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Allison S. Hyngstrom
Marquette University, allison.hyngstrom@marquette.edu

Spencer A. Murphy
Marquette University

Jennifer Nguyen
Marquette University

Brian D. Schmit
Marquette University, brian.schmit@marquette.edu

Francesco Negro
Marquette University

See next page for additional authors

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Allison S. Hyngstrom
Department of Physical Therapy, Marquette University, Milwaukee, Wisconsin
Spencer A. Murphy
Department of Biomedical Engineering, Marquette University, and the Medical College of Wisconsin Milwaukee, Wisconsin
Jennifer Nguyen
Department of Physical Medicine and Rehabilitation, Medical College of Wisconsin, Milwaukee, Wisconsin
Brian D. Schmit
Department of Biomedical Engineering, Marquette University, and the Medical College of Wisconsin Milwaukee, Wisconsin
Francesco Negro
Department of Clinical and Experimental Sciences, Università degli Studi di Brescia, Brescia Italy
David D. Gutterman
Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin
Cardiovascular Center, Medical College of Wisconsin, Milwaukee, Wisconsin

Matthew J. Durand
Department of Physical Medicine and Rehabilitation, Medical College of Wisconsin, Milwaukee, Wisconsin
Cardiovascular Center, Medical College of Wisconsin, Milwaukee, Wisconsin

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 neurological 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 yr poststroke) with hemiparesis before and after a single session of IC or sham on the paretic leg. IC consisted of 5 min of compression with a proximal thigh cuff (inflation pressure = 225 mmHg for IC or 25 mmHg for sham) followed by 5 min 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, whereas 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 submaximal contractions. Individuals who had the most asymmetry in strength between their paretic and nonparetic 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 & NOTEWORTHY

Present 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 neurological 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.

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, 38). Fundamentally, damage to cortical structures limits a stroke survivor's ability to optimally activate paretic motoneuron pools, thereby reducing force development (21, 28, 29), even during brief maximal efforts. Stroke rehabilitation interventions are presently 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 (33, 36, 44). 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 that results in improved motor performance. IC was first described in 1986 as a vascular stimulus to protect vital organs from ischemic injury (37). Subsequent studies in humans have shown that both local IC (performed on tissue of interest) and remote IC (performed on a remote limb) improve motor learning (27) and muscle performance (10) and delay muscle fatigue (5). Specifically, in healthy individuals, brief, repeated 5-min 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 (27), task duration during handgrip exercise (5), 5 km of running time (4), and maximal power output (10). In these studies, IC was shown to enhance force generation and muscle activation, and a proposed potential mechanism is that IC engages autonomic centers in the brainstem sensitive to ischemia and

exercise (8, 43, 45). 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 of a single session of IC on paretic leg strength and muscle activation in chronic stroke survivors. We hypothesize that IC will 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 prospective, single-blinded, randomized controlled trial with paired analysis and was registered on http://www.clinicaltrials.gov with the unique identifier NCT03095755. All subjects were studied twice, with a minimum of 1 wk 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 before study participation. Ten participants with chronic stroke (≥1 yr poststroke) 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 were *1*) history of multiple strokes, *2*) brainstem stroke, *3*) any uncontrolled medical condition, *4*) lower extremity contractures, *5*) uncontrolled hypertension, *6*) inability to follow two to three step commands, *7*) deep vein thrombosis, *8*) peripheral arterial grafts in the lower extremity, and *9*) any condition in which tissue ischemia is contraindicated. There was not an "upper limit" for the time since stroke.

Table 1. Characteristics of all subjects

Characteristic	*n* = 10
Sex	
Male (*n*)	4
Female (*n*)	6
Age, yr	60 ± 12
Height, cm	168 ± 11
Weight, kg	78 ± 16
Body mass index, kg/m^2	27 ± 4
Time since stroke, yr	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/wk	14 ± 7
Self-selected walking speed, m/s	0.81 ± 0.35

All values are expressed as no. (n) or means ± SD. MET, metabolic equivalent of task.

Torque measurements.

Participants were positioned in a dynamometer chair (Biodex Medical Systems, Shirley NY) 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. Custom-written LabVIEW (National Instruments) programs were used to acquire all data from the Biodex load cell. Torque signals were low-pass filtered and sampled at 1,000 Hz using a data acquisition card (National Instruments) and computer, as we have previously described (13).

Surface electromyography measurements.

Surface EMGs were obtained using a 64 channel 2D 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 the subject's skin was rubbed with an alcohol swab to remove superficial dead skin. The signals for each channel were differentially amplified between 1,000 and 5,000 vol/vol (subject dependent) and bandpass filtered between 10 and 500 Hz using the EMG-USB2+ amplifier. The signals were sampled at 2,048 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 that have used IC as an intervention (4, 32, 40). 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 5 min and then released for a 5-min recovery period, and five cycles of inflation/recovery were performed. Participants were told that if they perceived pain during the cuff inflation cycles that the protocol would be terminated. For the IC sham, the cuff was inflated to 25 mmHg, consistent with other groups that have used IC as an intervention (3, 4). 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. Subjects were blinded to the purpose of the different cuff inflation pressures. A minimum of 1 wk 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, 50, 51). Following each maximum voluntary contraction (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 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. 1*A* for protocol summary). Subjects were given visual and verbal encouragement but received no visual feedback regarding the magnitude of their MVC. MVC efforts were repeated until there was a <5% difference in torque between two subsequent MVCs. A minimum of five MVCs were performed. At least 1 min of 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-s graded contraction, 5-s hold at 40% of MVC, 4-s 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 min), subjects repeated the MVC, resting twitch, and submaximal 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 postmotor testing. An example of MVC torque traces from a single subject before and after either IC sham or IC (see below) are shown in Fig. 1, *B* and *C*, respectively.

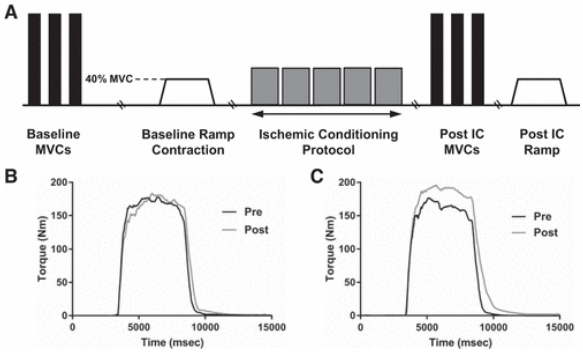

Fig. 1. *A*: protocol summary of the ischemic conditioning (IC) protocol. Subjects performed a series of isometric maximum voluntary contractions (MVC) of the knee extensor muscles, followed by a submaximal contraction equal to 40% of their maximum using a Biodex dynamometer. After the initial contractions were completed, the subjects moved to a bed, where the IC 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 (IC condition) or 25 mmHg (sham condition) for 5 min. After 5 min of inflation, the cuff was deflated for 5 min, 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. *B* and *C*: representative torque traces of an MVC from a single subject before and after the IC and sham conditions, respectively, are shown. Note the increase in MVC magnitude for the IC condition.

Data processing.

Knee extensor torque signals were zero phased low-pass filtered at 15 Hz using a second-order Butterworth filter before 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-s window during the hold portion of the ramp contraction, as previously described (25). The custom Matlab code can be made available upon reasonable request to the corresponding author.

Surface electromyography.

Single-motor unit action potential trains during the submaximal 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, 39). Individual motor units were tracked between the pre- and postmeasurements, and mean firing rates during a 4-s window in the hold phase of the submaximal contraction were calculated as well as the torque at which each motor unit was recruited and derecruited.

For global surface EMG measurements, the mean root mean square of the EMG for each of the channels during the 4 s hold of the MVC and during the 4 s window during the hold portion of the ramp contraction was calculated using a sliding window of 200 ms. To understand how IC affects the variability of the EMG measurement from each channel (49), the mean coefficient of variation (coefficient of variation = standard deviation of RMS/mean RMS × 100) was calculated during the 4 s 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. To understand how IC effects the homogeneity of the spatial activation of the muscle, modified entropy was calculated as

$$Entropy = -\sum_{i=1}^{59} p^2(i)\log_2 p^2(i),$$

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 is the same across all channels, i.e., if the muscle activity is very homogenous (14, 31). 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 response amplitudes. Main effects of time (pre and post) and condition (IC and IC-sham) and interaction effects of time × condition were determined. A Bonferroni post hoc test was used to test for differences between individual means. Because the coefficient of variation data during the 40% ramp and hold task were not normally distributed, a Friedman test was performed. Linear regression and goodness of fit analysis was performed to determine whether 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 evaluated only 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 α-level of 0.05 for significance. Data are reported as means ± SD.

RESULTS

Knee extensor strength and muscle activation were measured in 10 individuals with chronic stroke before and after a single session of IC or IC sham. In our study cohort, the time since stroke ranged from 2 to 31 yr, with a mean time since stroke of 16 ± 9 yr (Table 1). Although tolerability of the cuff inflation to 225 mmHg on the paretic leg was not measured per se, all 10 individuals were able to complete the IC session without incidence, and none of the subjects described the cuff inflation on their paretic leg as “painful.”

Consistent with previous studies performed in chronic stroke subjects from our group (13) and others (35), the paretic leg was weaker than the nonparetic leg (paretic vs. nonparetic MVC: 88.8 ± 50.2 vs. 139.0 ± 78.6 Nm, respectively; $P = 0.012$, paired *t*-test). Following IC, nine of 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 ($P = 0.001$ vs. pre-IC, 2-way repeated-measures ANOVA; Fig. 2*A*). 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. 2*B*). 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. 2*C*). Pretest MVCs were not different for all subjects between both the sham and IC treatment sessions ($P = 0.79$, paired *t*-test), demonstrating that baseline leg strength did not change between the sessions.

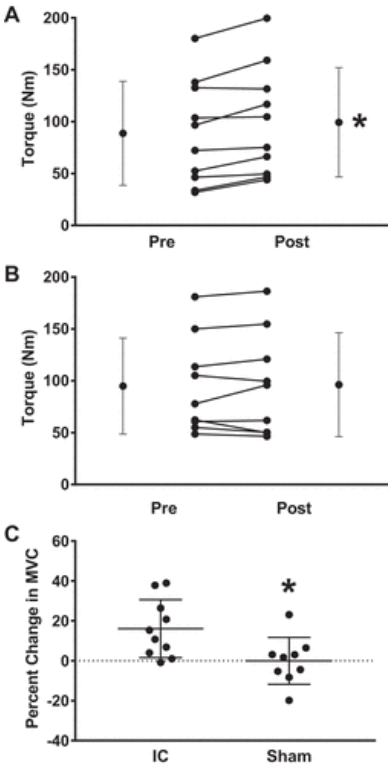

Fig. 2. Individual knee extensor maximum voluntary contraction (MVC) responses of the paretic leg before and after either ischemic conditioning (IC) or sham treatment. *A* and *B*: individuals in the IC group demonstrated an increase in knee extensor MVC following IC ($P < 0.05$; 2-way repeated-measures ANOVA; *A*), and no difference following sham treatment ($P > 0.05$; *B*). *C*: on average, individuals in the IC group demonstrated a 16.1 ± 14.5% relative increase in knee extensor strength following IC ($P < 0.05$). *$P < 0.05$, pre vs. post or IC vs. sham. ●, Individual measures.

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 with their nonparetic leg had the greatest relative increase in knee extensor MVC following IC ($P = 0.014$, $r^2 = 0.55$; Fig. 3*A*). 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 ($P = 0.008$, $r^2 = 0.61$; Fig. 3*B*). 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 ($r^2 = 0.33$; Fig. 3*C*); however, this result was not statistically significant ($P = 0.08$).

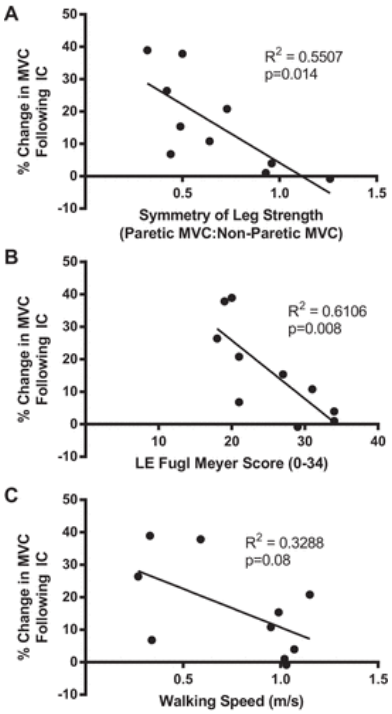

Fig. 3. Changes in knee extensor strength following IC as a function of leg impairment. *A*: there was a strong correlation between asymmetry in MVC magnitude between the paretic and nonparetic leg and %change in MVC in response to IC. Subjects who showed a greater degree of asymmetry in knee extensor strength between their paretic and nonparetic legs showed a greater improvement in paretic leg strength following IC (r^2 = 0.55, P = 0.014). *B*: subjects who had the lowest Lower Extremity Fugl Meyer Score also had the largest improvements in knee extensor strength following IC (r^2 = 0.61; P = 0.008). *C*: 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 (r^2 = 0.33, P = 0.08). ●, Individual measures.

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 (P = 0.01, paired t-test; Fig. 4*A*), which resulted in an overall 30.7 ± 15% increase in total EMG signal. Figure 4*B* 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. 4*C*), 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. 4*D*), which reflects an overall decrease in the variability in individual EMG channels.

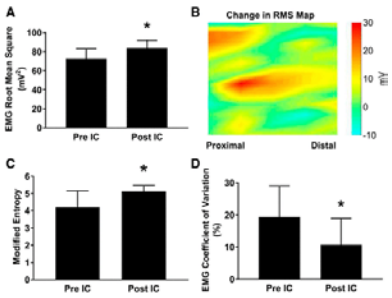

Fig. 4. Changes in vastus lateralis electromyography (EMG) measurements that accompanied IC-induced increases in knee extensor torque. *A*: average root mean square of the EMG signal during MVCs was increased following IC (P = 0.01; paired t-test). *B*: a single-subject spatial activation map of the 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 root mean square (RMS) of the EMG. *C*: modified entropy increased following IC (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). *$P < 0.05$, pre- vs. post-IC.

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, $P < 0.01$, paired *t*-test; Fig. 5, *A* and *B*). Submaximal 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 ± 3.7% vs. post = 3.9 ± 2.4%). The coefficient of variation tended to decrease, but the effect was not significant ($P = 0.06$; Friedman test).

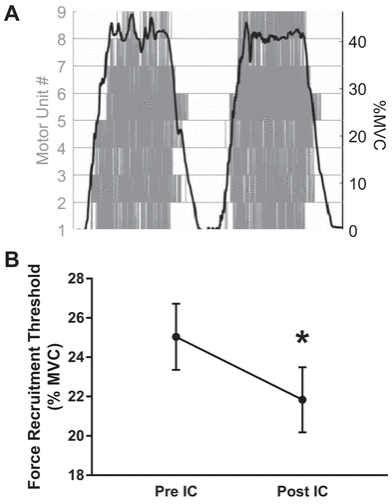

Fig. 5. Motor unit firing behavior and recruitment during the submaximal ramp and hold task. *A*: single-subject raster plot of incidences of action potentials superimposed on the torque generated during the ramp and hold pre- (*left*) and post-IC (*right*). Each row is a separate motor unit matched between time points. *B*: average force recruitment thresholds decreased following IC reflecting increased excitability of the motoneuron pools ($P < 0.01$; paired *t*-test).

Finally, 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 vs. 35 ± 13 Nm, respectively; sham IC pre/post: 28 ± 14 vs. 31 ± 13 Nm, respectively; $P = 0.60$, 2-way repeated-measures 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.

Very recently, two studies have shown that repetitive, remote IC performed on the arm prevents recurrence of stroke (34) and that daily remote IC over the course of 1 yr slows cognitive decline in patients with cerebral small-vessel disease-related mild cognitive impairment (48). We present the first study to our knowledge to apply IC as an intervention to improve motor function poststroke. We show specifically that IC increases 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, 4, 5), 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, a relative increase in strength of 16% in the paretic leg of chronic stroke survivors, indicating that IC has the potential to produce large strength gains in neurological populations. Furthermore, we show that those subjects with the largest degree of motor deficits tended to have the largest improvement following IC (Fig. 3). Although we recognize that this is a small pilot study and that these relationships only suggest a correlation between baseline physical function and the response to IC, this finding provides insight into which individuals may benefit the most from the IC intervention and can help direct the inclusion criteria for larger cohort studies.

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 (8, 43, 45). Importantly, these neuromodulators are known to increase the excitability of spinal motoneurons (18, 19, 43). Moreover, there is evidence that the group III and IV pathways in the paretic leg are hyperexcitable poststroke (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. Furthermore, the increased homogeneity (49) 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 poststroke the benefits of IC may be larger compared with 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, 30, 47). Similar to IC, investigators attribute the priming effects of hypoxia to engagement of neuromodulatory centers in the brainstem (11, 41) and forebrain (23). Although intermittent hypoxia may be advantageous for some, IC might be a strong alternative because it is noninvasive, 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 survivors and that it caused an improvement in knee extensor strength in nine of 10 of our study participants. A second limitation is that we did not test the effects of IC on the nonparetic leg or the remote effects of IC, (i.e., to perform IC on the nonparetic limb and test the paretic limb) and recognize these as important future study directions because the results of these studies will inform whether the nonparetic leg responds to the same magnitude as the paretic leg and whether IC has remote/systemic effects to improve leg strength. 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 h) and long (24–48 h) phase of IC-induced cardioprotection, and these phases are mediated by different mechanisms (42). Future studies examining the time course of IC-induced improvements on motor function are necessary to determine how long the

improvements in strength last and whether there are different mechanisms mediating the improvements. We also did not test the effects of multiple sessions of IC to determine whether there is an additive effect. Ultimately, our goal is to use IC as an adjunct to rehabilitation to optimize leg function for tasks such as walking. Given that a single session of IC improved leg strength, it is likely that multiple sessions alone or combined with other therapies may improve walking speed. Therefore, future studies that examine the effects of IC on walking speed and quality will be important. Finally, we performed our study only in individuals with chronic stroke, which limits generalization of results. Given that, on average, we saw a relative increase in strength of 16% following IC in people who were many years poststroke, future studies examining the effects of IC on subacute stroke patients (days to weeks poststroke) who are in a highly plastic recovery stage and undergoing physical therapy are warranted.

As our data show, IC is effective at increasing paretic muscle activation in stroke survivors. There are several important, nontrivial advantages of IC as an interventional adjunct to stroke rehabilitation: *1*) a wide range of patients can benefit because the technique does not require high levels of physical activity or function, *2*) IC is noninvasive, well-tolerated, and safe in cardiovascular populations, and *3*) IC can be accomplished with inexpensive equipment at home or in the clinic in <60 min. We propose that IC has the potential to be an ideal adjunct to physical therapy in patients with hemiplegia because it "primes" the nervous system to more fully activate the paretic muscle during exercise and is clinically feasible.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.S.H., B.D.S., D.D.G., and M.J.D. conceived and designed research; S.A.M., J.N., and M.J.D. performed experiments; A.S.H., S.A.M., J.N., B.D.S., F.N., and M.J.D. analyzed data; A.S.H., S.A.M., J.N., B.D.S., F.N., D.D.G., and M.J.D. interpreted results of experiments; A.S.H., S.A.M., and M.J.D. prepared figures; A.S.H. and M.J.D. drafted manuscript; A.S.H., B.D.S., D.D.G., and M.J.D. edited and revised manuscript; A.S.H., S.A.M., J.N., B.D.S., F.N., D.D.G.; and M.J.D. approved final version of manuscript.

AUTHOR NOTES

- Address for reprint requests and other correspondence: M. J. Durand, Dept. of Physical Medicine and Rehabilitation Medical College of Wisconsin. 8701 Watertown Plank Rd., Milwaukee, WI 53226 (e-mail: mdurand@mcw.edu).

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