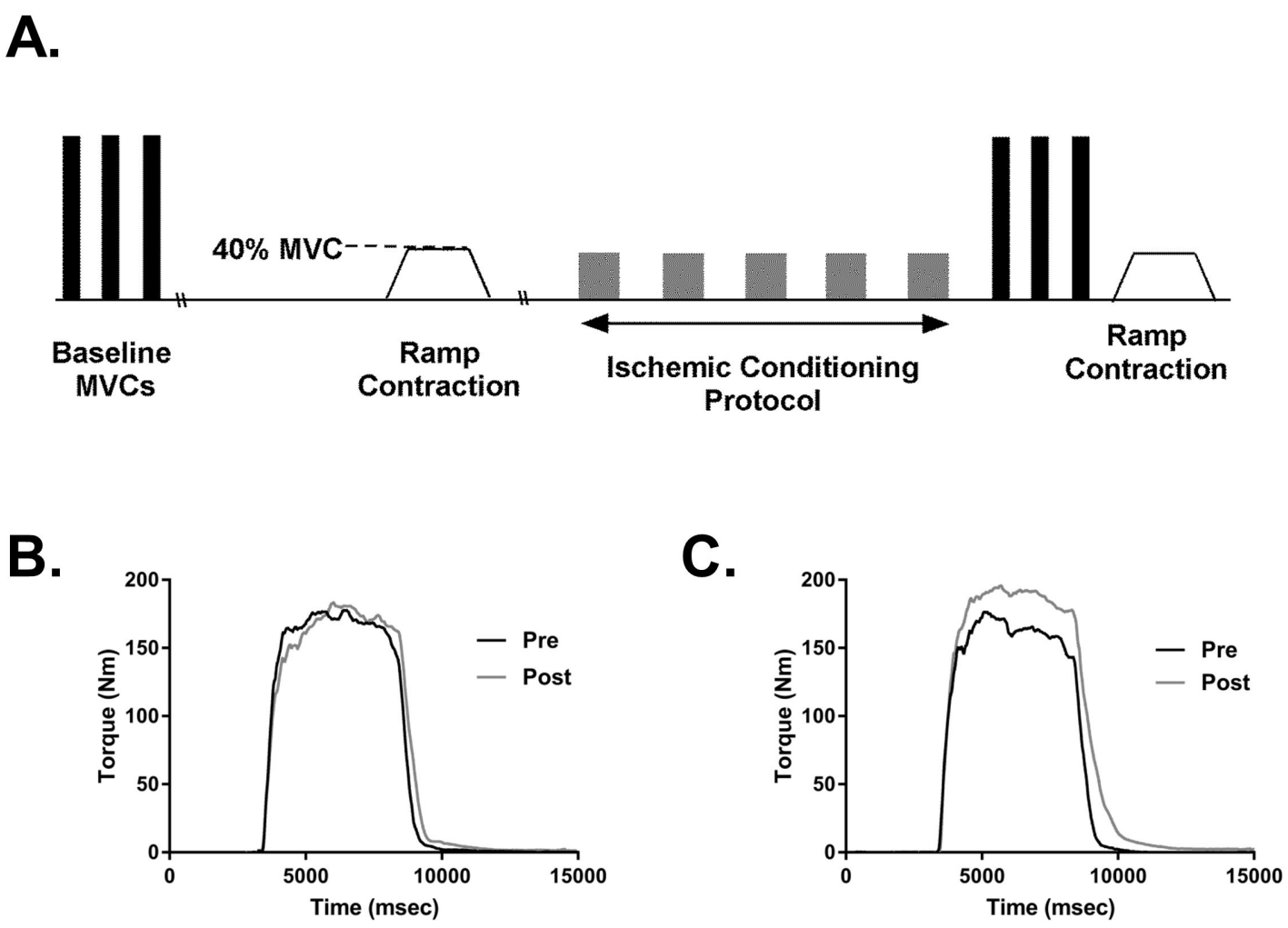

A.
40% MVC
Baseline MVCs
Ramp Contraction
Ischemic Conditioning Protocol
Ramp Contraction
B.
Torque (Nm)
200
150
100
50
0
0
5000
10000
15000
Time (msec)
Pre
Post
C.
Torque (Nm)
200
150
100
50
0
0
5000
10000
15000
Time (msec)
Pre
Post

FIGURE 2

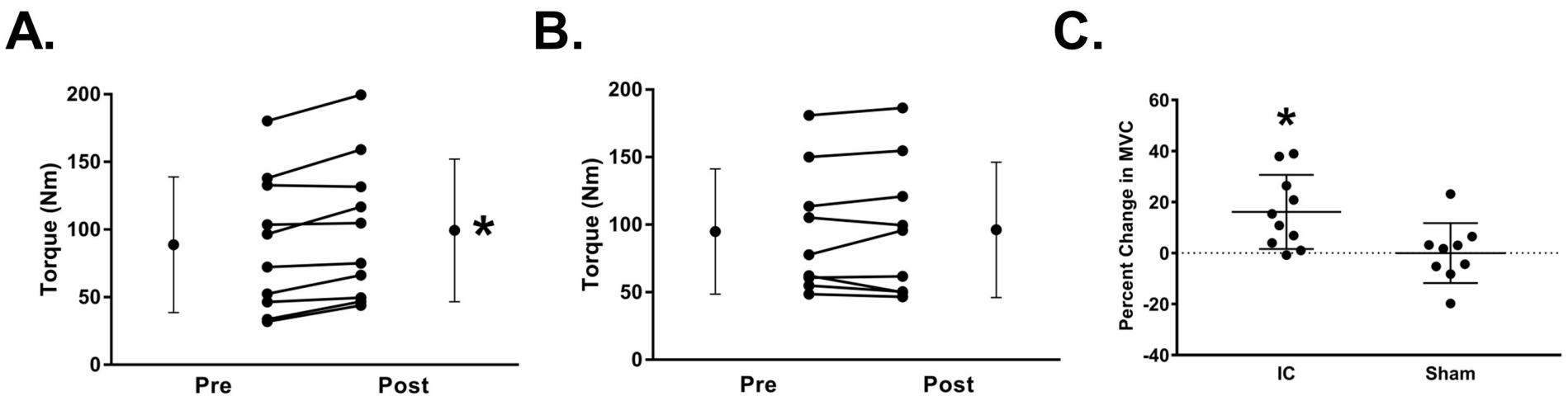

A.
B.
C.
Torque (Nm)
200
150
100
50
0
Pre
Post
*
Percent Change in MVC
60
40
20
0
-20
-40
IC
Sham

FIGURE 3

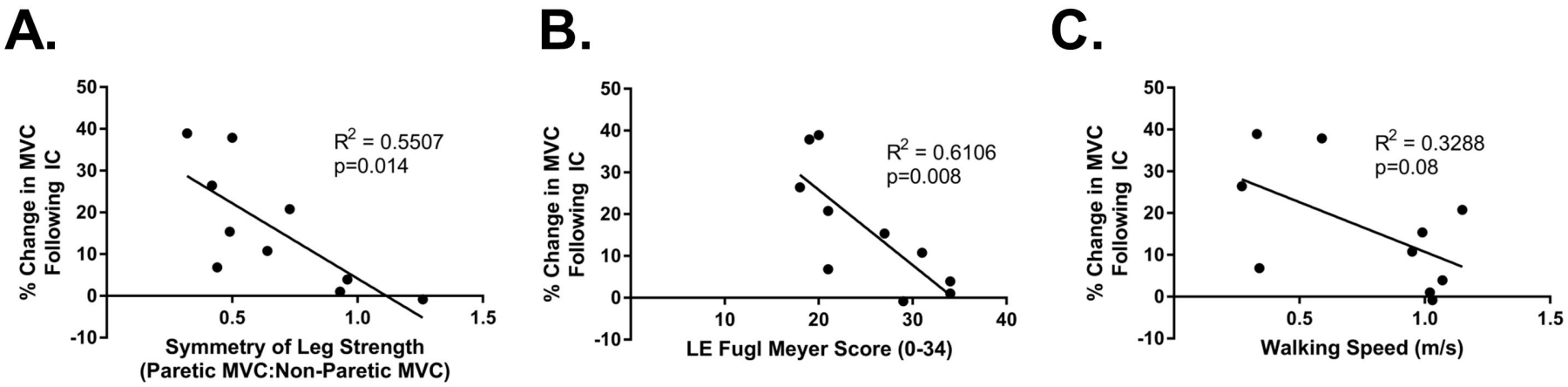

A.
% Change in MVC Following IC
50
40
30
20
10
0
-10
0.5
1.0
1.5
R^2 = 0.5507
p=0.014
Symmetry of Leg Strength
(Paretic MVC:Non-Paretic MVC)
B.
% Change in MVC Following IC
50
40
30
20
10
0
-10
10
20
30
40
R^2 = 0.6106
p=0.008
LE Fugl Meyer Score (0-34)
C.
% Change in MVC Following IC
50
40
30
20
10
0
-10
0.5
1.0
1.5
R^2 = 0.3288
p=0.08
Walking Speed (m/s)

FIGURE 4

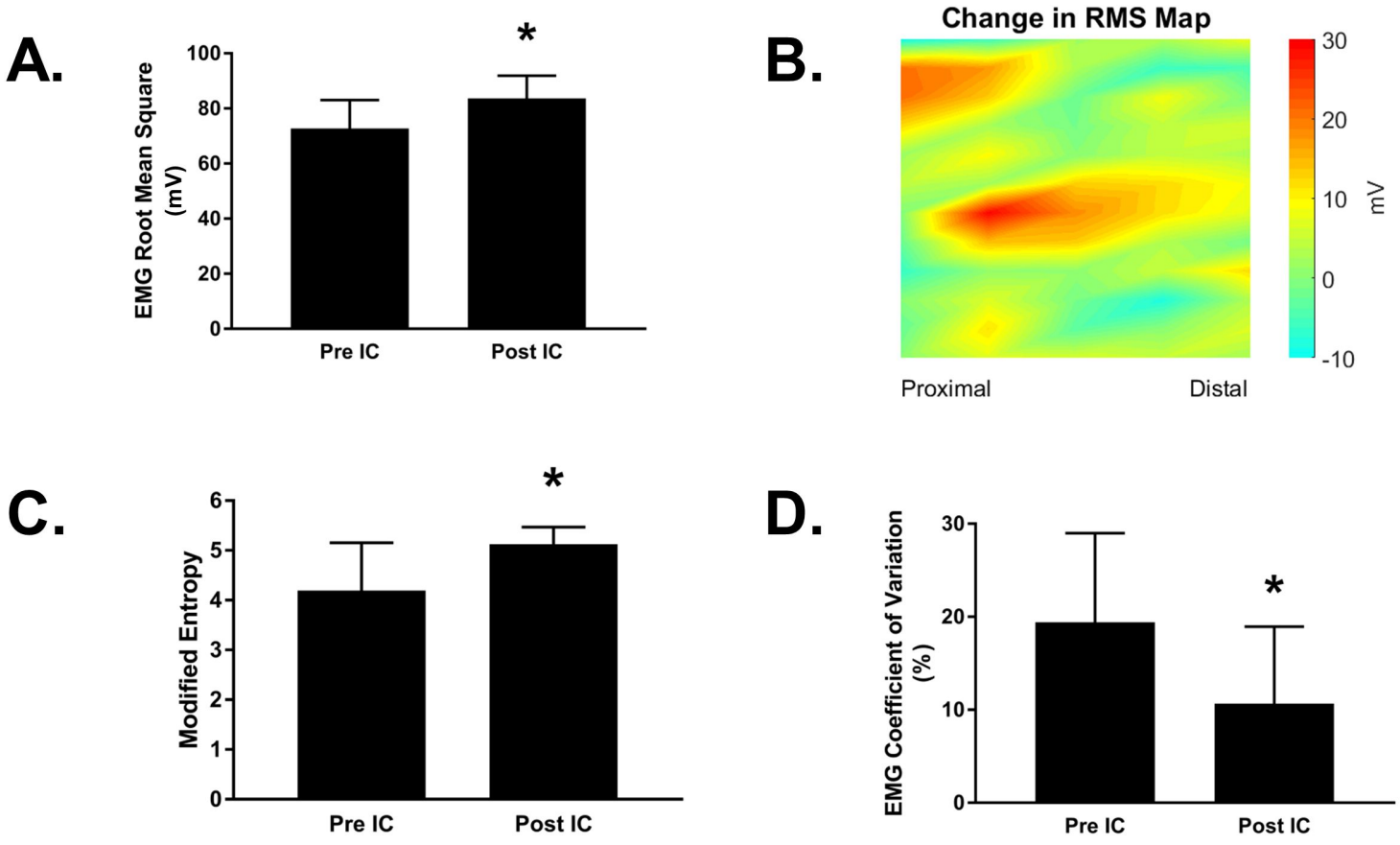
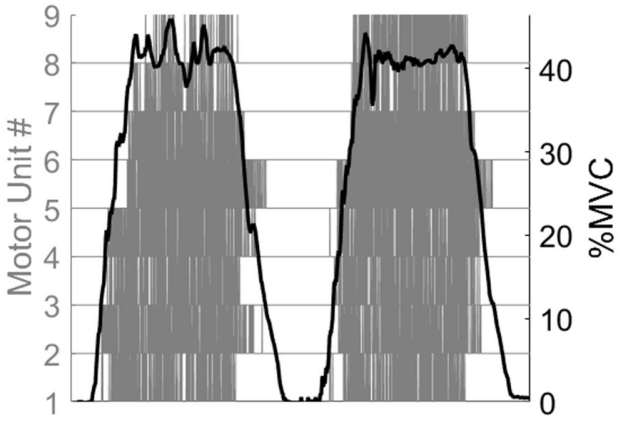

A.
EMG Root Mean Square (mV)
100
80
60
40
20
0
*
Pre IC
Post IC
B.
Change in RMS Map
30
20
10
0
-10
mV
Proximal
Distal
C.
Modified Entropy
6
5
4
3
2
1
0
*
Pre IC
Post IC
D.
EMG Coefficient of Variation (%)
30
20
10
0
*
Pre IC
Post IC

FIGURE 5

A.


Motor Unit #
9
8
7
6
5
4
3
2
1
40
30
20
10
0
%MVC

B.

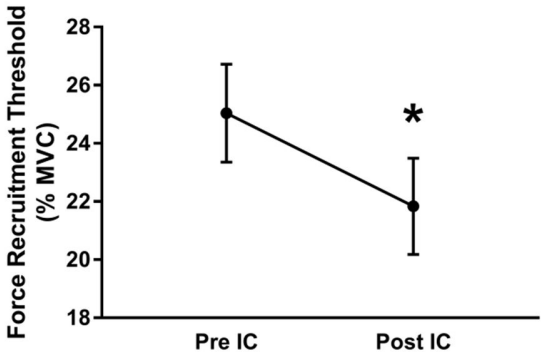

Force Recruitment Threshold
(% MVC)
28
26
24
22
20
18
*
Pre IC
Post IC

FIGURE 6