

Changes in passive ankle stiffness and its effects on gait function in people with chronic stroke

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Abstract—Mechanical impedance of the ankle is known to influence key aspects of ankle function. We investigated the effects of robot-assisted ankle training in people with chronic stroke on the paretic ankle's passive stiffness and its relationship to overground gait function. Over 6 wk, eight participants with residual hemiparetic deficits engaged in a visuomotor task while seated that required dorsiflexion (DF) or plantar flexion (PF) of their paretic ankle with an ankle robot (“anklebot”) assisting as needed. Passive ankle stiffness (PAS) was measured in both the trained sagittal and untrained frontal planes. After 6 wk, the PAS decreased in both DF and PF and reverted into the variability of age-matched controls in DF. Changes in PF PAS correlated strongly with gains in paretic step lengths (Spearman rho = -0.88 , $p = 0.03$) and paretic stride lengths (Spearman rho = -0.82 , $p = 0.05$) during independent floor walking. Moreover, baseline PF PAS were correlated with gains in paretic step lengths (Spearman rho = 0.94 , $p = 0.01$), paretic stride lengths (Spearman rho = 0.83 , $p = 0.05$), and single-support stance duration (Spearman rho = 0.94 , $p = 0.01$); and baseline eversion PAS were correlated with gains in cadence (Spearman rho = -0.88 , $p = 0.03$). These findings suggest that ankle robot-assisted, visuomotor-based, isolated ankle training has a positive effect on paretic ankle PAS that strongly influences key measures of gait function.

Key words: ankle impairment, ankle robot, ankle stiffness, chronic stroke, foot drop, hemiparetic gait, lower limb, motor control, rehabilitation, robotic therapy.

INTRODUCTION

With nearly 800,000 Americans experiencing a stroke each year [1], stroke rehabilitation remains a challenge. In the lower limb, a common condition that occurs following a stroke is weakness in the dorsiflexor muscles that lift the foot during walking, commonly referred to as “drop foot.” The two major complications of drop foot—slapping of the foot after heel strike (foot slap) and dragging of the toe during swing (toe drag)—present a major challenge to

Abbreviations: A/P = anterior-posterior, AROM = active range of motion, bEMG = background electromyography, DF = dorsiflexion, DOF = degree of freedom, DST = double-support stance, EMG = electromyography, EV = eversion, GAS = gastrocnemius, GRECC = Geriatric Research Education and Clinical Center, HC = home, INV = inversion, LC = limited community, MIT = Massachusetts Institute of Technology, PAS = passive ankle stiffness, PF = plantar flexion, PMS = prolonged muscle stretch, PROM = passive range of motion, ROM = range of motion, SD = standard deviation, SPCA = summed physiological cross-sectional area, SST = single-support stance, STP = step, STR = stride, TA = tibialis anterior, VA = Department of Veterans Affairs, VAMC = Department of Veterans Affairs Medical Center. *Address all correspondence to Anindo Roy, PhD; VA Maryland Healthcare System, Baltimore VAMC Annex, 209 W Fayette St, Ste 214, Baltimore, MD 21210; 410-200-0894; fax: 410-605-7913. Email: ARoy@som.umaryland.edu <http://dx.doi.org/10.1682/JRRD.2011.10.0206>

efficient gait since clearing the ground during the swing phase and maintaining ankle stability during the stance phase are essential for efficient gait. The ankle plays a fundamental role in locomotion in several ways. First, it contributes to the maintenance of stable upright posture in the frontal and sagittal planes during gait. Second, the ankle contributes to shock absorption during locomotion by attenuating the impact force at floor contact [2]. Third, the ankle muscles are the primary contributors to over-ground gait—the soleus is the propulsion prime-mover, the gastrocnemius (GAS) is the posture prime-mover, and the tibialis anterior (TA) is critical for toe-off [3]. All these aspects of ankle function may be characterized by its active and passive mechanical impedance, i.e., stiffness plus damping and any other dynamic factors. Studies have shown that humans adjust leg stiffness to accommodate surface changes [4–5] and changes in gait speed [6] primarily by modulating ankle stiffness [5–6]. Adequate ankle impedance is also needed to control body momentum (forward and downward vector components of the body center of mass) during gait [7].

The mechanical impedance of a joint is a function of both passive (e.g., mechanical stiffness of ligaments, tendons, and connective tissue) and active (e.g., muscle activation, contraction mediated by stretch reflex) mechanisms. In physical terms, passive stiffness is the change in tension per unit change in length (massless “spring” analogy), or in the context of muscle mechanics, it may be defined as the resistance to elongation or shortening of a muscle when it is quiescent, thus generating passive tension. Studies suggest that the series elastic and parallel elastic elements of muscle (e.g., tendon, structural proteins within the myofibril, connective tissue around the muscle fibers, and fascicles) play a role in generating this passive tension [8]. Evidence from animals [9] as well as disabled [10] and nondisabled [10] humans suggests that the stiffness accompanies a shortening of the muscle belly through the loss of sarcomeres in series. Studies have reported that structures such as perimysium that contain collagen within the muscle tendon unit contribute to passive stiffness, mostly at end-range (long sarcomere lengths). Within the physiological range of muscle length change, passive stiffness has been attributed to protein structures within the myofibril, such as titin [11–12].

In impaired patients, hypertonus and/or reflex hyperexcitability (spasticity) often disrupt the functional use of already-weakened muscles [13]. In fact, the manifestation of increased motor neuron excitability and an

increased resistance to passive movement have been observed in clinical assessments [14–18]. In addition, structural changes of muscle fibers and connective tissue may contribute to alterations in the intrinsic mechanical properties, e.g., stiffness of a joint. Our previous study [19], for instance, demonstrated that individuals with stroke have abnormal levels of passive ankle stiffness (PAS) at the paretic ankle in addition to complications such as hypertonia and spasticity [18–19].

Despite the ankle’s important role in locomotion, few rehabilitation practices actually focus on training the impaired ankle. Techniques such as prolonged muscle stretch (PMS) have been shown to increase the passive range of motion (PROM), decrease the passive resistance of ankle dorsiflexors, and suppress hypertonia [20]; however, these techniques tend to be highly subjective or preferential with little or no quantitative guidelines for clinical practitioners. To our knowledge, few studies have focused on the long-term effects of repeated stretching of hemiparetic ankles [20–21] and even fewer have measured and monitored changes in ankle stiffness over the course of some intervention [21–23]. Even so, it remains unclear whether changes in sagittal or frontal plane PAS affect locomotor function.

We have deployed in the clinic an impedance-controlled ankle robot (anklebot) [24] developed at the Massachusetts Institute of Technology (MIT) and are testing it with patients with chronic stroke at the Baltimore Department of Veterans Affairs (VA) Medical Center (VAMC). This 3-degrees of freedom (DOFs) wearable device provides actuation in two of these DOFs, namely dorsiflexion (DF)-plantar flexion (PF) and inversion (INV)-eversion (EV) [24]. In a recent study [25], we demonstrated that people with chronic stroke who used the anklebot for 6 wk (3 times/wk) to play a video game in a seated position with their paretic ankle in DF-PF ranges had reduced paretic ankle impairments (increased active range of motion [AROM] in PF), improved paretic ankle motor control (increased mean and peak speed, smoothness, and accuracy of ankle targeting), and increased unassisted floor-walking speeds as well as improvements in key spatiotemporal gait parameters (higher cadence, paretic stride [STR] length, and longer single-support stance [SST] duration with concomitantly shorter double-support stance [DST] duration). Using procedures described previously [19], we used the anklebot to estimate PAS in both DF-PF and INV-EV ranges of motion (ROMs) over the course of training in a sample of eight subjects with chronic stroke,

and we present additional data and analysis here as a follow-up to Roy et al. [19].

Our objective here was to evaluate the effects of visuomotor-guided, performance-based, progressive anklebot training on paretic PAS in chronic stroke and to assess the relationship between those changes and selected aspects of unassisted overground gait. In light of prior findings on passive ankle stretching [20–23] as well as our experience in upper-limb rehabilitation in stroke [26–33], we hypothesized that after 6 wk of anklebot training, the paretic PAS would change in the trained sagittal plane, i.e., DF-PF, but not in the untrained frontal plane, i.e., INV-EV. Moreover, we expected that, to be functionally meaningful, a robotic treatment protocol must emphasize a sequence and timing of sensorimotor stimuli similar to those naturally occurring during gait. Hence, we also hypothesized that changes in PAS resulting from training in the seated position would not carry over and confer improvements in functional recovery, e.g., gait.

METHODS

Participants

Eight subjects with chronic-stage stroke (6 female, 2 male) participated in this single-arm pilot study and were the same subjects we studied in a previous report [25]. Subjects were older than 21 yr at the time of examination, had their stroke more than 6 (ischemic) or 12 (hemorrhagic) mo preceding the study, had completed all conventional physical therapy prior to enrollment, possessed adequate language and neurocognitive function to comprehend instructions, and had residual hemiparetic gait and paretic ankle deficits. All subjects underwent routine medical and cardiovascular evaluations in the Baltimore VA Geriatric Research Education and Clinical Center (GRECC) Assessment Clinic prior to study enrollment.

Apparatus (Anklebot)

MIT's anklebot was used for training as well as stiffness measurement. Its design and measurement capabilities have previously been described [24]. Briefly, the impedance-controlled anklebot (Interactive Motion Technologies; Watertown, Massachusetts) is an exoskeleton that is backdriveable, possesses intrinsically low mechanical impedance, and allows normal ROM in all three DOFs of the foot relative to the shank during walking or while seated but provides independent, active assistance or resistance in only DF-PF and INV-EV.

Procedures

Training Protocol

Training procedures are described in detail elsewhere [25]. We report only the main features here. Subjects sat in a “barber’s” chair, wearing the anklebot on their paretic leg with the knee flexed at 45° and the heel placed on a base to provide a pivot point, thus isolating the foot so it could move freely about the ankle (**Figure 1(a)**). Training was three times per week and consisted of subjects playing a video game with their paretic ankle by making alternate movements in DF and PF, which moved a robot-controlled cursor “up” or “down” on a display screen in order to pass through targets that approached across the display screen at different vertical levels. Target locations were set at ± 80 and ± 40 percent of AROM in each direction. Each session, during which subjects made 560 targeted ankle movements, consisted of eight blocked trials, with the first and last being “record-only” blocks consisting of 40 targets (at 0.25 Hz) without any robotic assistance, while the six intermediate blocks each consisted of 80 targets (0.44 Hz) with robotic assistance decreased incrementally after every two blocks (100 Nm/rad to 50 Nm/rad to 25 Nm/rad). Note that when a target appeared in DF or PF, the robot generated torques as per the target location (which determined the command voltages to the motors); however, ankle movement was uncontrolled and unactuated in the INV-EV directions (i.e., no voltages were commanded to the motors in these directions)—in other words, the ankle was free to move in the untrained frontal plane. To sustain subject motivation, the video game adopted a performance-based progression algorithm (**Figure 2**) that included increasing the target ROM by 10 percent in weeks 3–4 and frequency of target presentation by 0.06 Hz in weeks 5–6 in the assisted trials, but only if tolerated; in this context, achieving at least 64 out of 80 targets in at least one assisted block with the new settings. Otherwise, we used the prior settings. We held the target presentations for the record-only trials constant throughout the training program.

Stiffness Measurement

The PAS measurement procedure has been previously described in detail [19]. Briefly, the anklebot stretched the paretic ankle at a constant (5°/s) velocity according to ramp up-hold-ramp down positional reference trajectory (**Figure 1(b)**). The rationale to stretch the ankle at 5°/s (both ramp

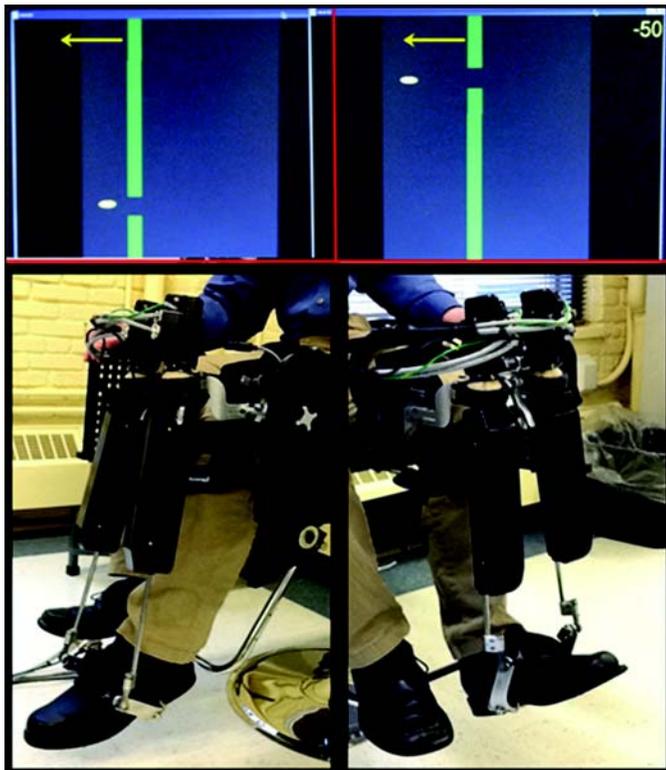


Figure 1.

Experimental setup showing subject with stroke training with Department of Veterans Affairs-Massachusetts Institute of Technology ankle robot (anklebot) in seated position while playing visually evoked, visually guided ankle targeting video game. Arrows denote motion of vertical gates that serve as targets for anklebot- and foot-controlled cursor. Subject is required to either plantar flex (left column) or dorsiflex (right column) his or her ankle from current position to move cursor toward appropriate approaching gate with anklebot assisting “as needed.” Bottom panel shows close-up view of subject’s foot movement in either dorsiflexion (DF) or plantar flexion (PF) while playing video game or, during stiffness assessment, when ankle is passively stretched by anklebot to measure torque-angle data used to estimate passive ankle stiffness. Knee brace (partly seen) is mounted to fixed plate that supports anklebot and restricts translational (but not rotational) knee movements, effectively isolating ankle movements in either DF-PF or inversion-eversion planes.

up and ramp down) was to avoid evoking stretch reflex, as reported in other studies [15,19,34–35]. Under the relaxed condition, subjects experienced a series of perturbations during which the ankle was stretched to a commanded position, held at steady state for 1 s, and returned to neutral. The

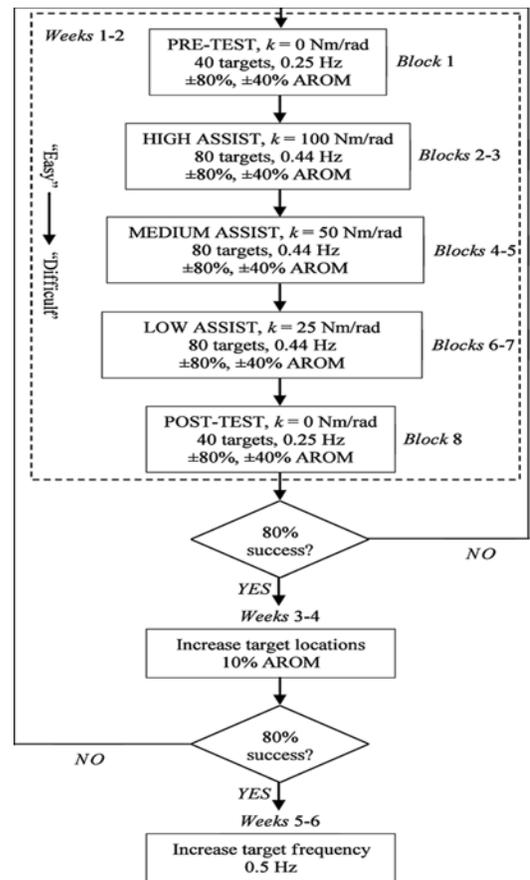


Figure 2.

Algorithm used for performance-based progressive training over 6 wk training period. Target locations in visuomotor task are set at each subject’s baseline active range of motion (AROM) for both directions (dorsiflexion and plantar flexion). “Easy-to-difficult” sequence in terms of progressively decreasing robotic support, determined by stiffness setting: K (Nm/rad), is same for each visit throughout training, but task difficulty in terms of vertical location of targets (challenging AROM) and speed of targets (challenging speed of ankle targeting) on screen are adjusted in weeks 3–4 and 5–6, respectively, based on prior subject performance in order to provide challenge where applicable (at least sustained 80% targetting success without robotic assistance in weeks 1 and 2) and sustain subject motivation.

range of stretch amplitudes depended on the plane and direction of movement; in the sagittal plane, displacements ranged from 20° in PF to the subject’s PROM in DF. In the frontal plane, stretch amplitudes ranged from 25° in INV to 20° in EV. Stretches were made in 5° increments (e.g., neutral to ±5° and back to neutral, neutral to ±10° and back to

neutral, and so on). Note that during stretch in one plane of movement (e.g., sagittal), the other plane of movement (e.g., frontal) was completely uncontrolled without any resistance or assistance, i.e., no movement (voltages) were commanded (see “Discussion” section for more details). Consistent with our previous study [19], we considered angles and torques in DF and EV positive and those in PF and INV negative. To ensure repeatability, subjects conducted each stretch three times at a given amplitude.

Outcome Evaluation

Measures

The primary outcome measure was PAS in the sagittal and frontal planes, evaluated at baseline, midpoint (3 wk), and termination (discharge), employing methods described elsewhere [19]. Data on paretic ankle impairment (e.g., DF-PF AROM and PROM, dorsiflexor strength, and Modified Ashworth scores), motor control, and measures of overground gait function have been previously reported [25]. Here, we report only the salient features of the stiffness measurement, assessment of gait outcomes, and computation of measures of ankle motor control.

Passive Ankle Stiffness Computation

We estimated PAS in each direction by fitting the pair-wise steady-state torque and angle data using least-squares linear regression (**Figure 3**) [19]. To minimize the confounding effects of any nonlinearities in the torque-angle curves (which may yield different stiffnesses at different operating ranges), we identified “outliers” and excluded them from the data analyses. We defined outliers as those data points that corresponded to either (1) actuator saturation, i.e., when the physical “hard limit” was reached during a stretch; or (2) “observable” nonlinearity, e.g., an isometric condition (finite torque but negligible movement), occurring typically at limbs of movement where the torque-angle relationship tended toward a vertical asymptote-type behavior.

Electromyography

To confirm our assumption of zero voluntary contribution during passive stretch, we recorded surface electromyography (EMG) (patch electrode with snap connector and encapsulated preamplifiers, Cadwell Laboratories, Inc; Kennewick, Washington) from both the paretic and nonparetic primary plantar flexor (GAS) and dorsiflexor (TA) muscles [19]. We recorded EMG from ipsilat-

eral (paretic) as well as contralateral (nonparetic) muscles in order to compare and establish background (quiescent muscle) activity. We sampled EMG recording at 1 kHz, commenced 5 s prior to the onset of each stretch, and continued until hold phase was completed. The raw EMG signals were filtered using an eighth-order, zero-lag, high-pass Butterworth filter with cutoff frequency of 475 Hz and subsequently rectified and de-trended. We established a baseline measure of background EMG (*bEMG*) as the average EMG activity in an artifact-free time window of 5 s prior to the onset of stretch. During each stretch, we compared the mean EMG activity against $bEMG \pm 1$ standard deviation (SD). Moreover, in order to identify presence of potential transient stretch reflex activity, we compared the EMG amplitude at each sample during stretch with its corresponding $bEMG \pm 1$ SD.

Gait Assessments

Subjects performed overground walking at self-selected comfortable speed on an 8 m instrumented walkway (CIR Systems; Sparta, New Jersey) with at least two STRs before the start and after the end for acceleration and deceleration [25]. Subjects walked without the use of any assistive devices. We did not include first and last steps (STPs) in the analyses to eliminate partial foot contacts at the extremes of the recording area. Spatiotemporal outcomes included mean speed (centimeters per second), paretic STR and paretic STP lengths (centimeters),* cadence (steps per minute), paretic-to-nonparetic STP length, and paretic single support and double support (%-cycle). Subjects repeated all tests three times, with 1 min rests between them, and we used the average across the three trials for analysis. We performed gait assessments at three time points during the training program: at baseline,† at 3 wk, and at termination or discharge (6 wk).

*We calculated paretic STP length as the distance between the points of heel strike of the nonparetic and paretic foot. We calculated STR length as the distance between successive points of heel strike of the paretic leg.

†For baseline and termination (discharge), we conducted gait assessments 1 wk before and after the first and last training visit, respectively. At 3 wk, we conducted the gait assessment on the same day as training but after a break (~30 min to 1 h) following the training session in order to maximize or “wash out” any potentially confounding effects resulting from fatigue.

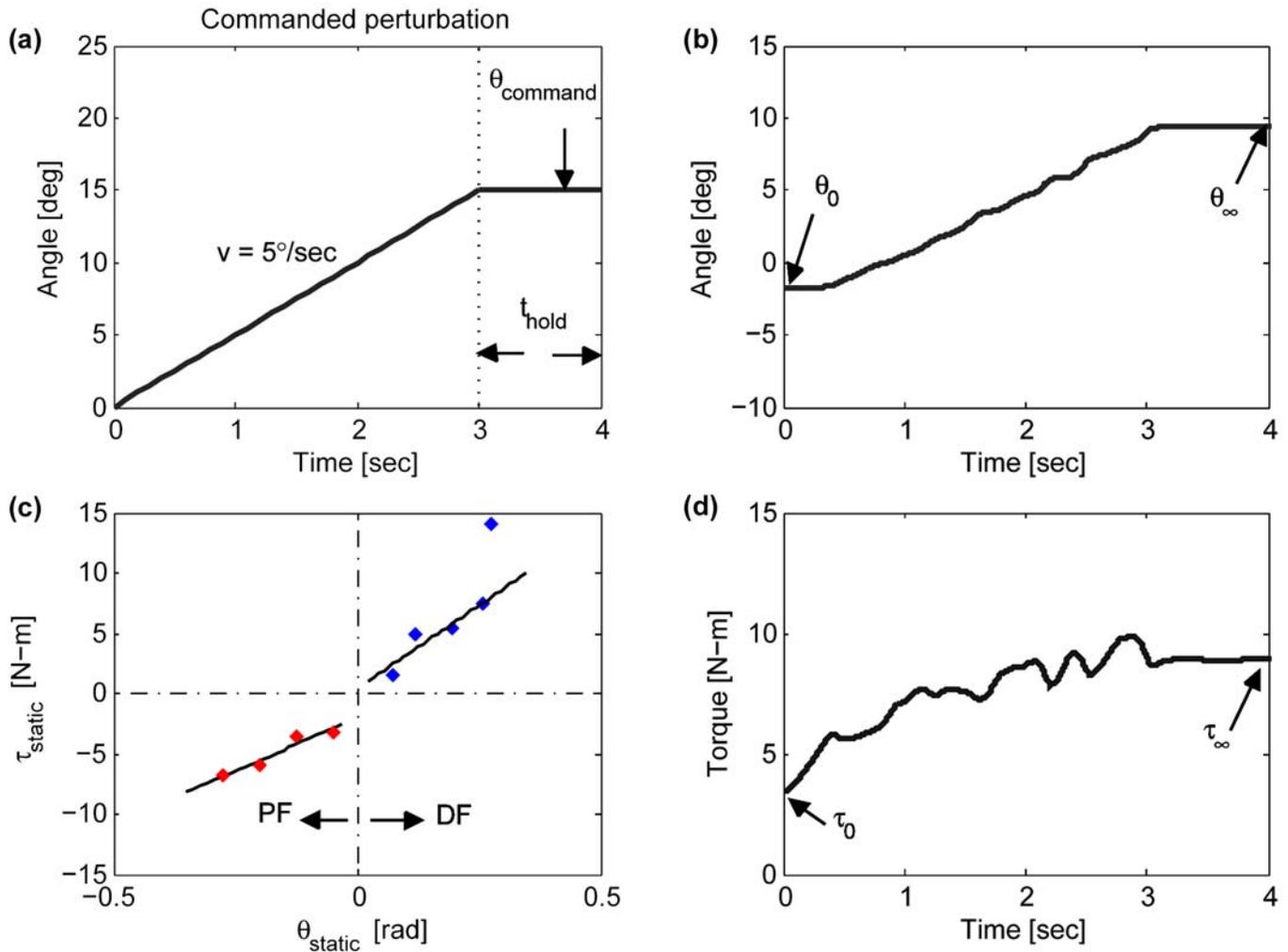


Figure 3.

Measurement of passive ankle stiffness using anklebot. (Reprinted with permission from Roy A, Krebs HI, Bever CT, Forrester LW, Macko RF, Hogan N. Measurement of passive ankle stiffness in subjects with chronic hemiparesis using a novel ankle robot. *J Neurophysiol.* 2011;105:2132–49.) **(a)** Commanded ramp-and-hold displacement perturbation (θ_{command}) of 15° in dorsiflexion (DF) with constant velocity (v) of $5^\circ/\text{s}$ and hold time (t_{hold}) of 1 s. Raw traces of **(b)** ankle angle and **(d)** torque resulting from each commanded positional perturbation taken from single representative subject with stroke, shown with initial (θ_0 , τ_0) and final (θ_∞ , τ_∞) conditions for a single trace. **(c)** Steady-state torque (τ_{static}) and angular displacement (θ_{static}) data are obtained by anklebot “slowly” stretching subject’s ankle over passive range of motion in sagittal plane (right positive: DF, left negative: plantar flexion) and computing resultant net torque ($\tau_\infty - \tau_0$) and angular displacement ($\theta_\infty - \theta_0$) under static conditions. Data are then fitted with least-squares linear regression line in each direction within plane of movement, slope of which is estimate of passive ankle stiffness in that direction.

Ankle Motor Control

We calculated measures of ankle motor control from positional data recorded by the anklebot during unassisted trials [25]. These included averages for number of successful targeted passages, peak and mean speed, and normalized jerk. We considered a movement (or submovement)

to have begun and terminated when the speed first rose above and dropped below 2 percent of the peak speed, respectively. We obtained movement speed and acceleration from the first and second derivatives of position; we used the speed profiles to calculate mean and peak speed. Movement smoothness was characterized by jerk; i.e., the

average rate of change or first derivative of acceleration in a movement. In order to eliminate the effect of speed on movement smoothness, jerk was normalized to each subject's peak speed.

Statistical Analyses

We chose the number of subjects (n) as sample of convenience. We computed group mean \pm SD at baseline, 3 wk, and termination (discharge). We used the Kolmogorov-Smirnov test to test for normality of distribution of data. For parametric data, we used paired t -tests to test for significant changes in any of the measures across the three time points; otherwise, we used the Wilcoxon sign rank test (Mann-Whitney U test). For nonparametric distribution, we reported the median. We computed correlations between two sets of data using the Pearson product-moment correlation (r^2) if parametric and using Spearman rank order correlation (ρ) if nonparametric. In addition, we ran multiple sample Kruskal-Wallis tests with nonparametric multiple comparisons. We set the significance level for comparison between two groups of data as well as correlations at $p < 0.05$. The sample size used for all statistical tests was $n = 8$.

RESULTS

Table 1 shows subject demographics and clinical outcomes at baseline. All eight subjects experienced their first unilateral stroke between 29 and 146 mo prior to

enrollment (mean: 72.5 mo), well beyond the 6 mo threshold for designation of chronic phase of stroke; were between 43 and 75 yr old (mean: 62.4 yr); had persistent lower-limb hemiparesis; had minimal resistance through ROM following catch (Modified Ashworth scores ≤ 2) and at least trace active DF-PF at their paretic ankles; and walked overground at self-selected speeds between 27 and 114 cm/s (mean: 51.4 cm/s). Six subjects used some type of assistive device for ambulation. All subjects successfully completed the training program.

Muscle Activity During Passive Stretch

Across subjects and across all trials, the mean EMG from both muscles did not significantly differ from the average b EMG activity during passive stretches in both sagittal and frontal planes, which confirmed our assumption of "passivity." Further evidence for this was the fact that the average b EMG was indistinguishable between the paretic and nonparetic limbs. Importantly, EMG during stretch at each sample was below its corresponding b EMG ± 1 SD that confirmed absence of stretch reflex activity.

Changes in Paretic Passive Ankle Stiffness Following Training

PAS data in each direction of movement and at each time point (baseline, 3 wk, and termination) were not distributed normally, necessitating the use of nonparametric statistics for comparison across time points. At baseline, the sagittal plane PAS was anisotropic, with significantly greater stiffness in DF (53.4 ± 8.2 Nm/rad) than in PF

Table 1.
Characteristics of subjects with stroke.

Subject	Age (yr)	Sex	Time Poststroke (mo)	Paretic Side	Assistive Device	Baseline Speed* (cm/s)	Modified Ashworth Score [†] (DF/PF)
1	75	M	146	R	SPC	114.4	0/0
2	73	F	84	L	SPC	28.7	1/1
3	60	F	89	R	AFO	71.9	1/1
4	66	M	79	L	AFO/4PC	25.2	0/0
5	43	F	60	L	—	68.1	0/0
6	65	F	29	L	AFO/SPC	26.7	2/1
7	64	F	56	R	—	45.1	0/0
8	53	F	37	R	AFO/SPC	31.6	0/2
Mean \pm SD	62.4 \pm 10.4	—	72.5 \pm 36.7	—	—	51.4 \pm 31.4	0–2

*Baseline speed refers to unassisted, self-selected floor-walking speed.

[†]Modified Ashworth scores range from 0 (no muscle tone) to 4 (limbs rigid in flexion or extension).

4PC = quad-point cane, AFO = assistive foot orthosis, DF = dorsiflexion, F = female, L = left, M = male, PF = plantar flexion, R = right, SD = standard deviation, SPC = single-point cane.

(13.2 ± 0.85 Nm/rad, $p = 0.001$); however, this was not the case in the frontal plane, i.e., the stiffness did not significantly differ between EV (51.6 ± 7.5 Nm/rad) and INV (44.6 ± 3.6 Nm/rad, $p = 0.72$) directions. After 6 wk of training, the PAS decreased in all four directions (DF, PF, INV, and EV), but we observed statistically significant changes only in the sagittal plane PAS, i.e., DF and PF (**Figure 4(a)**). In one of those directions, i.e., DF, the PAS (24.6 ± 4.1 Nm/rad) reverted into the ranges of young nondisabled subjects (DF: 12–48.2 Nm/rad) as well as age-matched controls (DF: 22.4–53 Nm/rad), whose data have been reported in a previous study [19]. In PF, however, the paretic PAS at termination (discharge) was outside the variability band of both young (10.7 – 25.5 Nm/rad) and age-matched nondisabled controls (12.2 – 13.8 Nm/rad) [19]. Similar to baseline, the PAS at discharge was anisotropic in the sagittal plane, i.e., significantly higher in DF (24.6 ± 4.1 Nm/rad) than in PF (10.0 ± 0.47 Nm/rad, $p = 0.03$), but not in the frontal plane (**Figure 4(b)**)—the stiffness did not significantly differ between EV (40.8 ± 8.6 Nm/rad) and INV (35.7 ± 6.8 Nm/rad, $p = 0.72$) directions. Importantly, no significant correlations (Spearman rank order coefficient) emerged between subjects' age and time poststroke versus changes in PAS in any direction.

Relationship of Changes in Passive Ankle Stiffness with Gait Outcomes

Following training, subjects significantly increased their self-selected overground walking speed through a combination of longer paretic STR lengths, faster cadence, and longer duration spent on paretic SST with concomitant decreases in DST duration [25]. However, spatial symmetry* of gait did not change significantly, improving only in three of eight subjects. Correlation analyses† between changes in PAS and gait outcomes (**Table 2**) revealed that changes in passive PF stiffness were significantly correlated with changes in two key spatiotemporal parameters of gait function, namely (1) paretic STP length ($\rho = -0.88$, $p = 0.03$) and (2) paretic STR length ($\rho = -0.82$, $p = 0.05$), suggesting that improvements in paretic STR and paretic STP length

*We calculated spatial symmetry as $[1 - (\text{paretic STP length} / \text{nonparetic STP length})]$.

†Similar to PAS data, each gait variable was not normally distributed, necessitating the use of Spearman rank order correlation.

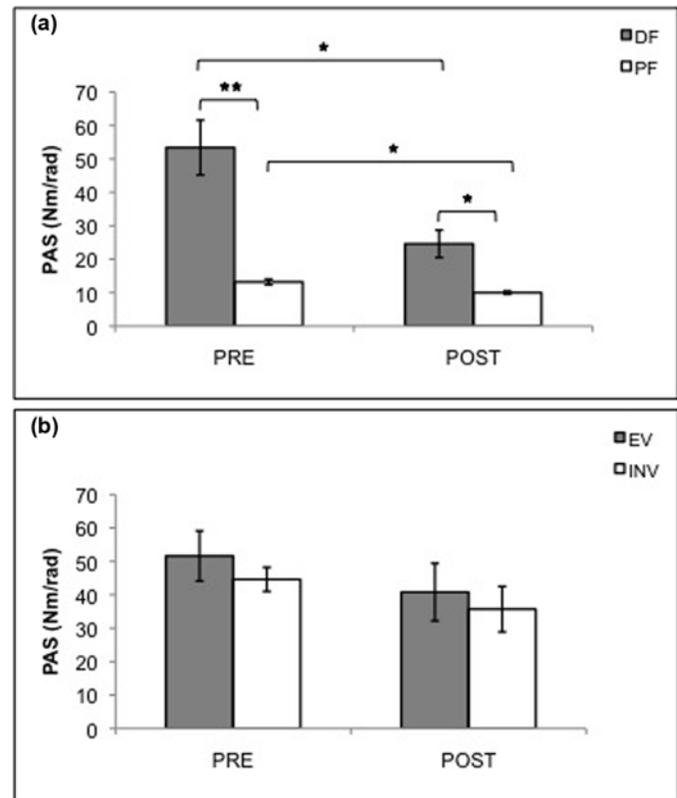


Figure 4.

Passive ankle stiffness (PAS) (Nm/rad) in each direction at baseline (PRE) and at termination (POST). Although PAS decreased in both planes of movement (sagittal and frontal) posttraining, changes were significant only in trained degree of freedom, i.e., sagittal plane. **(a)** Changes in sagittal plane PAS i.e., dorsiflexion (filled) and plantar flexion (unfilled) across time (PRE vs POST). In both directions, PAS decreased posttraining ($*p < 0.05$). PAS was anisotropic, i.e., higher in one direction versus another, at both time points, and this property was preserved across training with more pronounced difference between two directions at baseline ($**p < 0.01$). **(b)** Changes in frontal plane PAS, i.e., eversion (filled) and inversion (unfilled) across time (PRE vs POST). In both directions, PAS decreased posttraining but failed to achieve statistical significance. Unlike sagittal plane PAS, frontal plane PAS was not anisotropic at either time point.

occurred in part due to changes in the PF PAS that, in turn, contributed to improvements in overground gait speed. In both cases, the correlation was negative, indicating that subjects whose ankles became more compliant in PF with training took longer STPs and STRs on their paretic leg

Table 2.

Correlations between changes in baseline-to-termination passive ankle stiffness (PAS) (Nm/rad) and baseline PAS versus selected spatiotemporal gait parameters.

Variable	%Δ Gait Variable					
	Speed	Cadence	P-STP Length	P-STR Length	P-SST Duration	DST Duration
%ΔPAS-DF	-0.54	0.02	-0.54	-0.60	-0.40	-0.08
%ΔPAS-PF	-0.48	0.14	-0.88*	-0.82*	-0.60	0.20
%ΔPAS-EV	0.20	0.37	0.20	0.02	0.54	0.71
%ΔPAS-INV	0.77	0.54	0.54	0.60	0.65	0.08
PAS-DF	0.54	0.60	0.25	0.31	0.42	-0.25
PAS-PF	0.71	0.42	0.94*	0.82*	0.94*	0.08
PAS-EV	-0.54	-0.88*	-0.08	-0.14	-0.42	0.14
PAS-INV	0.14	0.25	-0.08	0.08	-0.20	-0.65

Note: Values reported are Spearman rank correlation coefficient (ρ). %Δ is relative change in variable between baseline and termination (discharge).

*Statistically significant correlation ($p < 0.05$).

DF = dorsiflexion, DST = double-support stance (% cycle), EV = eversion, INV = inversion, PF = plantar flexion, P-SST = paretic single-support stance (% cycle), P-STP = paretic step, P-STR = paretic stride.

during unassisted overground walking. Importantly, no significant correlations emerged between changes in any other gait outcomes, including spatial symmetry (paretic-to-nonparetic STP length) and changes in PAS in any other direction.

Influence of Changes in Ankle Motor Control on Gait Function

There were marked gains in paretic ankle motor control indexed by increased targeting accuracy, speed, and smoothness of unassisted movements in the DF-PF range during unassisted movements [25]. These improved motor control metrics suggested neural plasticity and motor learning in the chronic hemiparetic condition. We performed correlations between changes in measures of paretic ankle motor control and gait outcomes. Our findings were that decreases in DST duration were highly correlated with (1) improvements in the speed of targeting characterized by mean ($\rho = -0.83$, $p = 0.01$) and peak ($\rho = -0.73$, $p = 0.02$) speed and (2) improvements in movement smoothness characterized by normalized jerk ($\rho = 0.62$, $p = 0.05$).

Relationship of Changes in Gait Outcomes with Baseline Passive Ankle Stiffness

Correlations between baseline PAS and changes in gait outcomes (Table 2) revealed significant relationships between (1) passive PF stiffness at baseline and changes in paretic STP length ($\rho = 0.94$, $p = 0.01$), paretic STR length ($\rho = 0.82$, $p = 0.05$), and paretic SST duration ($\rho = 0.94$, $p = 0.01$); and (2) passive EV stiffness at baseline and changes in cadence ($\rho = 0.88$, $p = 0.03$). In each case

(except between PAS in EV and cadence), the correlation was positive, indicating that subjects who started training with greater impairments, i.e., higher paretic ankle PAS in the PF directions, improved more in selected aspects of gait function (including dynamic weight transfer during SST) and vice versa. The correlation was, however, negative between passive EV stiffness at baseline and changes in cadence. No significant correlations emerged between changes in any of the gait outcomes and baseline PAS in DF and INV directions.

DISCUSSION

Summary

This study revealed three important findings. First, interactive robotic training in a seated position exercising the paretic ankle in DF and PF positively affected sagittal, but not frontal, plane PAS in people with chronic stroke, with the DF PAS reverting into the PAS ranges of nondisabled age-matched subjects. Second, improvements in sagittal plane PAS specifically, in the PF direction, had a very strong and significant relationship with gains in selected spatiotemporal parameters of unassisted overground gait, namely paretic STP and paretic STR lengths. Third, positive gains in paretic STR length, paretic STP length, and SST of unassisted overground gait elicited by robot-assisted ankle training had a significant relationship with baseline PAS in the PF direction while improvements in cadence were strongly linked to baseline PAS in the EV direction. In the remainder of the article, we limit our discussion to these findings.

Passive Ankle Stiffness in One Plane of Movement is Not Influenced by Coupled Movement in Orthogonal Plane

During passive stretch in a given DOF (e.g., sagittal plane), movement in the orthogonal DOF (e.g., frontal plane) was left uncontrolled, i.e., the ankle was subject to synergistic movement in that DOF. The mechanical coupling (defined as the linear mapping between torques in one DOF to the resulting angular displacements in another DOF) may be represented as a compliance tensor. Each element of this tensor represents the ratio of angular displacement in one DOF to applied torque in an orthogonal DOF, and in particular, its off-diagonal terms represent the magnitude of cross-DOF coupling [19]. We found that the magnitude of coupling at rest across subjects was “weak” (lower by order[s] of magnitude compared with uncoupled, i.e., same DOF angle-to-torque compliances on the tensor diagonal). Notably, the coupling between DF and INV (vs DF and EV) and between PF and EV (vs PF and INV) was not weak, a finding consistent with our previous study [19]. As suggested by Roy et al., non-negligible cross-DOF coupling may be attributed to the inherent musculo-anatomical synergy between the sagittal and frontal planes [19]. For example, the ankle evertors (or invertors) play a role (albeit a weak one) as plantar flexors (or dorsiflexors) so one can expect appreciable coupling between INV (or EV) and DF (or PF) [19]. A deeper understanding of this cross-DOF coupling and a clearer interpretation of its potential relation to neurologic deficit would require direct evidence and is beyond the scope of the current study.

Can Trends in Paretic Passive Ankle Stiffness be Attributed to Muscle Physiology?

A primary finding of this study was that robotic training of the paretic ankle joint decreased its PAS in the sagittal plane; in one of those directions (DF), the PAS reverted into the ranges of younger and older nondisabled adults. Because of the long elapsed time since stroke, we assume that the ankle condition was stable and that the obtained improvements were not due to natural recovery. We considered the possibility that there might have been an underlying physiological basis for these changes. There is indirect evidence to link PAS to the summed physiological cross-sectional area (SPCA) and to the square of the mean moment arm of the antagonist group of muscles undergoing passive stretch [19]. It is possible that the robot-assisted, repetitive massed practice of the paretic ankle may have reduced the SPCA of plantar flex-

ors as a whole and this, in turn, caused the passive DF stiffness to reduce over the course of training.

A surprising finding, however, was that PAS changed (though not significantly) in the frontal plane despite no targeted movements made or commanded (volitional or by the anklebot) during training in INV-EV. We believe that the changes seen in the frontal plane PAS could be explained by the synergistic role played by the plantar flexor muscles that are also evertors of the ankle. As an illustration, the peroneus brevis and peroneus longus muscles are the primary evertors of the ankle but are also (weak) plantar flexors. A reduction in the plantar flexor SPCA could, therefore, potentially contribute to a reduction in the overall SPCA of the evertors taken as a muscle group. If true, this in turn would lead to a decrease in INV PAS, a prediction consistent with the findings in this study. Similarly, the TA is the primary dorsiflexor but also acts to invert the ankle, so a reduction in the dorsiflexor SPCA could contribute to a reduction in the invertors as a group. If so, one would expect to see a reduction in the PF and EV PAS that is consistent with our experimental findings. However, without direct evidence of muscle morphological data, we acknowledge that these are simply qualitative lines of reasoning, i.e., the observed changes in PAS resulting due to our intervention may not be caused by the changes in muscle SPCA. In fact, the addition of robot-assisted practice in ankle movements in a population that likely does not have a normal level of use could potentially increase the SPCA through a hypertrophy effect. If such is the case, changes in SPCA, e.g., an increase in the SPCA of plantar flexors, cannot account for changes in PAS, e.g., a decrease in the DF direction.

Training May Have Induced Intrinsic Changes Within Ankle Musculature

It is plausible that the PAS in a given direction may have been altered due to changes within the ankle musculature in either (1) the cellular structure or (2) the fiber-type distribution; however, the exact cause remains unclear without actual morphological muscle data. What could stimulate either (or both) of these mechanisms? We believe that this could be attributed to the large volume of robotic-driven exercise of the paretic ankle. It is known that exercise or training promotes a chronic increase in the so-called “collagen turnover” process in which collagen is broken down or degraded by as much as 50 percent [36–37]. Changes induced by collagen turnover have been shown to modify the biomechanical (e.g., viscoelastic)

[37] or structural (e.g., cross-sectional area) [37] properties of soft tissue, leading to altered resistance to loading [37]. Lieber et al. reported that a decrease in the collagen level led to a reduction in the ratio of collagen-to-muscle fiber tissue, thereby increasing muscle compliance [38].

An equally plausible conclusion is that repetitive exercise promoted changes in fiber-type distribution [39–42], i.e., an increase in the proportion of slow-to-fast twitch fibers; since the former type has a smaller diameter, it may have led to a decrease in the volume of the muscle undergoing passive stretching. Yet another possibility is that the PAS-altering mechanism was via changes in the thixotropic properties of antagonist muscles [43]. Yeh et al. suggested that the “gel component” of muscle (e.g., water and proteoglycans) may become less viscous after being stretched, resulting in lower PAS [44]. For this scenario to be credible, however, they rationalized that the muscle must not receive neural input because this may also modulate stiffness [44]. Because muscle activity measured using EMG has been shown to be negligible during passive stretch at these speeds [19], it is unlikely that neural mechanisms contributed to the PAS. While this rationale may explain the reduction of PAS in the DF and PF directions and appears to be consistent with other studies that attribute morphological and not just motoneuron transformations of spastic muscle over time [45], it fails to explain the changes in unexercised frontal plane PAS as reported here.

Improvements in Walking Speed May be Attributed to Changes in Passive Ankle Stiffness

A surprising and important finding that emerged was that the expected benefits of seated ankle training extended to whole-body function, such as overground gait speed and elements of gait, e.g., paretic SST and DST durations [25]. While this is certainly encouraging, it is contrary to our initial expectations and the concept of task-specificity of training. Given that subjects did not undergo gait training as part of our paradigm, we did not expect to see any improvements in overground gait and its constituent spatiotemporal parameters. It is unclear as to the exact cause(s) for the increases seen in gait speed. One possibility is that changes in paretic PAS could have potentially contributed to the increases in gait speed by means of increased STR and STP lengths on the paretic leg. Previous studies have shown, for example, that the active component of ankle stiffness varies with measures of mobility function, e.g., gait speed in nondisabled individuals [46]. Evidence also exists that PAS in the sagittal plane adds a unique contribution to walking speed in sub-

jects with diabetes and peripheral neuropathy [8,34]. This appears to be true in chronic stroke as well; in this study, we found a strong and significant correlation between changes in PF PAS with improvements in paretic STP and paretic STR lengths during unassisted overground gait. Because passive stiffness contributes to the total mechanical impedance of the joint, it is not inconceivable that these changes, in turn, may have enabled subjects to use their paretic ankle to position their foot more efficiently, thereby increasing their paretic STP and paretic STR lengths. For example, dorsiflexor control of the foot is essential to clear the ground during the swing phase of gait and for ecological landing. Changes in passive mechanisms such as reduction in the DF PAS would contribute to a reduction in the total mechanical impedance of the ankle (in DF) that may lead to better dorsiflexor control of the foot for greater swing clearance, as well as controlled landing. Similarly, the plantar flexors play a critical role in stabilizing the forefoot rocker action during terminal stance, and we know that plantar flexor muscle-tendons generate the largest power burst during trailing leg push-off [47–49]. The plantar flexor muscle-tendons are known to perform nearly 35 percent of the total lower-limb positive mechanical work and as much as 66 percent of the total ankle muscle-tendon positive work [50] in a single STR to enable forward propulsion. Therefore, a reduction in the total mechanical impedance in PF could in fact lead to increased anterior-posterior (A/P) positive propulsion during paretic SST. Indeed, our previous study with the same subjects [25] reported that a sub-set of the population (4 out of 5 subjects) increased their A/P positive propulsion by as much as 18 percent during the paretic SST phase.

Contribution of Neural Versus Mechanical/Muscle Physiology Factors

Although significant correlations emerged between changes in PF PAS and paretic STP length and paretic STR length (greater decreases in stiffness correlated with longer STPs and STRs), we need to interpret this finding with caution. Hemiparetic gait is often characterized by an asymmetry in which the paretic leg takes the longer STP, so it is not clear whether an increase in STP length is actually beneficial. Indeed, as reported in Forrester et al. [25], changes in paretic STP length did not contribute to improvement in independent floor-walking speed. Here, we investigated this issue further and found that changes in PF PAS did not influence changes in spatial gait symmetry. This raises the possibility that improvements in

PAS and gait function are not causal but rather a secondary correlation facilitated by some other causal relationship; that is, there might instead be a neural training effect that leads to better ankle motor control being responsible for the observed performance gains in gait function rather than resulting solely from changes to passive tissue. This is quite conceivable—after all, our training was an active (interactive) process in which the anklebot did not serve as a passive motion machine and it is doubtful that the training outcomes reported here would have been replicated by a passive stretching routine with the same number of movements. Indeed, short-term motor skill ankle training has been shown to increase cortical excitability to the TA that equal amounts of unskilled and passive ankle training do not [51]. The increased excitability has been associated with reduced errors on an ankle motor performance task, suggestive of improved motor control of ankle musculature [51]. If a similar mechanism is evoked by the anklebot training in our subjects, this may be the primary contributor to improved walking speeds reported in Forrester et al. [25].

Our correlation analysis revealed that decreases in DST duration (indicative of improved dynamic balance control during gait) were highly correlated with improved ankle motor control, in particular movement speed and smoothness. Subjects with higher gains in speed and smoothness of ankle targeting on the visuomotor task spent less time in double stance and vice versa. However, the lack of correlation between changes in paretic STP and paretic STR length to changes in any of the motor control metrics suggest that both neural and mechanical factors contributed to improvements in walking function. It appears that improved paretic ankle motor control and changes to passive tissue contributed independently by improving distinct elements of walking function; the former positively affected a key temporal element of walking, i.e., DST duration, while the latter improved spatial aspects of walking, i.e., STP and STR lengths.

Baseline Passive Ankle Stiffness May be Predictor of Improvements in Walking Function

Subjects with higher PAS in PF and lower PAS in EV showed greater improvements in walking function, specifically, paretic STR length, paretic STP length, paretic SST duration, and cadence. This may be of importance in identifying potential responders, especially to this type of intervention; however, the small sample size prevents an in-depth analysis of the predictive value of PAS. A sub-

ject-by-subject qualitative analysis does, however, reveal the underlying trends between baseline PAS and functional outcomes; for example, the two subjects with the highest PF PAS at baseline (subjects 2 and 8, respectively) also showed the greatest relative change in overground walking speed (118.6% and 27.4%, respectively), reflecting the positive correlation. This change was clinically significant as well in that their ambulation level (defined with respect to unassisted floor walking speed) changed; both subjects transitioned from home (HC) (<40 cm/s) to limited community (LC) (40–80 cm/s) ambulators. Conversely, the subject with the most compliant ankle in PF at baseline (subject 7) improved the least in gait speed (15%) with no change in ambulation category. We also observed similar trends reflecting a negative correlation between baseline PAS in EV and functional outcomes; the subject with the most compliant ankle in EV (subject 2) improved the most in gait speed (118.6%), transitioning from HC to LC ambulator, while the subject with the least compliant ankle in EV (subject 7) improved the least (15%), with no change in ambulation category.

Comparison with Previous Related Work

To the best of our knowledge, this is the first study to report changes in frontal plane PAS in people with chronic stroke. Independent training of the ankle joint is not a unique idea. For example, Mirelman et al. employed a different device and delivered visually guided and intention-driven training in the seated position, requiring subjects to attempt to make targeted movements [52]. Of the groups that measured stiffness, most employed passive stretching of the paretic ankle, e.g., PMS, and measurements in all those studies were made exclusively in the sagittal plane. For instance, Selles et al. investigated the effect of repeated feedback-controlled and programmed “intelligent” stretching of the ankle plantar flexors and dorsiflexors as a potential method to treat subjects with ankle spasticity and/or contracture in stroke and found significant improvements in paretic PAS in DF from a 4 wk intervention [23]. Yeh et al. quantified the immediate effect of PMS on the inhibition of ankle hypertonia in subjects with hemiplegia and ankle plantar flexor hypertonia [44]. Bressel and McNair used a slow, prolonged static and cyclic calf stretching of 30 min duration in patients with stroke to compare its short-term effects on PAS and reported a decrease in paretic PAS [22]. Generally speaking, the training-induced changes in sagittal plane PAS reported here differed from those published by others (Table 3).

Table 3.

Comparison of changes in passive ankle stiffness in this study (anklebot) with published literature.

Criterion/Study	Equipment	Experimental Conditions	Perturbation Characteristics	% $\Delta_{rel}K^*$ (<i>p</i> -Value, $\alpha = 0.05$)
At 5 Nm Torque				
Selles et al., 2005 [23]	Custom stretching device	Knee flexed (30°), 3 sessions/wk, 45 min/session	30°/s, 10–25 Nm [†] (DF), 5–10 Nm [†] (PF), 5 s hold	DF: -38.8 [‡] ; PF: 31.0 [‡]
Anklebot	2-DOF ankle robot	Knee flexed (60°), 1 session/wk, ~15 min/session	5°/s, ROH, 0–PROM (DF), 0–20° (PF), 1 s hold	DF: -24.8 [‡] ; PF: 5.5
Within ROM				
Selles et al., 2005 [23]	Custom stretching device	Knee flexed (30°), 3 sessions/wk, 45 min/session	30°/s, 10–25 Nm [†] (DF), 5–10 Nm [†] (PF), 5 s hold	DF: -36.36 [‡] ; PF: 28.57 [‡]
Anklebot	2-DOF ankle robot	Knee flexed (60°), 1 session/wk, ~15 min/session	5°/s, ROH, 0–PROM (DF), 0–20° (PF), 1 s hold	DF: -32.69; PF: -13.46
At Neutral				
Selles et al., 2005 [23]	Custom stretching device	Knee flexed (30°), 3 sessions/wk, 45 min/session	30°/s, 10–25 Nm [†] (DF), 5–10 Nm [†] (PF), 5 s hold	-31.81 [‡]
Anklebot	2-DOF ankle robot	Knee flexed (60°), 1 session/wk, ~15 min/session	5°/s, ROH, 0–PROM (DF), 0–20° (PF), 1 s hold	-14.73 [‡]
Within DF Range				
Yeh et al., 2004 [44]	Custom device	Supine, 30 min/session	Sinusoidal PMS, ± 3° amplitude, 1–15 Hz frequency, Assessment: 5°/s, PROM-DF	-48.51 to -42.69 ^{‡¶}
Bressel & McNair, 2002 [22]	Kim-Com dynamometer	Single session	CPM for 60 s, 0%–80% max ROM	Static: -34.67; Cyclical: -29.87
Anklebot	2-DOF ankle robot	Knee flexed (60°), 1 session/wk, ~15 min/session	5°/s, ROH, 0–PROM (DF), 0–20° (PF), 1 s hold	-66.74 [‡]

*Relative change in variable between pre- and postintervention.

†Peak torque.

‡Statistically significant differences (*p* < 0.05).

¶At sinusoidal 3 Hz frequency.

CPM = continuous passive motion, DF = dorsiflexion, DOF = degrees of freedom, PF = plantar flexion, PMS = prolonged muscle stretch, PROM = passive range of motion, ROH = ramp-and-hold position perturbation, ROM = range of motion.

Specifically, the reductions in paretic PAS in DF were—

1. Lower than those obtained by Selles et al. Since the mean time poststroke in Selles et al.'s (7.7 ± 6.6 yr) and our (6.04 ± 3.05 yr) studies was similar, the difference may be due to the sample age because Selles et al.'s study consisted of relatively younger patients with stroke (54.6 ± 9.1 yr) than our subjects (62.4 ± 10.4 yr).
2. Higher than those reported in Yeh et al.'s and Bressel and McNair's studies. Of notice, the PAS in Yeh et al.'s study was measured in a supine position.

Finally, it is worthwhile to point out that our success in PAS measurement of the paretic ankle in multiple DOFs parallel those for the upper limb, e.g., wrist [53–55] and arm [56], which could ultimately provide us with a clearer understanding of how the nervous system may take advantage of the direction(s) of higher compliance, albeit differently for the two cases.

Study Limitations

We have to interpret our results with caution. This was a pilot study that investigated the changes in PAS at

the hemiparetic ankle resulting from a 6 wk seated visuo-motor training using an impedance-controlled modular ankle robot. The sample size is small, limiting conclusions about ability to generalize the results. Because the number of subjects was chosen as a sample of convenience, we did not have information on statistical power available a priori. However, we did perform retrospective (post hoc) power analysis on PAS changes in those directions in which the baseline-termination changes were not statistically significant, i.e., EV and INV PAS. Our results showed that the minimum sample size needed to observe detectable differences and statistical significance was $n = 11$, which is not appreciably higher than the sample size in this study ($n = 8$). Also, despite not seeing correlations between changes in frontal plane PAS and gait function, those may emerge through improved motor control of the mediolateral stabilizer muscles if training was also conducted in the frontal plane. Furthermore, we did not collect follow-up data beyond the 6 wk period, limiting our ability to comment on the long-term retention of changes in PAS.

Clinical Implications

We are not claiming that training in the seated position is optimal. One might speculate that training both ankle control and task-oriented locomotor function might lead to even superior outcomes, and further testing is needed to elucidate the potential of each approach. Nonetheless, we were encouraged by the surprising result of meaningful functional gait changes that suggest that ankle training can positively affect locomotor function, possibly by means of changes in PAS leading to more efficient placement of foot and interlimb weight transfer during stance, and such paradigms might allow us to initiate training even sooner when the patient is unable to stand. Future studies are underway to measure PAS in people with stroke during the earlier stages of stroke recovery (subacute phase) and monitor changes in PAS resulting from the seated training paradigm in comparison with age-matched controls.

CONCLUSIONS

We presented pilot findings on the changes in PAS in the hemiparetic ankle after 6 wk of anklebot-assisted interactive therapy in people with chronic stroke. Our findings were that a performance-based, progressive

intervention that focuses on training the hemiparetic ankle not only decreases the PAS in PF and DF directions, but in fact reverts the PAS in the latter direction into the ranges of age-matched, nondisabled individuals. Even more important was the fact that increased compliance of the paretic ankle contributed to improvements in the quality of unassisted overground walking and that baseline PAS emerged to be a predictor of improvements in key spatiotemporal parameters of independent floor walking. We believe that these results constitute a first-of-its kind evidence that bridges the gap between an important and quantifiable measure of diseased ankle pathology and a whole-body functional task, i.e., gait. Future studies will use the anklebot to measure the (1) total mechanical impedance, i.e., passive plus active and other dynamic factors of the paretic ankle; (2) frontal plane PAS after training INV-EV movements; and (3) PAS in patients in the subacute phase of recovery, as well as in neurological populations besides stroke.

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Author Contributions:

Study concept and design: A. Roy, L. W. Forrester, R. F. Macko, H. I. Krebs.

Acquisition of data: A. Roy.

Analysis and interpretation of data: A. Roy, L. W. Forrester, R. F. Macko, H. I. Krebs.

Drafting of manuscript: A. Roy.

Critical revision of manuscript for important intellectual content: A. Roy, L. W. Forrester, H. I. Krebs.

Obtained funding: L. W. Forrester, R. F. Macko.

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