# High-Intensity Interval Training and Moderate-Intensity Continuous Training in Ambulatory Chronic Stroke: Feasibility Study

Pierce Boyne, Kari Dunning, Daniel Carl, Myron Gerson, Jane Khoury, Bradley Rockwell, Gabriela Keeton, Jennifer Westover, Alesha Williams, Michael McCarthy, Brett Kissela

**Background.** Poststroke guidelines recommend moderate-intensity, continuous aerobic training (MCT) to improve aerobic capacity and mobility after stroke. High-intensity interval training (HIT) has been shown to be more effective than MCT among healthy adults and people with heart disease. However, HIT and MCT have not been compared previously among people with stroke.

**Objective.** The purpose of this study was to assess the feasibility and justification for a definitive randomized controlled trial (RCT) comparing HIT and MCT in people with chronic stroke.

**Design.** A preliminary RCT was conducted.

**Setting.** The study was conducted in a cardiovascular stress laboratory and a rehabilitation research laboratory.

**Patients.** Ambulatory people at least 6 months poststroke participated.

**Intervention.** Both groups trained 25 minutes, 3 times per week, for 4 weeks. The HIT strategy involved 30-second bursts at maximum-tolerated treadmill speed alternated with 30- to 60-second rest periods. The MCT strategy involved continuous treadmill walking at 45% to 50% of heart rate reserve.

**Measurements.** Measurements included recruitment and attendance statistics, qualitative HIT acceptability, adverse events, and the following blinded outcome variables: peak oxygen uptake, ventilatory threshold, metabolic cost of gait, fractional utilization, fastest treadmill speed, 10-Meter Walk Test, and Six-Minute Walk Test.

**Results.** During the 8-month recruitment period, 26 participants consented to participate. Eighteen participants were enrolled and randomly assigned to either the HIT group (n=13) or the MCT group (n=5). Eleven out of the 13 HIT group participants attended all sessions. Participants reported that HIT was acceptable and no serious adverse events occurred. Standardized effect size estimates between groups were moderate to very large for most outcome measures. Only 30% of treadmill speed gains in the HIT group translated into overground gait speed improvement.

**Limitations.** The study was not designed to definitively test safety or efficacy.

**Conclusions.** Although further protocol optimization is needed to improve overground translation of treadmill gains, a definitive RCT comparing HIT and MCT appears to be feasible and warranted.

P. Boyne, PT, DPT, Department of Rehabilitation Sciences, College of Allied Health Sciences, University of Cincinnati, 3202 Eden Ave, Cincinnati OH 45220-0394 (USA), and Department of Environmental Health, College of Medicine, University of Cincinnati. Address all correspondence to Dr Boyne at: Pierce.Boyne@uc.edu.

K. Dunning, PT, PhD, Department of Rehabilitation Sciences, College of Allied Health Sciences, University of Cincinnati, and Department of Environmental Health, College of Medicine, University of Cincinnati.

D. Carl, PhD, Department of Rehabilitation Sciences, College of Allied Health Sciences, University of Cincinnati.

M. Gerson, MD, Departments of Internal Medicine and Cardiology, College of Medicine, University of Cincinnati.

J. Khoury, PhD, Department of Environmental Health, College of Medicine, University of Cincinnati, and Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

B. Rockwell, BS, Department of Rehabilitation Sciences, College of Allied Health Sciences, University of Cincinnati.

G. Keeton, BS, Department of Rehabilitation Sciences, College of Allied Health Sciences, University of Cincinnati.

*Author information continues on next page.*

J. Westover, BS, Department of Rehabilitation Sciences, College of Allied Health Sciences, University of Cincinnati.

A. Williams, BS, Department of Rehabilitation Sciences, College of Allied Health Sciences, University of Cincinnati.

M. McCarthy, PhD, School of Social Work, College of Allied Health Sciences, University of Cincinnati.

B. Kissela, MD, Department of Neurology and Rehabilitation Medicine, College of Medicine, University of Cincinnati.

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Stroke rehabilitation guidelines recommend moderate-intensity, continuous aerobic training (MCT) to improve mobility, aerobic capacity, and cardiovascular health.[1] However, accumulating evidence suggests that higher-intensity exercise may be significantly more effective than MCT for both aerobic and motor outcomes.[2,3]

High-intensity interval training (HIT) is a strategy that maximizes exercise intensity by using bursts of concentrated effort alternated with recovery periods.[4] This strategy has been shown to be more effective than MCT for improving aerobic capacity among healthy adults and people with heart disease.[3] During inpatient stroke rehabilitation, treadmill HIT has been shown to be more effective than extra therapy (based on the neurodevelopmental and proprioceptive neuromuscular facilitation approaches)[5] or other forms of nonaerobic treadmill training,[5,6] for improving gait speed,[5,6] spatiotemporal parameters,[5,6] and functional ambulation category.[5] In people with chronic stroke (>6 months after event), a single-group, pretest-posttest design study showed that treadmill HIT also was associated with significant improvements in aerobic capacity (peak oxygen consumption [$\dot{V}O_2$peak]) and metabolic cost of gait, in addition to gait speed, Timed "Up & Go" Test scores, and Six-Minute Walk Test scores.[7]

However, to our knowledge, no previous studies have compared HIT and MCT among people with stroke, and previous HIT protocols have varied widely among studies.[5–8] Our team developed an optimized HIT protocol for chronic stroke and preliminarily demonstrated the safety of this approach by comparing acute within-session exercise responses among 3 different protocols.[9] The purpose of the current study was to assess the feasibility and justification for a definitive randomized controlled trial (RCT) comparing HIT and MCT in people with chronic stroke.

# Method

## Design Overview

A preliminary RCT was conducted. Each participant had a medical record review, a clinical evaluation, and a maximal-effort graded treadmill exercise test (GXT) with electrocardiographic (ECG) monitoring (stress test) to determine eligibility.[9] After baseline testing, participants were randomly assigned to receive either HIT or MCT, each 25 minutes, 3 times per week, for 4 weeks. Feasibility of a definitive RCT was assessed with recruitment and attendance statistics and qualitative HIT acceptability. Justification for a definitive RCT was assessed with adverse event (AE) monitoring and outcome assessment. Outcome measures were administered by a blinded rater at baseline and within 1 week after completing the intervention.

## Setting and Participants

This study was approved by local institutional review boards and was performed in a cardiovascular stress laboratory and a rehabilitation research laboratory from October 2013 to August 2014. Participants were recruited from the community and gave informed consent prior to participation. Inclusion criteria were: (1) age 35 to 90 years, (2) unilateral stroke experienced >6 months prior to enrollment, (3) able to walk 10 m overground with assistive devices as needed without physical assistance, (4) able to walk 3 minutes on the treadmill at ≥0.3 mph (0.13 m/s) with no aerobic exercise contraindications,[10,11] (5) stable cardiovascular condition (American Heart Association class B,[10] allowing for aerobic capacity <6 metabolic equivalents), and (6) not currently participating in formal rehabilitation. Exclusion criteria were: (1) significant resting ECG abnormalities,[10] (2) evidence of myocardial ischemia or significant arrhythmia on stress test,[10] (3) hospitalization for cardiac or pulmonary disease within the previous 3 months, (4) pacemaker or implanted defibrillator, (5) lower extremity (LE) claudication, (6) unable to communicate with investigators or correctly answer consent comprehension questions, (7) severe LE spasticity (Ashworth scale score >2),[12] and (8) LE weight-bearing pain >4/10 on a visual analog scale.

## Randomization and Interventions

Randomization was performed by a person with no other role in the study who randomly drew a sealed opaque enve-

lope out of a container to determine participant allocation. The envelopes were prepared to achieve a 2:1 ratio of HIT: MCT group participants. The purpose of this 2:1 group weighting was to maximize the information gained about post-stroke HIT, as MCT has already been extensively studied in this population.[13]

**Common features between groups.** Training sessions were directed by the primary or backup treating physical therapist, with support from a research assistant for data collection. The training protocols were standardized between the therapists using a manual of procedures, frequent communication, and review of completed treatment session forms by the primary therapist.

Participants wore their habitual orthotic devices and a harness secured to an overhead support system (Offset Unweighting System, Biodex Medical Systems Inc, Shirley, New York) for fall protection (not weight support) during all treadmill walking (testing and training). An elastic band placed horizontally behind the participant at waist level served as a safety limit. If the participant drifted backward into this band, the therapist stopped the treadmill. No physical assistance was provided during training unless needed to help prevent injury when stopping the treadmill due to gait instability. Participants alternated handhold between the handrail on the overhead support system and the least supportive handhold (handrail, elastic band, or none) that still enabled achievement of minimum training targets (see Appendix for details). Both HIT and MCT protocols included a 3-minute warm-up at 30% to 50% heart rate reserve (HRR),* 20 minutes of training, and a 2-minute cool-down at 30% to 50% HRR.

**HIT.** The HIT protocol, developed in our previous study,[9] involved 30-second bursts of treadmill walking at maximum safe speed, alternated with 30- to 60-second recovery periods, where the treadmill was stopped. The initial treadmill speed each session was determined by a steep ramp test at the end of the warm-up. During this test, the speed was increased by 0.1 mph (0.04 m/s) every 5 seconds until the participant drifted backward into the safety band, exhibited gait instability, or requested to stop. Burst speed was then started at 0.1 mph (0.04 m/s) below this speed and was continuously progressed during the session based on participant performance (see Appendix for details). Recovery periods lasted 60 seconds during the first 3 sessions. For the remaining 9 sessions, recovery duration began at 60 seconds and changed to 30 seconds after the first 3 bursts.

**MCT.** The MCT intervention was based on an established stroke-specific protocol.[11] It involved continuous treadmill walking with speed adjusted to maintain 45%±5% HRR. Target heart rate (HR) was progressed to 50%±5% HRR after 2 weeks of training.[14]

## Outcome Measures and Follow-up

**Feasibility variables.** Recruitment feasibility was measured by the number of individuals who consented to participate and were enrolled per month. Training feasibility was measured by the number of sessions attended by each participant and the number of minutes of training completed during each session. High-intensity interval training acceptability was assessed with qualitative, semistructured recorded interviews after postintervention outcome testing for the last 8 participants to complete HIT. A phenomenological approach[15] was used to reduce and organize the transcribed interview data and to identify common themes.

**Training intensity variables.** Aerobic intensity was measured during each session by mean HR, captured with an ECG chest strap and HR computer (RCX5, Polar Electro Inc, Lake Success, New York). Neuromuscular intensity was measured by peak treadmill speed. Repetition of practice was measured by session step count, captured with an activity monitor (StepWatch, Orthocare Innovations LLC, Oklahoma City, Oklahoma) placed around the nonparetic ankle. Participants also wore this monitor for ≥3 days prior to starting training so that session step count could be expressed relative to mean daily step count. Rating of perceived exertion (RPE) was measured halfway through each session using the Borg 6–20 scale.[10] Training intensity variables were descriptively summarized for each training week by group.

**Safety monitoring.** At the beginning of each visit, participants were asked about AEs, including changes in medical status, medications, falls, and pain. At the end of each treatment session, participants were asked about AEs during the session, including pain, lightheadedness, and nausea. Each session included monitoring of ECG and blood pressure and observation for signs or symptoms of cardiorespiratory intolerance, new neurologic deficits, or orthopedic injury.[10] Identified AEs were categorized as either anticipated (included in consent form) or unanticipated and as either related or not related to study treatment. Adverse effects severity was graded using the Common Terminology Criteria for Adverse Events v4.0,[16] where grades 4 and 5 indicate serious AEs and grades 1 through 3 indicate nonserious AEs.

**Outcome variables.** Standardized outcome testing was administered by a trained and blinded rater at baseline and postintervention measurements. Aerobic capacity measures ($\dot{V}O_2$peak and ventilatory threshold) and treadmill gait measures (metabolic cost of gait, fractional utilization, and fastest treadmill speed) were administered on a separate day from overground gait measures (10-Meter Walk Test and Six-Minute Walk Test).

Aerobic capacity was measured using a maximal-effort GXT by the maximum 30-second average oxygen consumption ($\dot{V}O_2$) recording ($\dot{V}O_2$peak) and by $\dot{V}O_2$ at the ventilatory aerobic threshold ($\dot{V}O_{2VAT}$). Peak $\dot{V}O_2$ is the most common measure of aerobic capacity across populations and was our a priori primary outcome measure.[10] Oxygen consumption at the ventilatory aerobic threshold represents the transition point from aerobic to anaerobic metabolism and is the

* Heart rate reserve was calculated as: 30%−50%[HRpeak−HRresting]+HRresting, where HRpeak is peak heart rate from exercise testing and HRresting is resting heart rate.

upper intensity limit of prolonged activity.[17] It was determined according to published guidelines, using a combination of the V-slope and ventilatory equivalents methods.[18] The GXT followed the protocol of Macko et al,[11] which has shown reliability among people with stroke.[19,20] Briefly, speed was held constant at approximately 85% of the fastest comfortable speed from a steep ramp test (see fastest treadmill speed below), and incline was increased by 2% to 4% every 2 minutes. Test termination criteria included volitional fatigue, severe gait instability, or a cardiovascular safety limit.[10] Respiratory gases were measured with the TrueOne 2400 (Parvo Medics, Sandy, Utah), using a facemask interface.

Metabolic cost of gait was measured by steady-state $\dot{V}O_2$ during the final 2 minutes of a 5-minute walking bout at participant-selected comfortable treadmill speed. This measure is reliable[19,21] and valid[14] after stroke. Speed was kept the same for each participant at baseline and postintervention measurements.[22]

Fractional utilization was calculated by dividing the metabolic cost of gait by aerobic capacity to assess the relative physiologic demand of gait.[11]

Fastest treadmill speed was measured with a steep ramp test,[9] which started at comfortable speed (0% incline) for 15 seconds, then increased by 0.1 mph (0.04 m/s) every 5 seconds until the limit where the participant drifted backward into the safety band, exhibited gait instability, or requested to stop. Fastest treadmill speed was recorded as 0.1 mph (0.04 m/s) below this limit.

The 10-Meter Walk Test[23] measured walking speed over the middle 10 m of a 14-m course, which is reliable[24] and valid[25] after stroke. The test was standardized according to the Locomotor Experience Applied Post-Stroke (LEAPS) guidelines[23] and was performed twice at comfortable speed and twice as fast as safely possible.

The Six-Minute Walk Test[26] measured the distance that the participant was able to walk in 6 minutes,[26] which is reliable[27] and valid[28–30] after stroke. The test was standardized according to American Thoracic Society guidelines.[26]

## Data Analysis

Shapiro-Wilk tests were used to assess for deviations from normal distribution among the continuous variables. Demographics, baseline clinical characteristics, and baseline outcome measures were compared between groups using independent *t* tests for comparison of means and Fisher exact tests for comparison of proportions.

To obtain preliminary estimates of between-group safety differences, AE incidence rates were calculated for each group. Logistic regression models were then conducted using AE count divided by the number of treatment sessions per participant as the dependent variable and treatment group as the independent variable. Separate models were conducted for different types of AEs.

To test for outcome changes within each treatment group and to preliminarily compare changes between groups, separate mixed-effects models were conducted with each outcome measure as the dependent variable. These models included fixed effects for group, time, and the group × time interaction and a random effect for participant. Standardized effect sizes were calculated as the between-group difference in mean improvement divided by the standard deviation of change. Because this was a preliminary study, the primary analysis included only participants who completed the intervention (ie, on-treatment analysis). However, because this method can yield biased treatment comparisons, we also performed a sensitivity analysis that included all randomized participants regardless of study completion (ie, intention-to-treat analysis). For this sensitivity analysis, missing data were handled with the method of maximum likelihood, making the assumption of missing at random.

Because $\dot{V}O_2$peak on a treadmill GXT is the $\dot{V}O_2$ cost of gait at peak exercise, we were concerned that improved gait efficiency (decreased $\dot{V}O_2$ cost from baseline to postintervention measurement) might artificially decrease measured $\dot{V}O_2$peak at the postintervention measurement. Therefore, we performed a secondary post hoc analysis to examine $\dot{V}O_2$peak change within the HIT group after adjusting for change in the metabolic cost of gait. A >10% difference in the estimate for $\dot{V}O_2$peak change between the unadjusted and adjusted models was used as the threshold to indicate confounding by gait efficiency.[31] This secondary adjusted analysis also was performed with $\dot{V}O_{2VAT}$ change as the dependent variable for comparison, as $\dot{V}O_{2VAT}$ is considered to be more independent of motor function.[32]

All inferential statistics were 2-sided, and the significance level was set at .05. SAS version 9.3 (SAS Institute Inc, Cary, North Carolina) was used for analysis.

## Sample Size Calculations

With limited available information to guide sample size selection, we used previous HIT studies in different populations[5,6,33,34] to estimate the number of HIT group participants needed to detect significant within-group change in $\dot{V}O_2$peak and 10-Meter Walk Test scores. The MCT group sample size was selected to be half of that for HIT group to obtain a preliminary estimate of between-group differences. These calculations indicated that 10 participants were needed in the HIT group to detect significant change from baseline to postintervention measurement (standardized effect size of 1.4) with >80% power, yielding a total needed sample size of 15. To account for up to 20% attrition, we planned to randomize 19 participants.

## Role of the Funding Source

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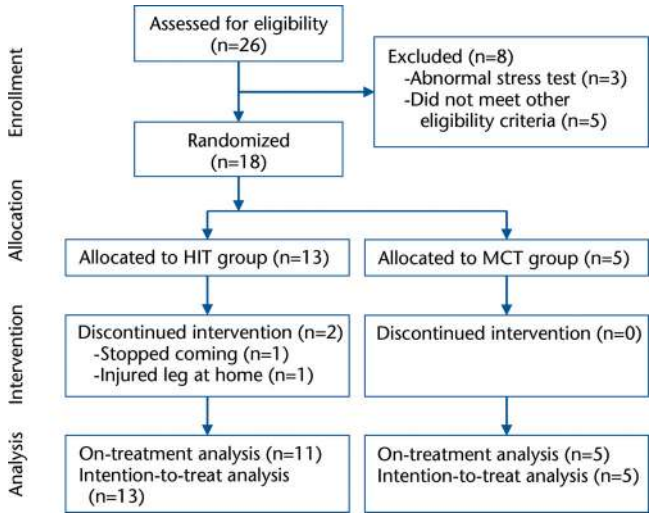


**Figure 1.**
Study flow diagram. HIT=high-intensity interval training, MCT=moderate-intensity continuous training.

# Results

## Recruitment and Training Feasibility

During the 8-month recruitment period, 26 participants consented, 8 were excluded for not meeting eligibility criteria, and 18 were enrolled, yielding mean recruitment and enrollment rates of 3.3 and 2.3 participants per month, respectively. Among the 18 enrolled participants, 13 were randomized to the HIT group, and 5 were randomized to the MCT group (Fig. 1). Two participants in the HIT group discontinued intervention: 1 participant completed 3 sessions and then withdrew due to osteoarthritis-related knee pain, and the other participant completed 6 sessions and then was withdrawn after colliding with a cabinet at home and injuring her nonparetic leg. Characteristics of the remaining 16 participants are summarized in Table 1. Baseline $\dot{V}O_2$peak and fractional utilization were significantly different between groups. There was no significant imbalance in any other baseline variables. Each of the 16 participants who completed training attended all 12 sessions, and 13 out of 16 participants completed 25 minutes of training during each session. In the HIT group, 3 participants were not able to complete all 25 minutes of training for 1 to 2 sessions, which ranged in duration from 22 to 23 minutes.

## HIT Acceptability

In qualitative interviews among the last 8 participants to complete HIT, acceptability of this intervention was generally favorable. Most participants reported initial feelings of apprehension, which were followed by increased confidence and enjoyment of HIT.

## Training Intensity

In the HIT group, average session HR progressed from a mean 53% HRR in the first week of training to 72% HRR in the fourth week (Fig. 2). Peak session treadmill speed progressed from 1.16 m/s to 1.44 m/s (200%–273% baseline fastest 10-Meter Walk Test). Mean session step count progressed from 1,057 to 1,381 (79%–103% baseline steps per day). Mean RPE progressed from 13.5 to 14.6.

In the MCT group, mean HR progressed from 48% HRR to 54% HRR. Peak treadmill speed progressed from 0.72 m/s to 0.83 m/s (92%–110% baseline fastest 10-Meter Walk Test). Mean session step count changed from 2,173 to 2,189 (65%–65% baseline steps per day). Mean RPE changed from 13.1 to 12.6.

## Adverse Events

No serious AEs occurred, and no unanticipated AEs occurred due to study procedures. In addition, no angina, significant ECG changes, abnormal BP changes, nausea, or new neurologic deficits were found. Participant questioning identified 13 treatment-related AEs over 141 HIT sessions and 4 treatment-related AEs over 60 MCT sessions. The odds ratios (HIT:MCT) for different types of AEs ranged from 0.21 to 3.03, and none were statistically significant (Tab. 2). In the HIT group, 4 of 13 participants engaged the harness a total of 7 times, without injury. In the MCT group, 1 of 5 participants engaged the harness 1 time, without injury.

## Outcome Measure Changes Within the HIT Group

Within the HIT group, statistically significant improvements from baseline to postintervention measurement were found for ventilatory threshold, metabolic cost of gait, fractional utilization, fastest treadmill speed, the 10-Meter Walk Test, and 6-minute walk distance (Tab. 3). These within-group changes also were statistically significant in the intention-to-treat sensitivity analysis. Improvement in fastest 10-Meter Walk Test speed averaged only 30% of the improvement in fastest treadmill speed (95% confidence interval [CI]=0%, 62%).

In the secondary analysis of $\dot{V}O_2$peak, adjusting for change in the metabolic cost of gait shifted the estimate for $\dot{V}O_2$peak change from 2.2 to 3.4 mL/kg/min and made it statistically significant ($P$=.054 to $P$=.029). This 55% shift in the $\dot{V}O_2$peak change estimate indicated confounding by gait efficiency change. When repeating the analysis with $\dot{V}O_{2VAT}$ change as the dependent variable, the same adjustment only shifted the estimate for $\dot{V}O_{2VAT}$ change from 4.4 to 4.6 mL/kg/min. This 5% shift indicated that $\dot{V}O_{2VAT}$ change was not confounded by gait efficiency change.

## Outcome Measure Changes Within the MCT Group

No statistically significant outcome changes were found within the MCT group from baseline to postintervention measurement. There was one outlier who showed greater improvement than the other MCT participants for most outcome measures. After this participant began treatment, we learned that he had

**Table 1.**
Participant Characteristics[a]

| Characteristic | HIT Group (n=11) | MCT Group (n=5) | *P* |
|---|---|---|---|
| Male, n (%) | 7 (63.6) | 2 (40.0) | .60 |
| Age (y) | 59 (9) [40–71] | 57 (12) [41–73] | .66 |
| Body mass index, kg/m$^2$ | 28.5 (5.2) [22.4–38.2] | 26.4 (4.8) [21.4–32.6] | .46 |
| Years poststroke | 3.8 (2.9) [1.0–10.3] | 6.3 (2.0) [4.5–9.1] | .09 |
| Ischemic stroke type, n (%) | 9 (81.8) | 2 (40.0) | .24 |
| Left affected hemisphere, n (%) | 3 (27.3) | 4 (80.0) | .11 |
| Coronary artery disease, n (%) | 2 (18.2) | 0 (0.0) | 1.00 |
| Taking a beta blocker, n (%) | 4 (36.4) | 0 (0.0) | .24 |
| Wheelchair use, n (%) | | | .70 |
| None | 8 (72.7) | 3 (60.0) | |
| Community only | 2 (18.2) | 2 (40.0) | |
| Home and community | 1 (9.1) | 0 (0.0) | |
| Habitual assistive device, n (%) | | | .76 |
| None | 4 (36.4) | 2 (40.0) | |
| Single-point cane | 3 (27.3) | 1 (20.0) | |
| Quad cane | 3 (27.3) | 2 (40.0) | |
| Pyramid cane | 1 (9.1) | 0 (0.0) | |
| Habitual orthotic device, n (%) | | | 1.00 |
| None | 4 (36.4) | 1 (20.0) | |
| Ankle-foot orthosis | 6 (54.6) | 3 (60.0) | |
| Foot drop stimulator | 1 (9.1) | 1 (20.0) | |
| Fugl-Meyer leg motor score, 0–34[35] | 24.2 (4.8) [16.0–31.0] | 23.2 (7.3) [11.0–30.0] | .75 |
| Functional ambulation category, n (%)[36] | | | 1.00 |
| Dependent on supervision | 3 (27.3) | 1 (20.0) | |
| Independent on level surfaces | 1 (9.1) | 0 (0.0) | |
| Independent | 7 (63.6) | 4 (80.0) | |
| Comfortable 10-Meter Walk Test (m/s) | 0.63 (0.48) [0.06–1.45] | 0.76 (0.36) [0.18–1.10] | .62 |
| % predicted[37] | 47.2 (36.2) [4.3–111.0] | 55.2 (25.2) [16.0–79.4] | .66 |
| $\dot{V}O_2$peak (mL/kg/min) | 16.0 (4.0) [9.0–21.7] | 21.6 (4.0) [17.3–26.0] | .02 |
| % predicted[17] | 64.4 (26.2) [27.3–100.5] | 83.4 (11.5) [69.9–96.5] | .15 |

[a] Data are presented as mean (SD) [range] unless otherwise noted. HIT=high-intensity interval training, MCT=moderate-intensity continuous training, $\dot{V}O_2$peak=peak oxygen consumption.

just returned from an extended sedentary vacation and had just begun exercising more at home, concurrent with the intervention. The effects of this outlier were most pronounced for the mean change in 6-minute walk distance, which was +15 m for the full MCT sample and +1 m without the outlier. Due to the small MCT sample size, he was not removed from the analysis in Table 3.

### Comparison of HIT and MCT Changes

The standardized effect size for the Six-Minute Walk Test was 0.00 (95% CI=−1.16, 1.16) with the MCT outlier and 0.97 (95% CI=−0.25, 2.16) without him. Standardized effect sizes for other outcomes ranged from 0.91 to 1.95 and were significantly different from 0 for ventilatory threshold, fractional utilization, fastest treadmill speed, and 10-Meter Walk Test (Tab. 3). In the intention-to-treat sensitivity analysis, these effect sizes ranged from 0.64 to 1.67, and between-group differences were statistically significant only for changes in ventilatory threshold and fastest treadmill speed.

## Discussion

Based on this preliminary study, a definitive RCT comparing HIT and MCT in chronic stroke appears to be feasible and justified. In terms of feasibility, we were able to recruit 18 eligible participants in 8 months; 11 of the 13 participants randomized to HIT attended all treatment sessions, and participants found HIT to be acceptable. In terms of justification, HIT was associated with significant within-group improvement in aerobic capacity and gait function. The mean improvement in aerobic capacity (Tab. 3) exceeded the minimal clinically important difference (MCID) threshold of 1.0 to 3.0 mL/kg/min,[8,38,39] the improvement in gait speed approximated the MCID threshold of 0.10 to 0.20 m/s,[23,40–43] and improvements in the metabolic cost of gait, fractional utilization, and fastest treadmill speed exceeded the 10% change threshold often used to identify clinically important change when the MCID has not been established.[44–46] Comparisons between HIT and MCT showed nonsignificant differences in AE rates and moderate-to-very large standardized effect size estimates for improvement in most outcome measures.

Although these results are promising, it is important to note that small preliminary studies such as the current study are not designed to test for between-group differences in safety or efficacy.[47] Significant differences should be interpreted with caution because the very large effect sizes needed to generate them with such small samples are uncharacteristic of medical and rehabilitation research.[48] Likewise, nonsignificant differences should not be interpreted as meaning there is no difference in safety or efficacy between the groups, because small pilot studies have limited power.[47] For example, our 95% CI values cannot rule out the possibility of a very large

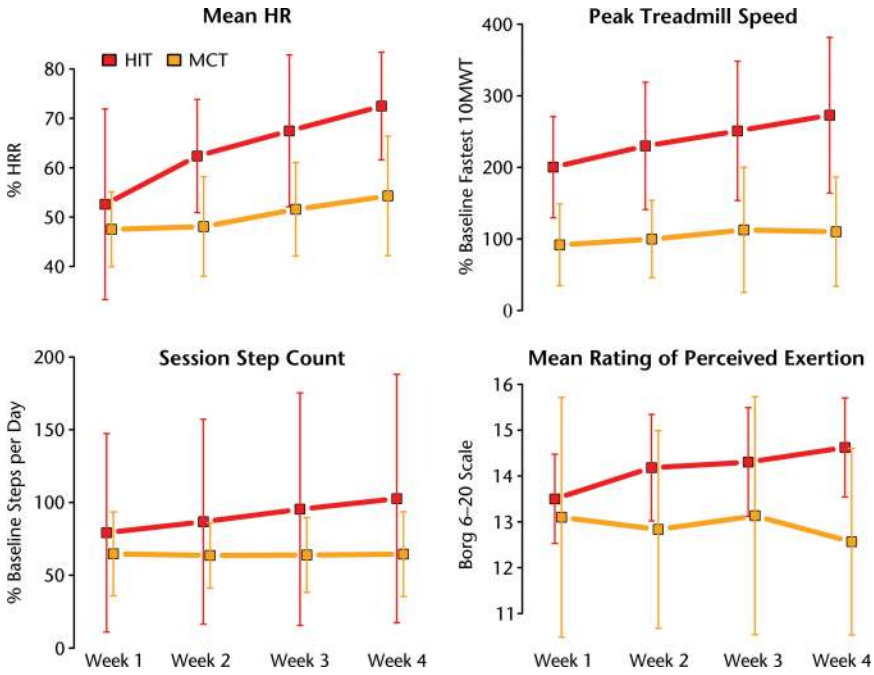


**Figure 2.**
Training intensity by week. Error bars represent 95% confidence intervals. HIT=high-intensity interval training group (n=11), MCT=moderate-intensity continuous training group (n=5), HR=heart rate, HRR=heart rate reserve, 10MWT=10-Meter Walk Test.

between-group difference for almost all safety and outcome variables. Another limitation of small preliminary studies is that the effect size estimates tend to be unstable.[47] For example, the removal of one outlier from the MCT group changed the between-group effect size for the Six-Minute Walk Test from 0 to very large. Clearly, a larger RCT is needed to provide more definitive information.

The recruitment, enrollment, and baseline data from this study will be useful for definitive RCT planning. For example, our results suggest that sites may need to recruit 44% more participants than they plan to enroll and that sites with strong recruitment resources could reasonably expect to enroll 20 participants in a year. Average scores on baseline outcome measures indicated that our recruitment methods were generally successful at obtaining a sample of participants with gait impairment and deconditioning. However, 2 participants in the HIT group had baseline $\dot{V}O_2$peak levels matching their predicted normative values, and one of these participants also had a baseline walking speed above her predicted value. Thus, eligibility criteria should be added to avoid ceiling effects on outcome measures and to ensure adequate generalizability to rehabilitation clinics. Between-group baseline comparisons also showed significant imbalances in mean $\dot{V}O_2$peak and fractional utilization. Assuming an unbiased randomization, these are false-positive findings due to multiple testing.[49] However, future studies should consider stratified or baseline covariate adaptive randomization to avoid imbalances on key prognostic variables.

The outcome data from this study will be useful for guiding revisions to the HIT protocol. In particular, improvements in overground gait function after treadmill HIT were not as large as expected based on previous studies in subacute stroke.[5,6] Furthermore, only 30% of treadmill speed improvement translated into the overground environment, despite systematic efforts to make treadmill training more task-specific to overground gait by minimizing handrail hold. It seems likely that adding overground gait training to the treadmill HIT protocol will improve translation and elicit greater changes in overground gait function,[50–53] but this factor will need to be tested prior to a definitive RCT.

The data from this study also provide guidance on outcome measure selection for a definitive RCT. Specifically, $\dot{V}O_2$peak had higher variability and less responsiveness than $\dot{V}O_{2VAT}$. Other investigators also have observed high variability in $\dot{V}O_2$peak changes from poststroke aerobic exercise,[46] and our data suggest that this finding may be related to concurrent changes in movement efficiency. After adjusting for changes in the metabolic cost of gait, our estimate for $\dot{V}O_2$peak change in the HIT group increased by 55% and became significant. This confounding of $\dot{V}O_2$peak change by changes in movement efficiency may explain why some previous stroke studies have not shown significant improvement in $\dot{V}O_2$peak after high-intensity treadmill training.[8,53,54] We did not find evidence of confounding between $\dot{V}O_{2VAT}$ and gait efficiency, suggesting that $\dot{V}O_{2VAT}$ may be a more pure measure of aerobic capacity changes than $\dot{V}O_2$peak poststroke.

High-intensity interval training appeared to be reasonably safe in this study, with no serious or unanticipated AEs and an AE rate comparable to that of MCT. Our HIT group AE rate (one grade 2 treatment-related AE per 47 sessions) also compares favorably with a recent safety study of moderate- to high-intensity continuous aerobic training among people with diabetic peripheral neuropathy (one grade 2 treatment-related AE per 12 sessions, calculated from data provided).[55] For both studies, muscle and joint pain was the most common AE. Previous studies of poststroke HIT have not specifically questioned participants and have reported fewer AEs, including one grade 1 case of vertigo,[5] 2 grade 2 muscle and joint pain AEs,[7] and 2 grade 2 incidents where the participants "felt unwell."[8] In summary, the risk-benefit ratio of poststroke HIT is encouraging from data collected to date, but further study and more systematic reporting are needed in this area.

A strength of this study is that it involved a clinically feasible training volume of only 25 minutes, 3 times per week, for 4

**Table 2.**
Adverse Events (AEs)[a]

| | HIT Group (n=13, sessions=141) | MCT Group (n=5, sessions=60) | HIT/MCT AE Odds Ratio (95% CI) |
|---|---|---|---|
| **All** | 9 (21) [14.9] | 4 (8) [13.3] | 1.14 (0.47–2.73) |
| **Related to intervention** | 6 (13) [9.2] | 1 (4) [6.7] | 1.42 (0.44–4.55) |
| Grade 1 (mild) | 5 (10) [7.1] | 1 (3) [5.0] | 1.45 (0.38–5.47) |
| Grade 2 (moderate) | 2 (3) [2.1] | 1 (1) [1.7] | 1.28 (0.13–12.59) |
| Grades 3–5 (severe–death) | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Cardiac disorder | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Joint/muscle pain | 5 (8) [5.7] | 1 (4) [6.7] | 0.84 (0.24–2.91) |
| Fatigue | 3 (3) [2.1] | 0 (0) [0.0] | 3.03 (0.15–59.56)[b] |
| Nausea | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Light-headedness | 1 (2) [1.4] | 0 (0) [0.0] | 2.15 (0.10–45.43)[b] |
| Other nervous system | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Fall | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Other injury | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| **Unrelated to intervention** | 6 (8) [5.7] | 3 (4) [6.7] | 0.84 (0.24–2.91) |
| Grade 1 (mild) | 5 (7) [5.0] | 2 (2) [3.3] | 1.51 (0.31–7.51) |
| Grade 2 (moderate) | 1 (1) [0.7] | 2 (2) [3.3] | 0.21 (0.02–2.33) |
| Grades 3–5 (severe–death) | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Atrial fibrillation | 1 (2) [1.4] | 0 (0) [0.0] | 2.15 (0.10–45.43)[b] |
| Other cardiac disorder | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Joint/muscle pain | 2 (2) [1.4] | 1 (2) [3.3] | 0.42 (0.06–3.03) |
| Fatigue | 1 (1) [0.7] | 0 (0) [0.0] | 1.28 (0.05–31.86)[b] |
| Nausea | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Light-headedness | 1 (1) [0.7] | 0 (0) [0.0] | 1.28 (0.05–31.86)[b] |
| Other nervous system | 0 (0) [0.0] | 0 (0) [0.0] | N/A |
| Fall | 1 (1) [0.7] | 2 (2) [3.3] | 0.21 (0.02–2.33) |
| Other injury | 1 (1) [0.7] | 0 (0) [0.0] | 1.28 (0.05–31.86)[b] |

[a] Data reported as no. of participants with AEs (total number of AEs) [AE incidence rate per 100 sessions=number of AEs/number of sessions per group × 100]. AE odds ratios are from logistic regression modeling of number of AEs/number of sessions per participant. HIT=high-intensity interval training, MCT=moderate-intensity continuous training, CI=confidence interval, N/A=not applicable.
[b] Continuity corrected by adding 0.5 AEs to each group so that AE odds ratios could be calculated.

weeks. The LEAPS trial (N=408) reported that standard outpatient rehabilitation following stroke involved a mean physical therapy volume of 54 minutes for 25 sessions.[56] Therefore, the current protocol would still leave approximately 30 minutes per session in the first 12 sessions and 13 full sessions for other activities. Aerobic deconditioning is a major barrier to stroke recovery, and conventional physical therapy rarely invokes aerobic intensity.[1] Therefore, including a time-efficient HIT protocol in the first month of outpatient therapy has the potential to improve stroke rehabilitation outcomes related to aerobic capacity, mobility, and cardiovascular health.

In conclusion, this preliminary RCT comparing HIT and MCT in chronic stroke showed that recruitment and training were feasible and that HIT was acceptable to participants and reasonably safe for further testing. Preliminary between-group outcome comparisons showed moderate-to-very large effect sizes for most outcome measures, thus justifying further study of efficacy. The results from this study also provide guidance for refinements to the eligibility criteria, randomization methods, HIT treatment protocol, and outcome measure selection. A definitive RCT appears to be feasible and warranted.

Dr Boyne, Dr Dunning, Dr Carl, Dr Gerson, Mr Rockwell, Ms Westover, Dr McCarthy, and Dr Kissela provided concept/idea/research design. Dr Boyne, Dr Dunning, and Dr McCarthy provided writing. Dr Boyne, Dr Dunning, Dr Carl, Dr Khoury, Mr Rockwell, Ms Keeton, Ms Westover, and Ms Williams provided data collection. Dr Boyne, Dr Dunning, Ms Keeton, and Ms Williams provided data analysis. Dr Boyne, Dr Dunning, Ms Keeton, and Ms Westover provided project management. Dr Boyne, Dr Dunning and Dr Kissela provided fund procurement. Dr Dunning, Ms Keeton, and Dr Kissela provided participants. Dr Dunning, Dr Carl, and Dr Gerson provided facilities/equipment. Dr Dunning and Dr Gerson provided institutional liaisons. Ms Westover provided administrative support. Dr Carl, Dr Gerson, Dr Khoury, Mr Rockwell, Ms Keeton, Ms Westover, Ms Williams, and Dr Kissela provided consultation (including review of manuscript before submission). The authors thank Colleen Meyrose, Renee Jeffreys, Brian Barney, Sarah Buhr, and the staff of the UC Medical Center Cardiovascular Stress Laboratory for their assistance with data collection.

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**Table 3.**
Outcome Measure Changes[a]

| Outcome Measure | HIT Group (n=11) | | | MCT Group(n=5) | | | HIT Δ – MCT Δ | Standardized Effect Size |
|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Δ (95% CI) | n | Baseline | Δ (95% CI) | | |
| **Aerobic capacity measures** | | | | | | | | |
| $\dot{V}_{O_2}$peak (mL/kg/min) | 11 | 16.0 (4.0) | 2.2 (–0.05, 4.5) | 5 | 21.6 (4.0) | –1.3 (–4.7, 2.1) | 3.5 (–0.6, 7.6) | 0.99 (–0.14, 2.09) |
| Ventilatory threshold (mL/kg/min) | 10 | 10.3 (3.6) | 4.4 (3.1, 5.7) | 5 | 13.9 (2.2) | 0.6 (–1.3, 2.5) | 3.8 (1.5, 6.1) | 1.95 (0.62, 3.23) |
| **Treadmill gait measures** | | | | | | | | |
| Metabolic cost of gait (mL $O_2$/kg/m) | 9 | 0.40 (0.26) | –0.10 (–0.17, –0.03) | 5 | 0.23 (0.07) | –0.01 (–0.10, 0.09) | –0.09 (–0.21, 0.03) | 0.91 (–0.26, 2.04) |
| Fractional utilization (%) | 8 | 110.0 (9.9) | –36.8 (–49.3, –24.3) | 5 | 84.9 (4.4) | –8.8 (–24.7, 7.0) | –28.0 (–48.2, –7.8) | 1.74 (0.38, 3.04) |
| Fastest treadmill speed (m/s) | 11 | 0.88 (0.46) | 0.36 (0.25, 0.47) | 5 | 1.06 (0.48) | 0.07 (–0.10, 0.24) | 0.29 (0.09, 0.49) | 1.68 (0.43, 2.88) |
| **Overground gait measures** | | | | | | | | |
| Fastest 10-Meter Walk Test (m/s) | 11 | 0.77 (0.54) | 0.10 (0.06, 0.13) | 5 | 0.91 (0.46) | 0.01 (–0.04, 0.06) | 0.08 (0.02, 0.14) | 1.44 (0.24, 2.60) |
| Comfortable 10-Meter Walk Test (m/s) | 11 | 0.63 (0.48) | 0.10 (0.06, 0.14) | 5 | 0.76 (0.36) | 0.02 (–0.03, 0.08) | 0.08 (0.01, 0.14) | 1.27 (0.10, 2.41) |
| 6-min walk distance (m) | 11 | 220 (153) | 15 (1, 29) | 5 | 247 (121) | 15 (–6, 36) | 0 (–26, 25) | 0.00 (–1.16, 1.16) |

[a] Data are presented as mean (SD) or mean (95% confidence interval [CI]) and are from unadjusted mixed effects models. Ventilatory threshold was not identifiable for one participant. Metabolic cost of gait was not obtained for 2 participants due to air leaking during baseline testing. Within group change (Δ) scores are from time contrasts. Between-group differences in change are from group × time interaction contrasts. Standardized effect sizes were calculated by dividing the between-group difference in mean improvement by the standard deviation of change. HIT=high-intensity interval training, MCT=moderate-intensity continuous training, $\dot{V}_{O_2}$peak=peak oxygen consumption.

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## Appendix.

HIT and MCT Protocols[a]

**HIT Protocol**

- Baseline questioning
  - Ask about changes in medical status, medications, falls, pain, and any other AEs
- Setup, baseline measures, and safety monitoring
  - Set up ECG, BP cuff, HR monitor, activity monitor, fall protection harness, elastic band safety limit, and handholds
  - Obtain baseline ECG, BP, and HR
    - Consider holding session and medical referral for any new ECG abnormalities, resting BP >180/100 mm Hg or resting HR >100 bpm
  - Calculate target HR zones using HRR method
    - Target HR = Target %HRR × (HRpeak − HRresting) + HRresting
  - Monitor ECG and HR continuously during session and observe participant for signs or symptoms of cardiorespiratory intolerance (eg, ventricular arrhythmia, >1-mm ST segment depression, angina, pallor, or cyanosis during bursts), new neurologic deficits (eg, near syncope, ataxia), or orthopedic injury (eg, rapid ankle inversion, acute pain)
    - Stop session and consider medical referral for any of the above
  - Take BP at 5:00 and 10:00 of HIT
    - More frequently if approaching BP safety limit (250 mm Hg systolic or 115 mm Hg diastolic),[1] below resting BP, or participant exhibiting signs or symptoms suggestive of hypotensive response during recovery (eg, pallor, nausea, light-headedness)
- Perform participant instruction
- Warm-up (3 min)
  - Gradually increase treadmill speed to achieve 40%±10% HRR within 2 min
  - At 2:15, begin steep ramp test by increasing speed 0.1 mph (0.04 m/s)/5 s. Stop the treadmill when one of the following occurs:
    - Gait fault
      - Drifting backward into safety band, or
      - Gait instability (eg, toe-drag into midswing, increased knee hyperextension or ankle inversion, stepping near edge of treadmill belt)
      - Participant requests to stop
    - Session time reaches 3:00 (45 s of steep ramp test)
- HIT (20 min)
  - Start HIT timer and begin recording HR
    - Timer beeps every 30 s for 20 min
    - HIT begins with 30 s of rest
  - Determine HIT starting speed
    - If there was a gait fault during the steep ramp test, start HIT at 0.1 mph (0.04 m/s) below the speed at which it occurred
    - If the participant reached 3:00 without a gait fault, start at the final speed achieved, continue steep ramp test during HIT bursts until a gait fault occurs, then start next burst at 0.1 mph (0.04 m/s) below gait fault speed
  - 30-s bursts: Perform 30-s bursts of fast treadmill walking and progress speed based previous burst performance

| Observation of previous burst | Speed change for subsequent burst |
|---|---|
| Successful (ie, no backward drift or gait instability) | ↑ 0.1 mph (0.04 m/s) |
| Gait fault (ie, drifted backward into band or exhibited gait instability) | ↓ 0.1 mph (0.04 m/s) |
| Intermediate (ie, some backward drift, but did not touch band, and no gait instability) | No change |

    - Record floor speed
      - Speed of first successful burst after first gait fault
  - Recovery periods: Provide 60-s rest periods (2 beeps of timer) between bursts initially, then progress to 30-s rest periods (1 beep of timer) as follows:
    - Increase recovery by 30 s (1 beep) if any of the following occur:

| | |
|---|---|
| Sessions 1–3 | 60-s recovery |
| Sessions 4–12: first 3 bursts | 60-s recovery |
| Sessions 4–12: bursts 4+ | 30-s recovery |

      - Speed decreases below floor speed (fatigue)
      - Unable to begin next burst at scheduled time due to breathlessness or participant requests more rest
      - BP response near safety limits
    - If any of these occur, attempt to resume target recovery duration as able
  - Progress handhold as tolerated
    - Use handrail only for first session and first half of second session
    - In the last half of session 2, attempt different handholds during bursts to determine the *least supportive handhold* that still enables successful bursts at treadmill speed above fastest overground speed

*(Continued)*

**Appendix.**
Continued

        - Options include:
            - Handrail (most support)
            - Elastic band placed horizontally in front of participant
            - No handhold (least support)
        - Sessions 3–12: begin with handrail until first gait fault, then begin alternating bursts between handrail and least supportive handhold
        - Determine speed separately for each handhold
    - Obtain RPE at 10:00
- Cool-down (2 min)
    - Start at warm-up speed and adjust to maintain 40%±10% HRR
- Postsession questioning, monitoring, and data collection
    - Ask about pain, light-headedness, nausea, and any other AEs
    - Monitor until HR and BP return to near-baseline levels
    - Record peak treadmill speed, session step count, and mean HR

**MCT Protocol**

- Baseline questioning, setup, baseline measures, and safety monitoring (same as HIT protocol)
- Perform participant instruction
- Warm-up (3 min)
    - Gradually increase treadmill speed to achieve 40%±10% HRR within 2 min and maintain for last minute
- MCT (20 min)
    - Start MCT timer and begin recording HR
        - Timer counts down 20 min
    - Perform continuous treadmill walking and adjust speed as needed to maintain target HR range
        - 45%±5% HRR in sessions 1–6
        - 50%±5% HRR in sessions 7–12
        - Decrease speed if any of the following occur:
            - Participant has gait fault or requests lower speed
            - BP response near safety limits
        - If any of these occur, attempt to resume training in target HR range as able
    - Progress handhold as tolerated—same as HIT except:
        - *Least supportive handhold* must still enable training in target HR range (rather than burst speed above fastest overground speed)
        - Alternate between handrail and least supportive handhold every 5 min (instead of every burst) in sessions 3–12
    - Obtain RPE at 10:00
- Cool-down, postsession questioning, monitoring, and data collection (same as HIT)

[a] HIT=high-intensity interval training, MCT=moderate-intensity continuous training, AE=adverse event, ECG=electrocardiogram, BP=blood pressure, HR=heart rate, HRpeak=peak heart rate, HRresting=resting heart rate, HRR=heart rate reserve, RPE=rating of perceived exertion.