International Journal of Cerebrovascular Disease and Stroke
Conroy SS et al. Int J Cerebrovasc Dis Stroke 7: 170.
www.doi.org/10.29011/2688-8734.000070
www.gavinpublishers.com

Research Article

# Treadmill Integrated Robot-assisted Ankle Dorsiflexion Training for Stroke Rehabilitation: A Pilot Randomized Controlled Trial

**Susan S Conroy[1,2*], Anindo Roy[1-3], Laurence S Magder[4], Derek J Eversley[2], Kate C Flores[2], Zachary Kerns[2], Steven J Kittner[1,5], Richard F Macko[1,2,4]**

[1]Department of Research and Development, VA Maryland Health Care System, Baltimore, Maryland, USA

[2]Geriatric Research Education and Clinical Center, Veterans Health Administration, Baltimore, Maryland, USA

[3]Department of Engineering, University of Maryland, College Park, Maryland, USA

[4]Department of Epidemiology and Public Health, University of Maryland, Baltimore, Maryland, USA

[5]Department of Neurology, University of Maryland, Baltimore, Maryland, USA

***Corresponding author:** Susan S Conroy, Department of Research and Development, VA Maryland Health Care System, Baltimore, Maryland, USA

**Citation:** Conroy SS, Roy A, Magder LS, Eversley DJ, Flores KC, et al. (2024) Treadmill Integrated Robot-assisted Ankle Dorsiflexion Training for Stroke Rehabilitation: A Pilot Randomized Controlled Trial. Int J Cerebrovasc Dis Stroke 7: 170. DOI: https://doi.org/10.29011/2688-8734.100170

**Received Date:** 31 December, 2023**; Accepted Date:** 05 January, 2024**; Published Date:** 08 January, 2024

## Abstract

Ankle hemiparesis is a common post-stroke problem that impairs walking and exoskeletal robots are an emerging joint-specific tool that can address ankle deficits and automate therapy. This single-blind randomized controlled trial compared 6-week treadmill-ankle robot (TMR) training to 6-week treadmill (TM) only training on paretic ankle motor control and gait performance. Forty-five participants with chronic stroke (>5 months to 6+ years) trained three times per week for six weeks. The groups were not statistically different at baseline, however, more TMR participants used ankle foot orthosis (AFO) (61%TMR; 36% TM). The primary analysis was based on intention-to-treat using a longitudinal regression model and analyzed post-training outcomes at week-six and at retention six-weeks and three-months after training. We found no significant between group ankle dorsiflexion (DF) and gait velocity change at week-six or at retention. The six-week mean peak paretic DF swing angle was 4.84 degrees (SD 6.83) and 4.2 degrees (SD 6.83) p=0.63 and the DF angle at foot strike was -0.70 degrees (SD 6.55) and -0.46 degrees (SD 5.70) p=0.84, respectively, in TMR and TM. Within group gait velocity improvement was similar with a mean increase of 0.54 m/s (SD 0.24) and 0.56 m/s (SD 0.32) p=0.48 in TMR and TM respectively, that was durable through retention. Integrating ankle robot training with TM walking was not significantly better than treadmill training alone. Future larger studies with refined eligibility criteria and randomization strata that balance key gait determinates are needed to further determine effectiveness on ankle function and gait.

**Keywords:** Stroke; Rehabilitation robotics; Ankle robot; Hemiparetic gait; Foot drop

## Introduction

Stroke is the leading cause of long-term adult disability and reduced ankle dorsiflexor (DF) strength, or foot drop, affects 20-30% of stroke survivors [1]. The ankle joint is an integral link between the limb and environment and loss of ankle strength after a stroke results in decreased walking endurance, temporal asymmetry and reduced gait velocity [1-3]. Hemiparetic gait compensations for DF weakness are characterized by poor foot clearance and impaired midstance stability and contribute to an increased metabolic cost of walking and fall risk [2,4,5]. Management is limited to passive external support via an ankle foot orthosis (AFO) and active gait training, if employed, is labor-intensive and does not deliver the timing, assistance, and intensity necessary for motor learning [4,6,7]. These methods may improve safety and speed but do not result in a sustained therapeutic effect characterized by functional independence when not worn [6,8-10].

Emerging adaptive assist-as-needed impedance control [11], modular wearable exoskeletal robot devices, and integrated sensor systems [12-14] can automate ankle training during gait and provide high intensity repetitive locomotor practice with somatosensory input. In this manner, experience-driven motor learning and neuroplasticity [15] can be maximized. Recommendations on the most effective control strategy and robotic ankle rehabilitation program is unclear, however, due to the heterogeneity of robot devices, small sample sizes and limited randomized controlled trials [16]. An unanswered question is whether the integration of robot-assisted neuromotor ankle control with treadmill training can positively impact the multi-faceted task of overground (OG) walking and have carryover when removed. We conducted a randomized controlled trial to investigate the benefit of precisely timed and graded robotic DF assist within the context of treadmill training to promote human-robotic cooperative locomotor learning across a broad population of individuals with stroke deficits. We hypothesized that treadmill-integrated ankle robot (TMR) training would improve our primary outcomes of DF and walking speed more than treadmill training alone (TM) and would have durable benefits while not wearing the robot 6-weeks and 3 months after training completion. This paper reports the comparative effectiveness of TMR versus TM based on unassisted (non-robotic) gait outcomes of peak paretic ankle dorsiflexion (DF) swing angle, DF angle at foot strike and self-selected OG gait velocity.

### Materials and Methods

This was a parallel group randomized controlled trial utilizing a single blind where assessors were blinded to group assignment. Recruitment and informed consent procedures followed approved practices by the University of Maryland, Baltimore Institutional Review Board and the Baltimore Veterans Affairs Research and Development Committee and the study was conducted in compliance with all ethical practices and guidelines. Randomization using permuted blocks in two strata occurred after baseline testing defined by baseline gait speed where speeds ≥0.5 m/s separated fast walkers from slow walkers. The study statistician sent the concealed computer-generated allocation to the study coordinator upon each assignment via e-mail using study identification number. Subjects were expected to participate 3-times a week in their randomized 6-week gait training program.

#### Subjects

Recruitment occurred between September 2015 through April 2019. Forty-five stroke survivors (28 males and 17 females) met all eligibility criteria and were randomized after baseline data collection to either treadmill robot training using the ankle robot (TMR) or treadmill training alone (TM). Inclusion criteria was as follows: (1) index stroke > 2-months prior to enrollment with residual lower extremity hemiparesis (2) indications of hemiparetic gait and symptoms of foot-drop assessed by clinical observation of poor foot clearance during swing phase and/or gait compensations of increased hip and knee flexion, lower extremity circumduction, or vaulting; (3) not participating in physical therapy; and (4) ability to walk on a treadmill with handrail support. Individuals with unstable angina, heart failure within the last 3 months, poorly controlled hypertension, a recent hospitalization for a severe medical condition, orthopedic or chronic pain, a history of orthopedic related gait problems or severe aphasia limiting informed consent were excluded from the study. All participants signed informed consent and underwent medical evaluations to establish eligibility (Figure 1).

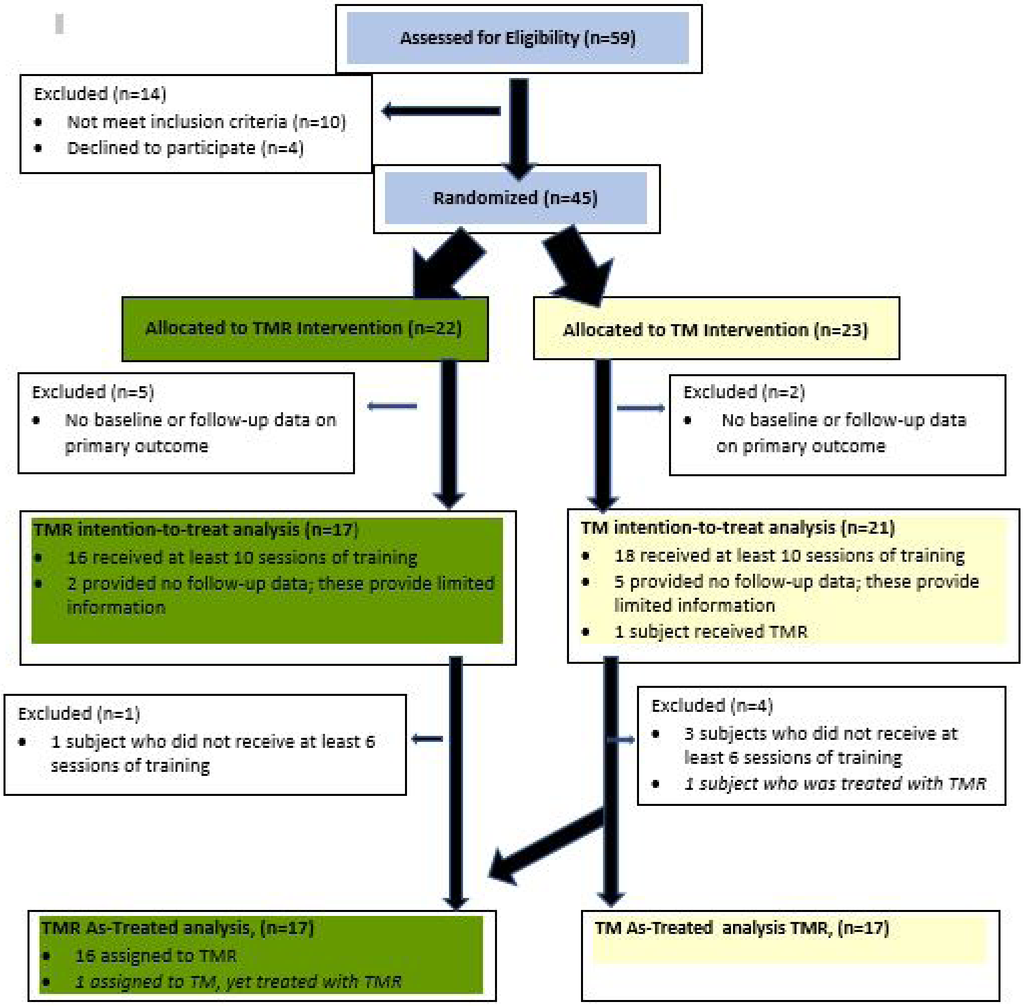


**Figure 1:** Consort diagram.

## Data collection

Assessments were performed in the research lab over a two-day period at baseline, after six weeks of training, and at two retention time points six weeks and three months after training completion by trained research staff blinded to subject randomization and not involved in the intervention. Day one included three Timed 10-Meter Walk Tests (10MWT) over an instrumented gait mat (GAITRite, CIR Systems, Havertown, Pa) to calculate spatiotemporal outcomes of mean gait speed (cm/s), stride length (cm), cadence (steps/min), and relative paretic single support and double support (%-cycle) times. Use of an assistive device (single or multi-point cane) was allowed and the average of the three walks determined self-selected OG walking velocity. Day two included Vicon supported three-dimensional kinematic gait evaluations of the primary paretic ankle DF angle outcomes. The three-dimensional kinematic calculations relied on retro-reflective markers on the anterior and posterior iliac spine, lateral mid-thigh, lateral mid-gastrocnemius, lateral aspect of the foot, the great toe and heel of each leg. Neutral stance alignment or "zero" angle was confirmed based on the lumbosacral (L5/S1) joint, bilateral anterior superior iliac spine, knee joint, ankle joint, and feet before all walking trials. All kinematic variables were expressed with respect to this neutral stance or "zero" angle. Once captured, participants walked with and without the robot across a 7.3-meter-long walkway at the baseline visit. A one-time baseline robot walking assessment calculated robot-wearing OG walking velocity to guide initial treadmill speed parameters for the TMR participants. Additional seated unassisted robot-based ankle metrics and positional data were collected for all time points as described elsewhere [17]. To minimize fatigue, participants had a two-day rest between the walking assessment days.

**Intervention**

All participants were supervised throughout the one-hour training with rest breaks as needed for five walking trials to achieve 30-40 minutes of activity per lab training session. The TM group's initial treadmill speed was matched with the baseline 10MWT and the TMR group's initial treadmill speed was matched with their baseline robot-wearing OG walking speed. Participants were encouraged to increase their treadmill speed or duration at each session and the targeted work intensity range was between 13-to-15 ("somewhat hard" -to- "hard") on the Borg Rating of Perceived Exertion Scale [18]. Training intensity was advanced within this guideline over 18 sessions (3x/week; 6 weeks) and stayed within prescribed heart rate and blood pressure thresholds set at the pre-study training cardiac stress test. AFO's were allowed as needed for the TM training group and removed for robot application in the TMR robot-assisted group.

For the TMR training, a 3-degree of freedom (DOF) wearable ankle exoskeleton (Anklebot; Interactive Motion Technologies; Watertown, MA) with 2-DOF actuation (DF-plantarflexion, inversion-eversion) assisted ankle DF during the treadmill walking as described in the literature [19]. This ankle robot, weighing less than 3.6 kg, had two key fundamental attributes: back-drivability, a feature of the actuators to allow the robot to "get out of the way" of the user based on user performance; and impedance control for gentle human-device assist-as-needed interaction. In brief, the robot commanded DF angles and assistance to normalize foot DF with assist-as-needed re-adjustments in the gait cycle based on a performance-based progression (Figure 2). The robot parameters were re-set and individualized at every session using pre-training ankle range of motion (ROM) and spatial-temporal gait cycle values from a 30 second unassisted robot treadmill walking warm-up trial. Robotic DF swing angle was guided by the warm-up trial ROM and set between 5°-9°. Paretic leg swing and stance cycle time was manually calculated through observation (e.g., average time over 10 strides for the same event) during this warm-up trial. Initial swing and heel-off-to-toe-off percentages were set in this manner; if not available nominal values of 35-40% and 20-25% were assigned for swing and stance respectively. Robotic assistance for the gait sub-events were precisely timed using insole microswitch sensors (Myopac Jr., Run Technologies, Mission Viego, CA). The robot dynamically modulated the DF robotic output (e.g. assist levels) for "human-informed" robotic actuation in the training session [19,20]. The training treadmills did not offer body weight support but were equipped with a support harness for safety in the event of loss of balance. The robot set-up included an adjustable shoulder strap worn by the user to offset the robot's weight and provide anti-gravity support through the swing phase of walking. A minimum of six sessions defined training participation based on the motor learning profile of the unassisted peak paretic swing ankle by Forrester et al. where at least 6 sessions were required for subjects to attain 80% of their steady-state post-training unassisted peak paretic swing ankle value [21].

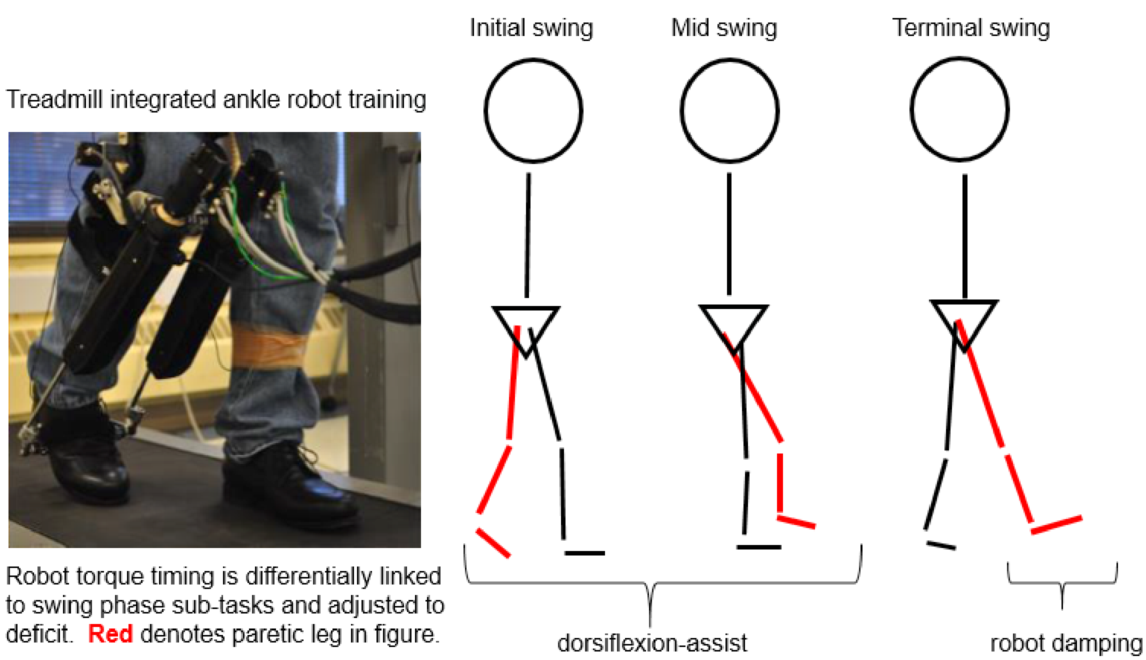


**Figure 2:** Treadmill integrated ankle robot training.

**Sample size**

The target sample size was 72 (36 per group). The sample size was calculated based on a two-sided 0.05-level two sample t-test where 36 participants per group provided 85% power to detect a difference between groups if the mean dorsiflexion changes differed by 0.72 standard deviations (i.e., an "effect size" of 0.72). However only 59 were assessed for eligibility in our ~3.5-year study period due to enrollment difficulties related to pre-existing medical conditions, limitations in transportation, and need for family support/assistance.

**Data analysis**

The analysis was pre-specified, and we report here on gait performance outcomes indexed by peak paretic DF swing angle, DF angle at foot strike, and gait velocity. The groups were compared with respect to the gait outcomes using a longitudinal regression model with outcomes measured at four time points (baseline, after six-weeks of training, and the two retention time points of six-weeks post-training completion (RT1), and three-months post-training completion (RT2). The model allowed for different variances at each time point in each group, and an unstructured within-person correlation pattern [22] and was fit by restricted maximum likelihood. An advantage of this approach over repeated measures ANOVA is that it makes fewer assumptions about the variance structure, it allows for inclusion of those with missing data at some time points, and it implicitly imputes missing values. Due to the randomization, the model incorporated the assumption that the groups were equivalent in expectation at baseline.

The primary analysis was based on the principle of intention to treat (ITT). However, since some of the participants did not contribute any data (baseline or follow-up) for the primary outcomes, these participants were not included in the primary analysis, making this a modified ITT analysis. In a secondary analysis, we compared groups defined by the treatment they received. In this "as treated" (AT) analysis, we excluded those who did not participate in at least six exercise sessions and we crossed one patient over who had been randomized to receive TM, but actually received TMR. In an exploratory analysis, we restricted the analysis to those who satisfied a biomechanical foot drop definition where peak DF swing angle was less than 0º at the swing phase of the gait cycle. Eight subjects (6 randomized to TMR; 2 randomized to TM) met this definition (see supplement).

## Results

Fifty-nine subjects were screened for study enrollment and forty-five proceeded to randomization: 22 to TMR and 23 to TM. The randomized groups were not significantly different in all baseline categories however, more TMR participants used AFOs (61% versus 36%) and 35% were more than six years post-stroke compared to 18% in TM group (Table 1). Seven subjects (5 TMR and 2 TM) did not have baseline or follow-up primary outcome measures and did not allow for imputation therefore these subjects were excluded from the primary (modified) ITT analysis. Among those included in the modified ITT analysis, one subject was randomized to the TM group but received the TMR intervention. This individual was switched to the TMR group for our subsequent "as-treated" analysis. In addition, four (1 in the TMR group and 3 in the TM group) did not participate in at least six exercise sessions and were later excluded from the as-treated efficacy analysis. Of note, all those who participated in at least six sessions received ten or more sessions. Reasons for study attrition included loss of interest (3), transportation issues (1), aggravation of pre-existing knee pain (2), and new onset cardiac issues (1).

| Characteristic | TMR (n=23) | TM (n=22) |
|---|---|---|
| Sex | | |
| Male | 14 (61%) | 14 (64%) |
| Female | 9 (39%) | 8 (36%) |
| Race | | |
| African American | 15 (65%) | 15(68%) |
| Asian | 2 (9%) | 1 (5%) |
| Caucasian | 6 (26%) | 6 (27%) |
| Age | | |
| 18-to-65 years | 8 (35%) | 10 (45%) |
| >= 65 years | 15 (65%) | 12 (55%) |
| Years since stroke | | |
| <2 | 4 (18%) | 2 (9%) |
| 2-4 | 7 (30%) | 9 (41%) |
| 4-6 | 4 (17%) | 7 (32%) |
| 6+ | 8 (35%) | 4 (18%) |
| Paretic Side | | |
| Left | 16 (70%) | 13 (59%) |
| Right | 7 (30%) | 9 (41%) |
| AFO | | |
| No | 9 (39%) | 14 (64%) |
| Yes | 14 (61%) | 8 (36%) |
| Assistive Device (AD) | | |
| No | 4 (17%) | 7 (32%) |
| Yes | 19 (83%) | 15 (68%) |
| Walking Speed (m/s) | | |
| Unable to walk without AD | 6 (26%) | 4 (18%) |
| Limited ambulator (<0.2 m/s) | 0 (0%) | 3 (14%) |
| Household (0.2-0.4 m/s) | 4 (17%) | 3 (14%) |
| Limited Community (0.4-0.8 m/s) | 5 (22%) | 2 (9%) |
| Community (>1.2 m/s) | 8 (35%) | 10 (45%) |

**Table 1:** Participant characteristics.

Primary outcome results are presented in Table 2. Due to randomization, this modified ITT model assumed equivalence in expectation at baseline for all groups. Based on this analysis, no significant week-6 post-training kinematic ankle DF or gait velocity differences were found. The mean post-training peak paretic DF swing angle and DF angle at foot strike was (4.84 p=0.32; 4.24; p=0.73) and (-0.70 p=0.14; -0.46 p=0.14) in TMR and TM respectively and this was neither statistically significant nor did it reach a clinically significant 5-degree increase [4]. Retention ankle DF gains were also not statistically significant. The 6-week mean post-training gait velocity was 0.54 m/s (p=0.0030) and 0.56 m/s (p=0.0008) in TMR and TM respectively, representing similar within group gain at week-6 without between group significance (p=0.48). The within group velocity improvement was significant and durable through retention (3-months post-training completion) in both groups.

For the as-treated cohort, no significant between group difference in ankle DF kinematics and gait velocity was seen. TMR had a within group trend for ankle DF angle gains at foot strike (p=0.07), but no values reached statistical significance. Significant within group gait velocity increases occurred in TMR and TM and were sustained at the three-month retention visit. In a post-hoc analysis of a small subset of subjects meeting strict biomechanically defined foot drop criteria (n=8; 6 TMR, 2 TM), therapeutic improvement in functional ankle DF was seen within group in TMR participants after 6 weeks of training but the small sample size precludes detailed statistical analyses or conclusions (see supplemental data).

| Measure | Time Point | Modified intention-to-treat cohort[2] | | | | | As-treated cohort[3] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TMR (n=17) | | TM (n=21) | | *P*-value[5] | TMR (n=17) | | TM (n=17) | | *P*-value[5] |
| | | Mean (SD) | *P*-value[4] | Mean (SD) | *P*-value[4] | | Mean (SD) | *P*-value[4] | Mean (SD) | *P*-value[4] | |
| Peak DF Angle at swing | BL | 3.95 (6.83) | | 3.95 (6.83) | | | 3.87 (7.22) | | 3.87 (7.22) | | |
| | Post | 4.84 (6.83) | 0.32 | 4.24 (6.83) | 0.73 | 0.63 | 5.07 (7.19) | 0.17 | 3.82 (7.19) | 0.95 | 0.30 |
| | RET1 | 4.34 (6.26) | 0.58 | 3.27 (6.26) | 0.38 | 0.29 | 4.34 (6.58) | 0.51 | 3.13 (6.58) | 0.34 | 0.23 |
| | RET2 | 3.33 (6.72) | 0.56 | 3.43 (6.72) | 0.62 | 0.95 | 3.41 (7.02) | 0.66 | 3.20 (7.02) | 0.52 | 0.88 |
| Peak DF Angle at Foot Strike | BL | -1.83 (5.03) | | -1.83 (7.31) | | | -1.44 (4.68) | | -1.44 (7.69) | | |
| | Post | -0.70 (6.55) | 0.14 | -0.46 (5.70) | 0.14 | 0.84 | -0.06 (6.22) | 0.063 | -0.50 (5.96) | 0.32 | 0.72 |
| | RET1 | -2.18 (6.27) | 0.67 | -2.15 (6.16) | 0.57 | 0.97 | -1.73 (5.96) | 0.72 | -1.95 (6.48) | 0.37 | 0.83 |
| | RET2 | -2.99 (5.96) | 0.28 | -1.58 (6.71) | 0.79 | 0.31 | -2.51 (5.76) | 0.31 | -1.39 (7.01) | 0.96 | 0.42 |
| Gait Velocity[6] (m/s) | BL | 0.48 (0.21) | | 0.48 (0.34) | | | 0.49 (0.21) | | 0.49 (0.35) | | |
| | Post | 0.54 (0.24) | **0.0030*** | 0.56 (0.32) | **0.0008*** | 0.48 | 0.54 (0.24) | **0.0081*** | 0.57 (0.33) | **0.0015*** | 0.31 |
| | RET1 | 0.53 (0.24) | **0.052*** | 0.55 (0.33) | **0.0017*** | 0.54 | 0.53 (0.24) | 0.11 | 0.56 (0.34) | **0.0019*** | 0.30 |
| | RET2 | 0.52 (0.23) | **0.052*** | 0.55 (0.33) | **0.0014*** | 0.10 | 0.53 (0.23) | **0.041*** | 0.58 (0.36) | **0.011*** | 0.23 |

**Abbreviations:** *BL* baseline, *DF* dorsiflexion, *SD* standard deviation, *RET1* Retention visit one at 6 weeks post-training, *RET2* Retention visit two at 3 months post-training, *TM* treadmill training, *TMR* Treadmill-integrated ankle robot training.

**Table 2:** Model-based estimated means[1] of the three primary measures by treatment for the primary analysis.

Between group comparisons are the primary outcome and were not significant in the modified intention to treat or the as-treated cohort. Within group comparisons were significant for within group comparisons in both cohorts and noted in bold.

[1]Model based estimates of expectation of outcomes at each time point. Due to randomization, model assumes equivalence in expectation at baseline. *significance p<0.05.

[2]Includes each subject in the group to which they were randomized irrespective of what intervention (if any) was actually received)

[3]Includes each subject based on the treatment received and excludes those who did not attend at least 6 sessions.

[4]*P*-value for changes from baseline within group based on a longitudinal regression model.

[5]*P*-value for statistical significance of difference between groups based on a longitudinal regression model.

[6]Gait Velocity measured either using or not using an assistive device.

### Treatment fidelity

We examined participant adherence to the three-times weekly intervention and the amount of training time received at each visit. Over the six-week training period, TMR had greater training visit adherence and TM had a greater treadmill training time (Table 3). Overall, TMR trained for fewer minutes per visit compared to TM, respectively (22.0 minutes; 33.6 minutes p=0.04).

| Parameter | Group | Median | Min/Max | P-value[1] |
|---|---|---|---|---|
| Number of visits | TMR | 18 | 18/18 | 0.013 |
| | TM | 18 | 3/18 | |
| Duration (minutes) | TMR | 22.0 | 13/17 | 0.040 |
| | TM | 33.6 | 10.7/52.3 | |
| Treadmill Speed (mph) | TMR | 1.01 | 0.21/1.48 | 0.068 |
| | TM | 1.41 | 0.26/2.98 | |
| Heart Rate (bpm) | TMR | 109.4 | 76.2/141.2 | 0.37 |
| | TM | 107.7 | 75.2/135.0 | |
| [1]P-value based on a two-sample Wilcoxon test using a t-approximation. | | | | |
| **Abbreviations:** TMR treadmill robotic training; TM treadmill. | | | | |

**Table 3:** Training adherence and performance parameters.

## Discussion

This randomized study in persons with chronic hemiparetic stroke found that ankle robotics integrated with treadmill training was not superior to a matched amount of treadmill training alone for clinically diagnosed foot drop. Both interventions improved gait velocity, and this was sustained throughout each retention period. Difficulty reaching our target number of subjects, randomization based on gait velocity and use of a clinical definition of ankle dysfunction may have limited our findings. Future studies that enroll a larger number of subjects, uses a randomization stratum that balances key gait determinates like AFO use, and employs eligibility criteria based on a biomechanical definition of ankle dysfunction are needed to further determine the effectiveness of integrated ankle robot (TMR) treadmill training on paretic ankle motor control and gait performance.

### Foot drop outcomes

Several ankle specific robot studies have shown an immediate benefit, or an assistive effect, on ankle dorsiflexion while the device is worn [23-25]. These studies utilized a variety of exoskeletal designs and control strategies and showed an immediate effect of robot-assisted treadmill training on walking performance. Few studies examine the rehabilitative or lasting therapeutic effect of ankle joint-specific robotic gait training [14,26,27]. In addition, robotic control strategies vary widely and the best type of controller to maximize human-robot ankle rehabilitation has yet to be determined [26]. One strategy using a seated ankle robot paradigm, showed improved paretic motor function and positive unassisted walking gains in early and chronic stroke recovery [17,26]. An expansion of this paradigm in a small study using treadmill-based ankle robot training found this combined training to be more effective in improving unassisted gait in chronic hemiparetic stroke [21].

Our RCT sought to determine the therapeutic effect of repetitive ankle robot treadmill training on walking biomechanics and speed in individuals with chronic stroke deficits. When considering the intention to treat analyses for all randomized persons with clinical foot-drop, there were no significant differences in ankle dorsiflexion outcomes. This may be a reflection of the ambulatory status of our groups or the heterogeneity of hemiparetic gait. Baseline status, however, not statistically significant, may have limited the impact of the intervention on outcomes due to a higher percentage of AFO use, stroke chronicity, and slower walking ability in the TMR group. We did not biomechanically define our inclusion criteria, and this may have resulted in variability of deficits. There are a variety of altered kinematic walking patterns post-stroke and strategies to compensate for foot drop during paretic swing phase can occur in the frontal and sagittal plane [28,29]. Our intervention focused on sagittal plane ankle (dorsiflexion) deficits and did not account for potential frontal plane strategies (pelvic hiking, hip circumduction). A key finding of this study is that participant selection for robot-assisted ankle dorsiflexion trials should include biomechanically defined parameters for foot drop. In this manner, predominant sagittal plane ankle deficits can be identified with greater certainty than solely relying on clinical observation where the heterogeneity of deficits (i.e.: strength, spasticity, ROM, diminished sensation) and compensatory movement strategies make it difficult to discern. We estimate a large percentage of persons with hemiparetic gait would meet this conditional criterion given the extensive use of AFO's. Moreover, a more rigorous biomechanical definition would assist in identifying treatment responders versus non-responders.

### Gait velocity outcomes

Gait velocity improved similarly in both groups by a range of approximately 11-15% for unassisted timed walks. This is consistent with the literature showing that treadmill training translates into faster self-selected OG gait velocity in persons with chronic stroke [30-32]. Notably, our treatment fidelity tracking shows that the TMR group spent approximately 33% less time in actual training and trained at approximately 26% slower training velocities, compared to TM alone. These findings suggest that the dose-intensity characteristics of ankle robotics integrated treadmill training are different than those for TM alone to increase OG walking velocity, and indeed training time may be lower to produce comparable gains. While this study cannot determine the mechanisms for these differences, compensatory walking strategies common post-stroke can produce functional walking speeds despite poor coordination of the paretic leg [29,33]. Improved gait as measured by self-selected walking speed is not necessarily accomplished by a normalized gait pattern [29]. Inadequate ankle joint DF can be the result of plantarflexor spasticity, passive joint stiffness, muscle weakness or poor motor control and each can alter different aspects of gait performance [2]. Identifying the predominating ankle joint impairment may assist in determining intervention requirements to effectively improve gait. In summary, TMR and TM may improve walking speed by different compensatory strategies, which may impact dose-intensity of training and outcomes. Further studies are needed to understand differences in impairment, dose-intensity and the efficiencies of robotic versus non-robotic locomotor training after stroke.

## Study Limitations

Study limitations include a small sample size, enrollment of subjects at different stages of stroke chronicity (several months to 6+ years), and inclusion criterion based on clinical diagnosis of foot drop rather than a strict biomechanical definition. As a result, our inclusion criteria may have contributed to variable treatment responses influenced by chronicity and functional ability. Although the groups were not statistically different, the TMR group presented with greater stroke chronicity and reliance on AFO use. Neuromotor learning and physical activity dependent brain plasticity can occur, even years after a stroke [7,34] however these changes are associated with high volumes of motor practice, rich sensory input, and challenging experiences [35]. The increased reliance on AFO use outside the intervention time may have contributed to less potential change. Another consideration was the exercise training progression. Participants were encouraged to increase their time and treadmill speed each session, but in practice the treadmill speed was defaulted to the participants' reported level of comfort and tolerability. While reflective of exercise training in general community practice, this may have introduced differences in intensity and response. Additionally, training was limited to a dorsiflexion-assist paradigm, leaving out potential benefits of training ankle plantarflexion for improved propulsion or inversion-eversion movements for improved mediolateral control and foot stability [26,33].

## Conclusion

We found that integrating adaptive ankle robotics into task-specific treadmill training was not significantly better than treadmill training alone. Both interventions improved gait velocity. Further studies are needed to determine the benefit of robotics to improve gait in specific subgroups defined by deficit severity and recovery phase and to consider earlier application where literature review suggests exoskeleton training in the sub-acute phase may confer added benefits [36].

## Acknowledgements

The authors would like to thank Erica Cikanek for her contributions to data collection and study coordination and Dr. Leslie Katzel for his critical review of the manuscript.

## Funding

This work was supported by Merit Review Award N1699-R from the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service. This material is the result of work supported by the Baltimore VA Geriatric Research, Education, and Clinical Center (GRECC) and VA Maryland Health Care System, Baltimore, Maryland. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

## COI

Two authors, Drs. Anindo Roy and Richard Macko, declare a potential conflict of interest as inventors on U.S. Patent Pending "Method and apparatus for providing deficit-adjusted adaptive assistance during movement phases of an impaired joint (application no.14/549.370) and hold equity positions in Next Step Robotics Inc., a company that manufactures a similar type of robotic technology. The robot used in this study differed significantly in function and design. Drs. Roy and Macko contributed to funding submission, study design, and authorship but were not involved in data analysis. All analysis was performed by the study statistician Dr. Magder.

**Clinical Trial Registration:** Clinical trials.gov id: NCT02483676. Registered June 29, 2015, https://clinicaltrials.gov/ct2/show/NCT02483676

## References

1. Peishun C, Haiwang Z, Taotao L, Hongli G, Yu M, et al (2021) Changes in gait characteristics of stroke patients with foot drop after the combination treatment of foot drop stimulator and moving treadmill training. Neural Plast.
2. Lin PY, Yang YR, Cheng SJ, Wang RY (2006) The relation between ankle impairments and gait velocity and symmetry in people with stroke. Arch Phys Med Rehabil 87: 562-568.

3. Ng SS, Hui-Chan, CW (2012) Contributions of ankle dorsiflexor strength to walking endurance in people with spastic hemiplegia after stroke 93: 1046-1051.
4. Shin B, Chen X, Yue Z, Yin S, Weng , et al. (2019) Wearable ankle robots in post-stroke rehabilitation of gait: A systematic review. Front Neurorobot 13: 63.
5. Ramnemark A, Nyberg L, Borssen B, Olsson T (1998) Fractures after Stroke. Osteoporos Int 8: 92–95.
6. Bosch PR, Harris JE, Wing K (2014) Review of therapeutic electrical stimulation for dorsiflexion assist and orthotic substitution from the American Congress of Rehabilitation Medicine Stroke Movement Interventions Subcommittee. Arch Phys Med and Rehab 95: 390-396.
7. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, et al. (2014) What is the evidence for physical therapy post-stroke? A systematic review and meta-analysis. PLoS One 9: e879-887.
8. Kluding PM, Dunning K, O'Dell MW, Wu SS, Ginosian J, et al. (2013) Foot drop stimulation versus ankle foot orthosis after stroke: 30-week outcomes. Stroke 44: 1660-1669.
9. Sheffler LR, Bailey SN, Wilson RD, Chae J (2013) Spatiotemporal, kinematic, and kinetic effects of a peroneal nerve stimulator versus an ankle foot orthosis in hemiparetic gait. Neurorehabil Neural Rep 27: 403-410.
10. Everaert DG, Stein RB, Abrams GM, Dromerick AW, Grancisco GE, et al. (2013) Effect of a foot-drop stimulator and ankle-foot orthosis on walking performance after stroke: A multicenter randomized controlled trial. Neurorehabil Neural Rep 27: 579-591.
11. Hogan N (1984) Impedance control: An approach to manipulation: 1984 American Control Conference, San Diego, CA, USA.
12. Bae J, Siviy C, Rouleau M, Menard N, O'Donnell K, et al. (2018) A lightweight and efficient portable soft exosuit for paretic ankle assistance in walking after stroke: 2018 IEEE International Conference on Robotics and Automation, Brisbane, Australia: 2820-2827.
13. Yeung L, Ockenfeld C, Pang M, Wai H, Soo O, et al. (2018) Randomized controlled trial of robot-assisted gait training with dorsiflexion assistance on chronic stroke patients wearing ankle-foot-orthosis. J NeuroEngineering Rehabil 15: 51.
14. Roy A, Krebs HI, Barton JE, Macko RF, Forrester LW (2013) Anklebot-assisted locomotor training after stroke: a novel deficit-adjusted control approach. In: Proceedings IEEE Int Conf Rob Auto (ICRA), Karlsruhe, Germany: IEEE: 2175-2182.
15. Marchal-Crespo L, Reinkensmeyer DJ (2009) Review of control strategies for robotic movement training after neurologic injury. J Neuroeng Rehab 6: 20.
16. Zhang M, Davies CT, Xie S (2013) Effectiveness of robot-assisted therapy on ankle rehabilitation-a systematic review. J NeuroEng Rehabil 10: 2-16.
17. Forrester LW, Roy A, Krebs HI, Macko RF (2011) Ankle training with a robotic device improves hemiparetic gait after a stroke. Neurorehabil Neural Rep 25: 369-377.
18. Williams N (2017) The borg rating of perceived exertion (RPE) scale. Occupational Medicine 67: 404-405.
19. Roy A, Krebs HI, Williams DJ, Bever CT, Forrester LW, et al. (2009) Robot-aided neurorehabilitation: A robot for ankle rehabilitation. IEEE Trans Rob 25: 569-582.
20. Roy A, Krebs HI, Barton R, Macko RF, Forrester L (2013) Anklebot-assisted locomotor training after stroke: A novel deficit-adjusted control approach. 2013 IEEE International Conference on Robotics and Automation, Kurlsruhe, Germany: 2175-2182.
21. Forrester LW, Roy A, Hafer-Macko C, Krebs HI, Macko RF (2016) Task-specific ankle robotics gait training after stroke: A randomized pilot study. J NeuroEng Rehabil 13: 51.
22. Magder L (2011) Modelling the Covariance. In: Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis 2nd edition. Wiley: 168.
23. Dollar AM, Herr H (2008) Lower extremity exoskeletons and active orthoses: challenges and state-of-the-art," in IEEE Transactions on Robotics 24: 144-158.
24. Shorter KA, Xia J, Hsiao-Wecksler ET, Durfee WK, Kogler GF (2013) Technologies for powered ankle-foot orthotic systems: Possibilities and challenges," in IEEE/ASME Transactions on Mechatronics 18: 337-347.
25. Awad LN, Bae J, O'Donnell K, DeRossi SM, Hendron K, et al. (2017) A soft robotic exosuit improves walking in patients after stroke. Sci Transl Med 9: 1-12.
26. Forrester LW, Roy A, Goodman RN, Rietschel J, Barton JE, et al. (2013) Clinical application of a modular ankle robot for stroke rehabilitation. NeuroRehabilitation 33: 85-97.
27. Srivastava S, Kao P, Kim SH, Stegall P, Zanotto D, et al. (2015) Assist-as-needed robot-aided gait training improves walking function in individuals following stroke. IEEE Trans Neural Syst Rehabil Eng 23: 956-963.
28. Olney SJ, Richards C (1996) Hemiparetic gait following stroke. Part I: Characteristics. Gait and Posture 4: 136-148.
29. Stanhope VA, Knarr BA, Reisman DS, Higginson JS (2014) Frontal plane compensatory strategies associated with self-selected walking speed in individuals post-stroke. Clin Biomech 29: 518-522.
30. Macko RF, Ivey FM, Forrester LW (2005) Task-oriented aerobic exercise in chronic hemiparetic stroke: Training protocols and treatment effects. Top Stroke Rehabil 12: 45-47.
31. Liston R, Mickelborough J, Harris B, Hann WE, Tallis RC (2000) Conventional physiotherapy and treadmill re-training for higher-level gait disorders in cerebrovascular disease. Age Ageing 29: 311–318.
32. Mehrholz J, Thomas S, Elsner B (2017) Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev 8: CD002840.
33. Bowden MG, Balasubramanian CK, Neptune RR, Kautz SA (2006) Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. Stroke 37: 872-876.
34. Langhorn P, Sandercock P, Prasad K (2009) Evidence-based practice for Stroke. Lancet Neurol 8: 308-309.
35. French B, Thomas LH, Coupe J, McMahon NE, Connell L, et al. (2016) Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev 11: CD006073.
36. Louie DR, Eng JJ (2016) Powered robotic exoskeletons in post-stroke rehabilitation of gait: A scoping review. J NeuroEngineering Rehabil.