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Contributions of Stepping Intensity and Variability to Mobility in Individuals Post-stroke: A Randomized Clinical Trial

T. George Hornby, PhD[1,2,3], **Christopher E. Henderson, PhD**[1,2], **Abbey Plawecki, DPT**[2], **Emily Lucas, BS**[2], **Jennifer Lotter, DPT**[2], **Molly Holthus, DPT**[2], **Gabrielle Brazg, DPT**[4], **Meghan Fahey, DPT**[4], **Jane Woodward, DPT**[4], **Marzieh Ardestani, PhD**[1,2], **Elliot J. Roth, MD**[3,4]

[1]Department of Physical Medicine and Rehabilitation, Indiana University School of Medicine, Indianapolis IN

[2]Rehabilitation Hospital of Indiana, Indianapolis, IN

[3]Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Northwestern University, Chicago, IL

[4]Shirley Ryan Ability Lab, Chicago, IL

Abstract

Background and Purpose: The amount of task-specific stepping practice provided during rehabilitation post-stroke can influence locomotor recovery, and reflects one aspect of exercise "dose" that can affect the efficacy of specific interventions. Emerging data suggest that markedly increasing the intensity and variability of stepping practice may also be critical, although such strategies are discouraged during traditional rehabilitation. The goal of this study was to determine the individual and combined contributions of intensity and variability of stepping practice to improving walking speed and distance in individuals post-stroke.

Methods: This Phase 2, randomized, blinded assessor clinical trial was performed between May 2015-November 2018. Individuals between 18-85 years old with hemiparesis post-stroke of >6 months duration were recruited. Of the 152 individuals screened, 97 were randomly assigned to 1 of 3 training groups, with 90 completing >10 sessions. Interventions consisted of either high intensity stepping (70-80% heart rate [HR] reserve) of variable, difficult stepping tasks (high-variable), high intensity stepping performing only forward walking (high-forward), and low intensity stepping in variable contexts at 30-40% HR reserve (low-variable). Participants received up to 30 sessions over 2 months, with testing at baseline, post-training and a 3-month follow-up. Primary outcomes included walking speeds and timed distance, with secondary measures of dynamic balance, transfers, spatiotemporal kinematics and metabolic measures.

Results: All walking gains were significantly greater following either high-intensity group vs low-variable training (all $p<0.001$) with significant correlations with stepping amount and rate ($r=0.48$-60; $p<0.01$). Additional gains in spatiotemporal symmetry were observed with high-

Corresponding Author: T. George Hornby, PhD, PT, Department of Physical Medicine and Rehabilitation, Indiana University School of Medicine, Phone: 317-329-2353; tghornby@iu.edu.

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intensity training, and balance confidence increased only following high-variable training in individuals with severe impairments.

Conclusion: High intensity stepping training resulted in greater improvements in walking ability and gait symmetry than low-intensity training in individuals with chronic stroke, with potential greater improvements in balance confidence.

Clinical Trial Registration-URL: https://clinicaltrials.gov/. Unique Identifier: NCT02507466

Keywords

locomotion; rehabilitation; exercise

Introduction

The increasing incidence[1] and current survival rates of individuals who experience a stroke has resulted in a substantial patient population with neurological deficits that limit locomotor capacity and postural stability[2, 3]. In individuals with chronic (>6 months) stroke, mobility limitations[4, 5] lead to reduced cardiopulmonary capacity that can further exacerbate locomotor deficits[3]. Previous work[6, 7] suggests specific exercise training parameters, including the frequency, intensity, time and type, can influence changes in health and fitness in individuals with and without neurological injury[8]. These parameters represent the "dose" of exercise interventions, although their contributions to locomotor recovery post-stroke are uncertain. Early studies advocated that large amounts of stepping practice with focus on normalizing gait patterns was a critical determinant of improved mobility[9-11]. Unfortunately, a multicenter trial utilizing this strategy revealed limited gains beyond conventional approaches[12]. Additional research indicate treadmill exercise at submaximal aerobic intensities determined during baseline testing can improve walking endurance post-stroke[13-15], although changes in walking speed or other mobility outcomes (balance or transfers) are inconsistent or negligible. The combined findings imply that these dosage parameters may not be critical to locomotor recovery post-stroke.

An alternative hypothesis is that specific training variables can influence locomotor recovery when their manipulation substantially challenges the physiological demands associated with functional mobility. In particular, pilot studies indicate stepping training at cardiovascular intensities that are oftentimes greater than those achieved during baseline testing can improve multiple measures of locomotor and cardiopulmonary function[16-18]. In addition, increasing the variability and difficulty of stepping tasks (e.g., multidirectional walking, stair climbing, overground walking on uneven or compliant surfaces) requires increased neuromuscular coordination and postural control that may improve mobility and dynamic stability[16, 17, 19].

Despite these findings, clinical implementation of high intensity stepping training in variable contexts is limited. Specific concerns include the potential for cardiovascular events[20], despite data indicating no additional risks compared to standard interventions[21]. Additional concerns include practice of abnormal kinematic strategies, particularly in those with severe neuromuscular impairments during difficult, variable tasks. Such training deviates considerably from traditional interventions that focus on correcting abnormal gait patterns[9, 10, 12], although available data suggest gait kinematics can improve with variable stepping training[16, 17, 22].

The present study examined the relative contributions of stepping intensity and variability on mobility outcomes in ambulatory individuals with chronic stroke. Using a randomized, controlled trial design, we hypothesized that high intensity stepping training in variable contexts would result in greater gains in locomotor outcomes as compared to more traditional training focused on forward walking, or low intensity training of variable stepping tasks. Additional outcomes included alterations in transfers, dynamic balance and balance confidence, spatiotemporal kinematics, peak metabolic capacity, and potential adverse events. Results from this trial could indicate the potential utility of high intensity training of variable, difficult tasks to improve mobility post-stroke.

Methods

The data that support the findings of this study are available from the corresponding author upon request. The present study was conducted between May 2015 to November 2018, and all procedures were approved by the local Institutional Review Board, with written informed consent and physician clearance to participate.

Study Sample and Design

Individuals with unilateral hemiparesis following a stroke >6 months previously were recruited. Eligible participants were required to walk 10 m overground without physical assistance but at self-selected speeds (SSS) <1.0 m/s, with their customary assistive devices and below-knee bracing as needed. Exclusion criteria consisted of additional central or peripheral nervous system or orthopedic injury that limits independent ambulation, evidence of cerebellar ataxia, currently participating in physical therapy, uncontrolled cardiorespiratory or metabolic disease, or inability to follow 3-step commands. Participants could receive botulinum toxin in their paretic leg <3 months prior to enrollment if injected only in their lower leg and the participant used an ankle-foot orthoses during testing. Subjects were stratified according to their initial SSS (<0.5 m/s or 0.5–0-1.0 m/s), and randomized to one of 3 stepping training groups, including high intensity stepping training in variable contexts (HV), high intensity stepping training forward on a treadmill and overground with minimal variability (HF), and low intensity variable stepping training (LV). Participants were randomized (allocation ratio: 1:1:1) using a computer-generated blocked design (6 participants per block) with allocation concealed. Preliminary data for high-intensity variable[16], high-intensity forward[13-15, 23-25], and lower intensity paradigms[24, 25] indicated 90 participants would provide 98% power for primary walking outcomes (speed and timed distance) and 88–94% power for transfer and balance outcomes between HV and HF or LV groups.

Intervention

Training was performed in laboratory or outpatient clinical settings, and consisted of ≤30 1-hr training sessions over 2 months (3–5 sessions/wk), with ≤40 minutes of stepping practice each session. Each training paradigm has been described previously[16]. All participants wore accelerometers (StepWatch, Modus, Inc. Washington DC) on their paretic limb to estimate stepping amount and rate per session. Heart rates (HRs) were monitored using pulse-oximeters or chest-worn monitors and documented every 3–5 minutes as possible, along with ratings of perceived exertion (RPE) using the Borg scale (range: 6–20)[26]. Blood pressures were monitored with training cessation if pressures could not remain below 210/110 mmHg.

The goals of experimental HV training were to maximize stepping practice in variable contexts while achieving high cardiovascular intensities. Training HR ranges were calculated using age-predicted maximum (208-(0.7*age)[27]), and training HRs were established 70–80% HR reserve using the Karvonen formula[28]. For participants on β-blockers, HR ranges were decreased by 10 beats/min[29, 30]. Training sessions were divided into ~10-minute increments between speed-dependent treadmill training, skill-dependent treadmill training, overground training, and stair climbing. Speed-dependent treadmill training was performed with an overhead safety system, with goals to achieve walking speeds sufficient to reach the targeted HRs. Body weight support and swing assistance were provided only as needed to achieve HRs. Therapists did not focus on lower extremity kinematics unless there were concerns regarding musculoskeletal injury. Criteria for successful stepping included positive bilateral step lengths, lack of stance-phase limb collapse, and sagittal/frontal plane stability[16]. Skill-dependent treadmill training was performed by applying perturbations to challenge postural stability, propulsion, and limb swing as selected by therapists, and included walking in multiple directions, over inclines and obstacles, and/or with weighted vests and leg weights with limited handrail use as tolerated. Perturbations were applied such that 2–5 different tasks were alternated and repeated within ~10 minutes. Task difficulty was reduced if participants were not successful for 3–5 consecutive steps. Overground training focused on achieving high speeds or performing variable tasks as described above, and included negotiating uneven, compliant or narrow surfaces, with use of a gait belt or overhead suspension system. Stair climbing was performed over static or rotating stairs (Stairmaster, Vancouver, WA) using reciprocal gait patterns with progression to higher speeds or reduced handrail use. If specific tasks were not practiced during individual sessions, subsequent sessions focused on missed tasks.

Training in the HF group consisted of maximizing stepping practice on a treadmill and overground while achieving 70–80% HR reserve. Only forward stepping was performed for ≤20 minutes on a treadmill and ≤20 minutes overground, and task difficulty was altered by increasing walking speeds to achieve the targeted intensities.

Participants randomized to LV training performed stepping activities at 30–40% HR reserve although in variable contexts, similar to HV training described above, with therapist determination of tasks performed based on individual impairments. Therapists were allowed to cue participants to alter kinematics to improve engagement during stepping tasks.

Outcomes

Primary outcome measures were performed by blinded assessors at baseline, post-training, and at 3-month follow-up assessments. Specific outcomes included self-selected (SSS) and fastest-possible speeds (FS) over short distances using a pressure-sensitive walkway (GaitMat, Chalfont, PA, or GaitRite, Haverton, PA) and walking distance during the 6-minute walk test (6MWT) performed at FS[16]. Device and bracing use were consistent for each participant across all assessments. If participants required physical assistance during the 6MWT, the distance completed independently was recorded. Secondary gait measures from the SSS and FS assessments included indices of spatiotemporal symmetry. Temporal symmetry was evaluated as % paretic single-limb stance at SSS and FS. Spatial symmetry was determined using step-length symmetry[16] calculated as below with negative values (i.e., negative step lengths) omitted as outliers:

$$100\,\% * \left(1 - \left|\left(1 - \frac{nonparetic\;step\;length}{paretic\;step\;length}\right)\right|\right)$$

Secondary clinical measures with blinded assessors included the Functional Gait Assessment (FGA) to assess dynamic postural stability, and the 5-times sit-to-stand (5XSTS) performed using an adjustable height chair (3 in increments). Speed of sit-to-stand performance (repetitions/sec) was calculated to include data from those unable to perform the task. Subjective measures included the Activities-specific Balance Confidence (ABC) Scale, and the Physical Function/Mobility score of the Patient Reported Outcomes Measures. Additional measures included peak O_2 consumption (VO_2; ml/min/kg; Cosmed, Chicago, IL), HR, and RPE during a modified graded exercise testing using 12-lead ECG assessments. Participants walked on a treadmill at 0.1 m/s with an overhead safety system for 1 min, with speed increased 0.1 m/s every minute until gait instability, abnormal ECG recordings consistent with absolute testing contraindications, symptoms of angina, or participants requested to terminate testing[31]. Peak treadmill speed was determined following completion of 1 min at the highest velocity, with VO_2, HR, and RPE collected over the last 30 sec. Additional baseline assessments included the lower limb Fugl-Meyer assessment[32] and the Charlson Comorbidity Index[33]. Measures of training activities included number of sessions, mean duration, HR reserve, RPE, and steps per session and steps/min to estimate both amount and intensity of stepping.

Incidence of adverse events were tabulated, and included serious adverse events such as death, falls with injury outside of training, and cardiovascular events requiring hospitalization, and minor events of musculoskeletal pain, falls without injury outside of training, dizziness/loss of consciousness, excessive shortness of breath, or episodes of hypertension, hypotension or angina that limited training[12].

Analysis

Parametric data were tested for normality prior to analyses. On-protocol analyses established *a priori* utilized data for participants who completed ≥10 training sessions, with additional intent-to-treat analyses for primary locomotor and secondary balance and transfer measures using all participants enrolled. Regression imputation for participant drop-outs using complete results was utilized for follow-up for on-protocol analyses and post-training and follow-up for intent-to-treat analyses. Training variables were compared between treatment groups using one-way ANOVAs, with mean (95% confidence intervals) in tables and figures.

Primary and secondary outcomes were analyzed using a 3-way repeated-measures ANOVA with main factors of treatment (HV, HF, LV), level of severity (<0.5, 0.5–1.0 m/s), and repeated for time (baseline, post-training, follow-up). Post-hoc ANOVAs were performed between specific groups or level of severity with significant interactions for group*X*time and group*X*time*X*severity. Significance was set at α=0.0167 with Bonferroni corrections made for primary walking outcomes (SSS, FS, and 6MWT), and α=0.05 for post-hoc and secondary measures. Correlations analyses were used to estimate associations between steps/session, steps/min, and HR reserve with walking outcomes. Serious and minor adverse events were categorized by training, with X^2 analyses performed by combing the two higher-risk groups (HV, HV) as compared to low-intensity training (LV).

Results

Screening evaluations were performed on 152 individuals, with 97 meeting all inclusion criteria and randomized (Figure 1). Seven individuals (HV:3; HF:3; LV:1) completed <10 training sessions, with reasons for termination including: difficulty of exercise training (HV:2, HF:1); lack of desire to continue (HF:1), scheduling conflicts (LV:1), family medical emergency (HV:1) and paretic hand pain unrelated to training (HF:1). Table 1 provides demographic characteristics and baseline impairments of the 90 participants who completed post-testing, with means (95% confidence intervals) indicating no differences between groups. Nine individuals (HV:2; HF:3; LV:4) could not attend follow-up.

Details of training interventions (Table 2) indicate similar number of sessions between groups with ~3 min longer sessions with LV training. Conversely, greater HRs and RPEs were observed during either high-intensity group vs low-intensity groups (p<0.001), with HR reserves calculated using both age-predicted and observed maximum HRs at baseline (Table 2). Training HRs in both high-intensity groups averaged above HRs at baseline testing. Differences in steps/sessions were observed, with 500 to 1000 more steps/session in HF than HV or LV, respectively, and consistent with differences in stepping rates (p<0.001, Table 2).

Baseline measures (Tables 3-4) were not significantly different across groups. Following training, significant group*X*time interactions for SSS, FS, and 6MWTs were observed favoring both HV and HF at post-training and follow-up, with non-significant interactions for severity. Intent-to-treat analyses resulted in similar findings (Supplement Table 1). Figure 2A-B demonstrates changes in SSS and 6MWT (mean and 95% CI), with thresholds for minimally clinically important differences for SSS (0.10 m/s) and 6MWT indicated (50 m[34]; dotted lines). For all walking outcomes, 57–80% of participants in HV or HF groups surpassed minimally clinically important differences, whereas only 9.3–31% surpassed this thresholds following LV training. Mean differences between either high intensity-training group as compared to low intensity training were also larger than minimally important differences for SSS and FS at post-training and follow-up, and approached or exceeded these thresholds for 6MWT.

Secondary measures of spatiotemporal symmetry demonstrated no differences for step length symmetry, but greater improvements in paretic single-limb stance in either high-intensity group vs low-intensity training. An additional group*X*time*X*severity interaction was observed during SSS in participants with severe gait impairments in both high-intensity groups.

Secondary blinded clinical assessments revealed non-significant between-group interactions for the Functional Gait Assessment or 5X sit-to-stand (Table 4), although the former was significant with intent-to-treat analyses (Supplemental Table 1). Changes in subjective assessments revealed significant group*X*time*X*severity interactions for the Activities-specific Balance Confidence scale, indicating greater improvements following HV training in those with severe gait impairments. Specific improvements in this subgroup (ΔABC = 17 (95% CI: 7–28) pts at post-training and 17 (5–28) pts at follow-up) were approximately 7–10 points greater than other training groups. Additional changes in graded exercise performance indicated significant differences in peak treadmill speeds following both high- vs low-intensity training, with no differences in peak VO_2.

Correlation analyses of specific dose vs response relationships revealed significant low to moderate associations between gait outcomes and mean steps/session (r=0.41–0.59, all p<0.001), with negligible to low correlations with mean HR reserve (r=0.09–0.29). Correlations using steps/min during walking practice revealed slightly higher associations (r=0.48–0.60; all p < 0.001) as indicated in Fig 2C-D for SSS and 6MWT.

Serious adverse events during training were not observed in any group. Minor adverse events consisted primarily of musculoskeletal pain (HV:27; HF:20; LV:18) and falls outside of training not resulting in injury (HV:8; HF:10; LV:16). Additional cardiopulmonary concerns included hypertension, angina, or shortness of breath (HV:6; HF:4; LV:8), and dizziness/loss of consciousness occurred in 5 individuals (HV:2; HF:3). If deemed necessary, participants were cleared by physicians following these episodes and continued participation. Adverse event rates were not different between both high- vs low-intensity groups (p=0.73).

Discussion

The present data extend upon preliminary studies detailing the efficacy of high intensity stepping training[16, 17, 19] to improve locomotor function in individuals post-stroke. The cardiovascular intensities achieved during training (as determined using age-predicted maximum HRs) resulted in higher physiological demands than typically achieved during standard aerobic training studies[13-15] and statistically and clinically significant differences between high vs low-intensity training groups for all walking measures. Greater HRs during high-intensity training were likely driven by elevated neuromuscular demands, as evident by differences in amount and rate of stepping between training groups. The contributions of these dosage parameters are highlighted by the relationships between stepping rates and amounts to changes in locomotor outcomes.

The contributions of task variability and difficulty are less clear, given the lack of significant differences in the Functional Gait Assessment or the 5X sit-to-stand test following the *a priori* on-protocol analyses (≥10 sessions completed). While differences in the Functional Gait Assessment with intent-to-treat analyses are promising, the clinical significance of a 2-

point mean difference between groups is uncertain. Improvements in balance confidence (ABC) in those with severe gait impairments indicate additional potential benefits of HV training. Limitations of these combined findings include their clinical implications, as subjective measures of mobility were not different across groups. Indeed, a limitation of this study is that stepping activity in the home and community is not reported, and further work will evaluate potential changes in community mobility following these training paradigms.

Additional findings include differences in %single paretic-limb stance following high- vs low-intensity training, despite limited focus on kinematic patterns. Such data may mitigate concerns regarding reinforcing abnormal locomotor strategies. Conversely, changes in peak VO_2 were not significant, and surprising given the differences in cardiovascular demands during high- vs low-intensity training and prior studies indicating consistent gains in peak VO_2[13-15]. This latter finding may be due to changes in neuromuscular efficiency that contributed to reduced submaximal metabolic costs[35], and further work can provide insight into mechanisms of altered locomotor function.

Specific limitations include the sample size, although initial power calculations indicated this sample was sufficient to identify differences in primary and secondary outcomes. The lack of ability to accurately predict or estimate maximum HRs in patients with mobility dysfunction post-stroke is also a primary concern given the locomotor benefits observed here and the potential risk of cardiovascular events. We specifically utilized age-predicted maximum HRs secondary to neuromuscular deficits that can limit exercise performance and subsequent cardiovascular demands, particularly at baseline assessments. While observed maximum HRs at baseline testing are typically used to determine aerobic training thresholds, patients often surpass these levels during standard clinical testing[31]. Further work is needed to determine maximal HRs to allow safe aerobic training in clinical practice.

Finally, the lack of differences in adverse events are important given the cardiovascular concerns post-stroke, and previous studies also do not indicate additional cardiovascular risks with such training[21]. Further work is warranted to delineate the incidence of cardiovascular or other non-serious events in larger cohorts. Such studies will be critical given the consistent differences in locomotor outcomes with high-intensity training, and the potential changes observed with stepping in variable contexts.

Conclusions

Providing stepping training at high intensities with or without practice of variable, difficult stepping tasks elicits gains in walking function and gait symmetry as compared lower intensity activities. Changes in balance and balance confidence suggest a possible benefit of practicing difficult stepping tasks during high-intensity training in variable contexts. Despite non-significant differences in adverse events, future studies should further identify the potential risks for this patient population. The relative contributions of volume, intensity and variability may be important, and future studies are needed to further define optimal training parameters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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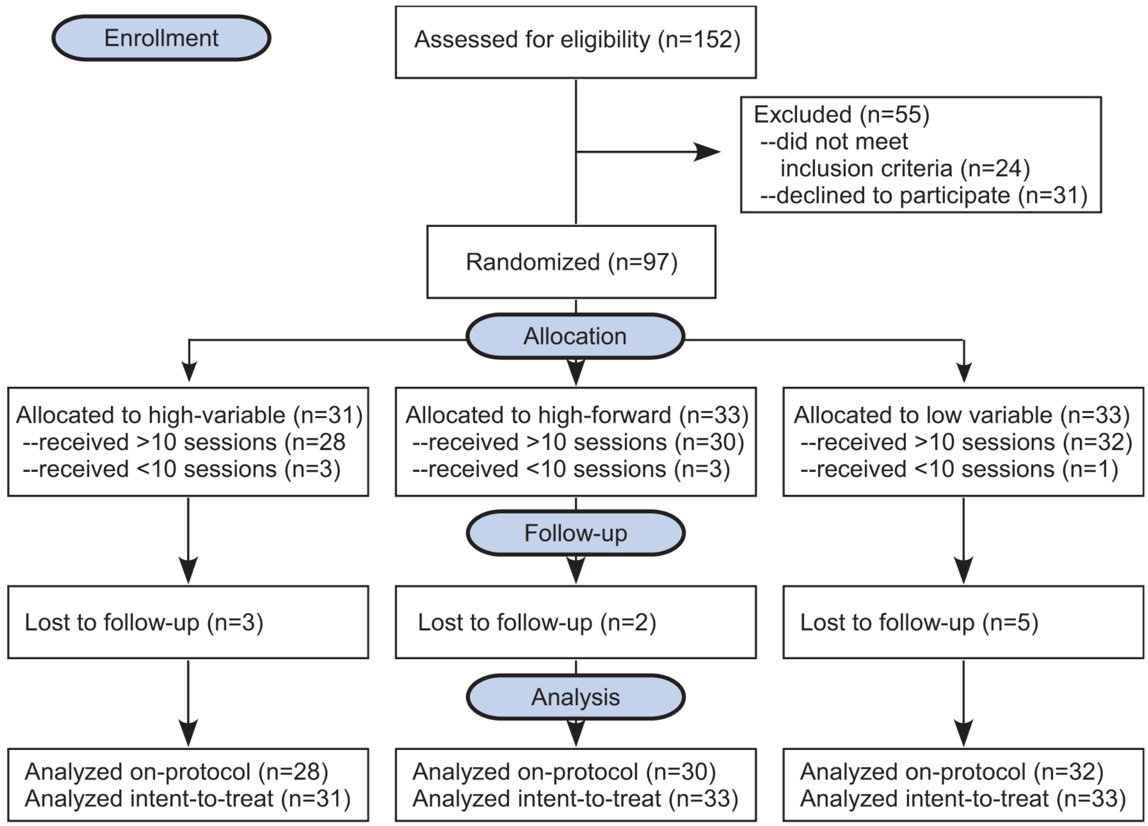

Figure 1.
CONSORT diagram of enrollment

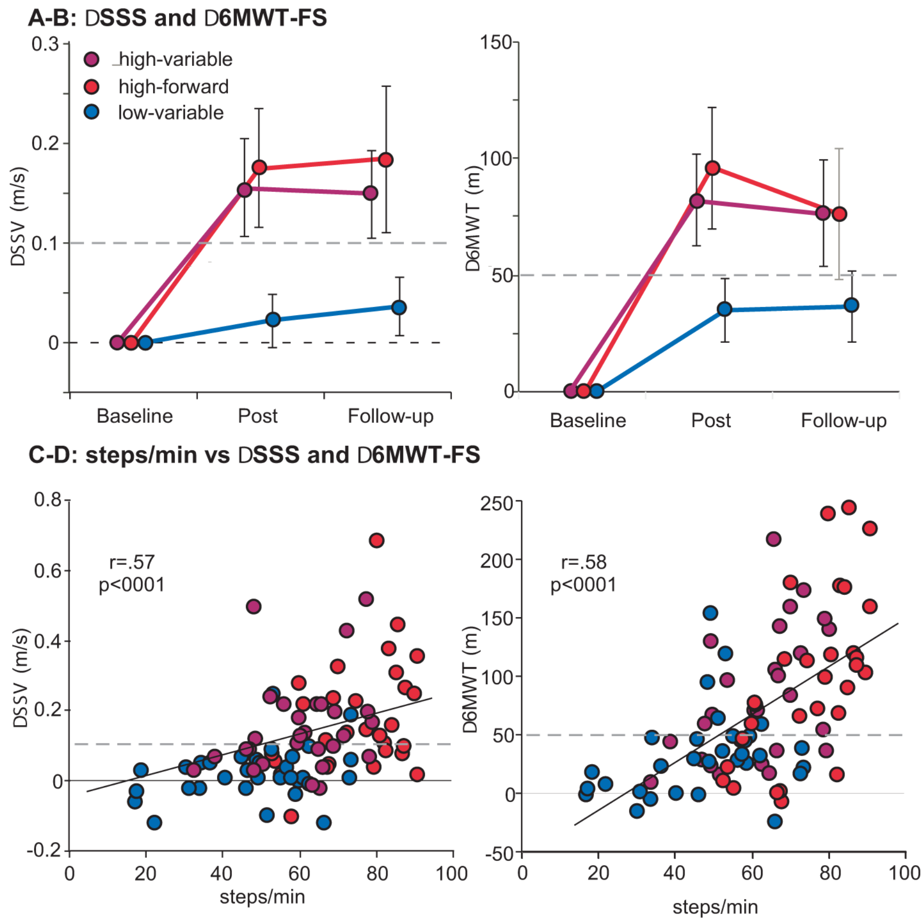

Figure 2.

A-B: Changes in SSS (2A) and 6MWT-FS (2B) in training groups at each assessment (mean and 95% CIs) with post-hoc significance ($p<0.0001$) denoted by asterisk (*). C-D: Associations between stepping rate and changes in Δ SSS and Δ6MWT-FS ($p<0.01$).

Table 1.

Demographic and baseline characteristics; mean (95% CIs).

	High-intensity variable (n=28)	High-intensity forward (n=30)	Low-intensity variable (n=32)
Demographics			
Age (yrs)	59 (55-62)	60 (56-64)	56 (52-60)
Duration post-stroke (mos)	60 (14-106)	31 (19-42)	27 (18-36)
Gender, male (%)	23 (82%)	17 (57%)	18 (56%)
Race, white (%)	19 (68%)	21 (70%)	22 (66%)
Side of paresis, left (%)	16 (57%)	15 (50%)	19 (59%)
Ischemic, number (%)	23 (82%)	20 (67%)	23 (72%)
Ankle foot orthosis, number (%)	17 (61%)	22 (73%)	25 (78%)
Assistive device, number (%)	22 (79%)	21 (70%)	28 (88%)
Baseline impairments			
Fugl-Meyer – lower limb (a.u.)	23 (20-25)	23 (21-25)	21 (19-24)
Charlson Comorbidity Index (a.u.)	3.0 (2.6-3.4)	3.0 (2.5-3.5)	2.8 (2.4-3.3)
Severe/moderate gait deficits	13/15	15/15	15/17

Table 2.

Training parameters with mean (95% CIs) and between-group p-values.

Training characteristics	High-intensity variable	High-intensity forward	Low-intensity variable	group effects
sessions	27 (26-29)	27 (25-28)	27 (25-29)	0.79
duration/session (min)	34 (33-35)	33 (32-35)	37 (36-38)	<0.001 LV > HV, HF
%HRR (predicted HR_{max})	67 (61-72)	61 (54-67)	40 (35-44)	<0.001 HV, HF > LV
%HRR (observed HR_{max})	111 (97-126)	108 (97-119)	63 (58-70)	<0.001 HV, HF > LV
RPE (a.u.)	16 (16-17)	17 (16-18)	14 (13-14)	<0.001 HV, HF > LV
steps/session	2675 (2368-2982)	3156 (2822-3491)	2164 (1798-2530)	<0.001 HF > HV > LV
steps/min	62 (57-66)	75 (71-80)	48 (42-54)	<0.001 HF > HV > LV

Table 3.

Primary walking outcomes with mean (95% CIs) at baseline (BSL), post-training (POST) and follow-up (F/U) and between-group and severity interactions p-values.

	High-intensity variable	High-intensity forward	Low-intensity variable	group × time interaction	group × severity × time interaction
Self-selected velocity (m/s)					
BSL	0.52 (0.41-0.63)	0.50 (0.39-0.61)	0.50 (0.40-0.59)	<0.001 HV, HF > LV	0.21
ΔPOST	0.16 (0.10-0.21)	0.17 (0.11-0.24)	0.02 (0.00-0.05)		
ΔF/U	0.16 (0.11-0.20)	0.19 (0.11-0.26)	0.04 (0.01-0.07)		
Single limb stance-SSV (% gait cycle)					
BSL	21 (19-24)	22 (19-24)	22 (19-25)	<0.001 HV, HF > LV	<0.001 HV/HF-severe> others
ΔPOST	2.1 (0.7-3.4)	3.5 (1.9-5.0)	0.5 (−0.4-1.4)		
ΔF/U	2.6 (0.9-4.3)	3.8 (2.0-5.5)	0.9 (−0.4-1.6)		
Step length asymmetry-SSV (%)					
BSL	72 (60-83)	76 (68-83)	69 (60-78)	0.95	0.45
ΔPOST	4.9 (−1.1-11)	1.7 (−6.2-9.7)	2.4 (−5.4-10)		
ΔF/U	3.9 (−4.3-12)	3.6 (−4.2-11)	3.8 (−4.3-12)		
Fastest velocity (m/s)					
BSL	0.70 (0.55-0.85)	0.65 (0.50-0.80)	0.65 (0.51-0.78)	<0.001 HV, HF > LV	0.43
ΔPOST	0.24 (0.17-0.31)	0.29 (0.20-0.37)	0.07 (0.03-0.11)		
ΔF/U	0.20 (0.14-0.27)	0.23 (0.16-0.31)	0.07 (0.03-0.12)		
Single limb stance-FV (% gait cycle)					
BSL	24 (21-26)	23 (20-26)	23 (20-26)	0.005 HV, HF > LV	0.15
ΔPOST	2.5 (0.8-4.3)	4.1 (2.2-6.1)	0.9 (−0.1-1.8)		
ΔF/U	2.6 (1.0-4.3)	3.6 (1.8-5.4)	0.9 (−0.3-2.0)		
Step length asymmetry-FV (%)					
BSL	73 (65-82)	75 (67-82)	70 (61-80)	0.65	0.99
ΔPOST	7.4 (2.9-12)	4.6 (−2.1-11)	3.7 (−4/1-12)		
ΔF/U	6.1 (1.3-11)	4.7 (−1.2-11)	0.5 (−6.0-6.9)		
Six min walk test –fastest speed (m)					
BSL	212 (160-264)	197 (149-244)	197 (149-246)	<0.001 HV, HF > LV	0.96
ΔPOST	82 (61-104)	96 (69-123)	34 (21-48)		

	High-intensity variable	High-intensity forward	Low-intensity variable	group × time interaction	group × severity × time interaction
ΔF/U	77 (53-101)	76 (46-105)	38 (23-53)		

Table 4.

Secondary mobility outcomes with mean (95% CIs) at baseline (BSL), post-training (POST) and follow-up (F/U) and between-group and severity interactions p-values.

	High-intensity variable	High-intensity forward	Low-intensity variable	group × time interaction	group × severity × time interaction
Functional Gait Assessment (au.)					
BSL	13 (11-15)	12 (9.9-14)	11 (9.2-13)		
ΔPOST	2.2 (1.1-3.3)	0.7 (−0.6-2.0)	1.8 (0.3-3.4)	0.06	0.46
ΔF/U	2.6 (1.2-3.9)	1.4 (0.3-2.5)	0.4 (−0.9-1.6)		
Five-times sit-to-stand (repetitions/sec)					
BSL	0.33 (0.29-0.38)	0.31 (0.26-0.37)	0.28 (0.22-0.33)		
ΔPOST	0.00 (−0.04-0.04)	0.00 (−0.05-0.05)	0.03 (0.00-0.07)	0.58	0.92
ΔF/U	0.02 (−0.02-0.06)	0.00 (−0.03-0.03)	0.01 (−0.02-0.05)		
Mobility – PROMIS (a.u.)					
BSL	38 (34-41)	37 (34-41)	36 (32-39)		
ΔPOST	4.0 (1.1-7.0)	2.4 (0.5-4.3)	4.3 (2.2-6.4)	0.50	0.90
ΔF/U	3.5 (0.5-6.6)	1.4 (−0.6-3.5)	1.7 (−0.4-3.8)		
Activities-specific Balances Confidence scale (ABC; a.u.)					
BSL	61 (51-70)	53 (46-61)	49 (40-57)		
ΔPOST	10 (4.9-16)	4.1 (−0.1-8.4)	7.4 (3.3-11)	0.13	0.03 HV-severe > others
ΔF/U	9.6 (3.4-16)	2.6 (−1.4-6.7)	4.0 (−1.1-9.1)		
Peak treadmill speed (m/s)					
BSL	0.78 (0.61-0.95)	0.70 (0.54-0.87)	0.74 (0.56-0.91)		
ΔPOST	0.36 (0.30-0.42)	0.37 (0.28-0.46)	0.13 (0.07-0.18)	<0.001 HV, HF > LV	0.74
ΔF/U	0.31 (0.24-0.39)	0.31 (0.24-0.37)	0.14 (0.09-0.19)		
VO_2peak (ml O_2/kg/min)					
BSL	14 (12-16)	14 (12-16)	14 (12-16)		
ΔPOST	2.3 (−0.3-4.8)	1.5 (0.4-3.0)	1.6 (0.2-3.0)	0.85	0.16
ΔF/U	2.9 (1.3-4.6)	1.3 (0.3-3.5)	2.3 (0.9-3.6)		