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Effects of exoskeleton rehabilitation robot training on neuroplasticity and lower limb motor function in patients with stroke

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Abstract

Background Lower limb exoskeleton rehabilitation robot is a new technology to improve the lower limb motor function of stroke patients. Recovery of motor function after stroke is closely related to neuroplasticity in the motor cortex and associated motor areas. However, few studies investigate how rehabilitation robots affect the neuroplasticity of stroke patients.This study sought to determine the effects of lower limb exoskeleton robot walking training on neuroplasticity and lower limb motor function in patients with stroke.

Methods A total of 25 (50.26 ± 11.42 years, 68.0% male) patients(age 18–75 years, onset between 2 weeks and 6 months) with a stable condition after having a stroke were randomized into a treatment ($n = 13$) and control group ($n = 12$). Bilateral Exoskeletal Assistive Robot H1 (BEAR-H1) walking training was provided to the treatment group, whereas conventional walking training was provided to the control group. Both groups completed two training sessions per day for 30 min each and were trained 5 days a week for 4 weeks. Transcranial magnetic stimulation, Fugl–Meyer Assessment lower extremity, Functional Ambulation Category 6-min walking distance test, intelligent gait analysis, and surface electromyography of the lower limbs were performed before and 4 weeks after treatment.

Results Both groups showed obvious improvements in all evaluation indicators ($p < 0.05$). Compared with the control group, the treatment group exhibited a decreased resting motor threshold and increased motor-evoked potential amplitude and recruitment curve slope ($p < 0.05$). The treatment group performed better than the control group ($p < 0.05$) in the 6-min walk test and knee flexion co-contraction ratio (CR). Correlation analysis showed that resting motor threshold, motor-evoked potential amplitude, and the recruitment curve slope were significantly correlated with the 6-min walk test, CR on ankle dorsiflexion, the root mean square of the tibialis anterior, biceps femoris, and medial gastrocnemius ($p < 0.05$).

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Conclusion Walking training using the bilateral exoskeletal assistive robot H1 improved cerebral cortical excitability in patients with stroke, which facilitated changes in neuroplasticity and enhanced lower limb motor function.

Registration Chinese Clinical Trail Registry: ChiCTR1900028262. Registered Date: December 16,2019. Registration-URL: http://www.chictr.org.cn

Keywords Lower limb rehabilitation robot, Motor function, Neuroplasticity, Stroke, Transcranial magnetic stimulation

Introduction

Stroke is one of the most common cerebrovascular diseases worldwide. Unfortunately, approximately 63% of stroke survivors suffer from lower limb motor dysfunction, [1] including gait dysfunction and decreased joint stability, muscle strength, and muscle endurance. Functional recovery of lower limb function, particularly walking ability, is fundamental to the daily activities of patients with stroke. Regaining walking ability is an important objective of post-stroke rehabilitation, considering that restrictions in walking function severely affect patient's daily life and mental state, and increase the burden on their families. Impaired walking function can improve early after the onset of stroke, usually within the first 3–6 months [2].

Recovery of motor function after stroke is closely associated with neuroplasticity in the motor cortex and associated motor areas [3] Neuroimaging studies have already demonstrated that motor recovery after a stroke is usually associated with cortical reorganization and motor network connectivity [4, 5] Recovery of lower limb motor function depends on the reorganization of brain function and activation of cortical excitability in damaged brain areas [6] Interestingly, one study showed that lower limb movement or walking training can promote neuroplastic changes in the brain [7].

Conventional training methods for lower limb motor function, such as stepping and walking training, have been proven to be effective in restoring the walking ability of patients with stroke [8] However, considering that conventional training involves segmented training of a single muscle group or a single joint, coordinating active and antagonistic muscle movements through this training approach becomes difficult. To address this, robotic lower limb rehabilitation using exoskeletons or training pedals, for example, achieves symmetrical training of both lower extremities. Previous studies have shown that symmetrical walking training is positively correlated with walking stability among patients [9] Repetitive exercises for specific tasks are an effective approach for improving neuroplasticity, which may be related to an increase in the efficiency of cortical recombination or synaptic transmission. Moreover, some studies have shown that substantial benefits can only be achieved after engaging in an appropriate amount of repetitive walking training [10, 11] Lower limb rehabilitation robots allow patients to engage in high-intensity repetitive training while maintaining a steady standing position. French et al.,[12] who conducted a meta-analysis on repetitive training to improve limb movement disorders in patients with stroke, pointed out that repetitive training helps improve the body's motor function, expands the innervation area of the trained site in the cerebral cortex, and improves the transmission efficiency of neural circuits [13] Lower limb rehabilitation robots can help patients engage in active training. Active movement patterns can stimulate the affected limb and cause expansion of the cortical areas. Lower limb rehabilitation exoskeleton robots imitate the gait cycle and provide ground walking training for patients in a real environment [14] This approach is based on resistance training patterns and provides assistance according to the patient's gait phase [15] Jaeger et al.,[16] who used a magnetic resonance-compatible stepping robot and concluded that patients under active training stimulation exhibited significantly increased cortical signals. However, because most current studies have focused on the effects of rehabilitation exoskeleton robot training on improving limb motor function, little attention has been paid to determining the effects of such training on changes in neuroplasticity.

Transcranial magnetic stimulation (TMS) provides valuable information for predicting motor recovery in patients with stroke. It can explore the mechanisms of neural recovery by measuring the activation of the primary motor cortex (M1). The parameters provided by TMS can be used to identify motor cortical reorganization after a stroke, such as the resting motor threshold (rMT) and motor-evoked potential (MEP), which have been used to explain changes in corticospinal excitability after a stroke [17] One study showed that restoration of motor function is associated with improved corticospinal conduction and that MEP is a good indicator of functional recovery in patients with stroke [18] Studies on MEP and hand function of patients with chronic stroke found that shorter MEP latency, shorter central motor conduction time (CMCT), higher motor-evoked potential amplitude (pMEPamp), and diminished rMT were positively correlated with motor function recovery [19] TMS is an ideal tool for investigating cortical excitability in patients with stroke and may support the diagnosis and evaluation of clinical conditions [20] Therefore, this study used TMS to measure cortical plasticity in patients

with hemiplegia. In addition, the main neural structures involved in this study include Primary motor cortex (M1), Corticospinal tract, Cerebral motor network, Peripheral nervous system components.

This study investigated the effects of bilateral exoskeletal assistive robot H1 (BEAR-H1) training and its impact on neuroplasticity in patients with stroke with hemiplegia using TMS analysis. Simultaneously, we used surface electromyography (sEMG) analysis, intelligent wearable gait analysis, the Functional Ambulation Category (FAC) scale, and the Fugl–Meyer Assessment (FMA) scale to explore the relationship between improvement in lower limb motor function and changes in neuroplasticity. The findings of this study provide a theoretical basis for the clinical application of lower limb rehabilitation robots.

Methods

Patients

Eligible patients were admitted to the Department of Rehabilitation and Department of Neurology at Zhujiang Hospital between June 2019 and February 2021 (Guangzhou, China). The inclusion criteria were as follows: (1) stable condition and trainable; (2) age 18–75 years; (3) acute and subacute first stroke (2 weeks–6 months); (4) slow and unstable pace, (5) no restriction in joint motion, (6) normal cognition, and (7) no previous robotic rehabilitation training experience. The exclusion criteria were as follows: (1) severe joint limitation that affects walking, (2) skin injury or infection in the lower limbs, (3) serious cardiovascular or cardiopulmonary conditions, (4) contraindications to TMS examination, (5) contraindications to sEMG examination, (6) poor compliance, and (7) other contraindications or complications that may affect walking.

This study was approved by the Ethics Committee of Zhujiang Hospital (No.2019-QX-004-01). Informed consent was obtained from each patient. The study was registered at Chinese Clinical Trial Registry (ChiCTR1900028262) and Registration Date: December 16, 2019.

The first patient was enrolled for the study on December 20, 2019. All procedures involving human participants were conducted in accordance with the principles of the Declaration of Helsinki.

Patient and public involvement

To have scientifically rigorous clinical trials and reliable results, patients of this trial were not involved in the design, recruitment, or conduction of the study. After the last visit, the patients will be informed by the physician about the study results by pictures and text.

Randomization and blinding

Using a computer-generated random sequence, all enrolled patients were randomly assigned to a treatment or control group.

This trial was a double-blind design, with subjects and investigators (including outcome measures and statisticians etc.) not aware of the grouping.

Device

Device BEAR-H1 (Milebot Robotics Co., Ltd, Shenzhen, China) is a lower limb exoskeleton robot that was developed to assist patients in walking and was adapted to the wearer's body size. Regarding the joint configuration, BEAR-H1 closely resembles the lower limb joints of humans. The robot is suitable for patients between 150 and 190 cm in height and weighing up to 85 kg. This adjustable exoskeleton is equipped with a gait monitoring and evaluation system that allows physical therapists or family members to monitor the patient's movement data through a touch screen in real time (Fig. 1).

Intervention

The treatment group received BEAR-H1-assisted walking training, whereas the control group received conventional walking training with the help of a therapist (standing balance training, muscle strength training, load-bearing training, and step training). Both groups completed two training sessions per day for 30 min each and were trained 5 days a week for 4 weeks.

During each BEAR-H1 training session, the therapist adjusted the robot's leg to the appropriate length based on the patient's lower limb, assisted the patient in putting the device on, and fixed the bandage. After being set in smart mode, the exoskeleton can synchronize the patient's pace over a range of frequencies. Participants in both groups walked for 30 min on the same path, which was flat and predominantly straight. Treatment was performed under the supervision of the attending physician. To verify whether the patients were able to complete the task, they were required to undergo adaptive walking training for 3–5 days before enrollment. Only those who completed the adaptive training were formally enrolled.

Both groups underwent basic rehabilitation (functional, stabilization, mobility, and postural control training) based on the patient's condition.

Primary outcomes

Assessments were mainly conducted at three time points: T0 (baseline, before the start of training), T1 (after 2 weeks of training), and T2 (after 4 weeks of training). All assessments were conducted simultaneously by a qualified physician and therapist who were blinded to the patients' grouping.

Fig. 1 BEAR-H1 robot is consist of backpack control box, touch screen display, waist, and two leg parts. On the joint configuration, the BEAR-H1 is approximately consistent with the human lower limb joints, having hip joints, knee joints, and ankle joints. The robot is suitable for patients between 150 and 190 cm in height and weighing < 85 kg. The size of exoskeleton is adjustable

The primary outcomes were key parameters of neuroplasticity assessed by TMS (MagNeuro100; Nanjing VISHEE Medical Technology Co., Ltd.) at T2. TMS was performed in accordance with published guidelines [21] The assessment was performed in a quiet room with patients seated in a wheelchair or a high back chair to remain relaxed and their hands resting on their lap. We explained to the patients how the stimulation worked and what they might feel. Thereafter, they were instructed to keep their eyes open, similar to that while awake. The abductor pollicis brevis muscle was selected as the target muscle. The electrode was attached to the belly of the muscle abductor pollicis brevis, and the reference electrode was attached to the ulnar styloid. Neuroplasticity was evaluated using four parameters: rMT, recruitment curve (RC) slope, pMEPamp, and CMCT, all of which have good reliability and validity [22].

rMT data collection

A properly sized positioning cap was placed on each patient. The examiner placed the coil tangentially on the scalp over a representative area of the primary motor cortex (M1) of the affected side. TMS was assessed using a single pulse, and the TMS coil was slowly moved in 1-cm increments to a position 1–2 cm anterior and lateral to the Cz point of the affected side (M1). An intensity of 30% was used for initial stimulation. rMT was defined as the lowest TMS intensity that can cause the relaxed abductor pollicis brevis muscle to produce an MEP amplitude of at least 50 μV in at least 5 of 10 consecutive stimulations, which was determined as the lowest output intensity for inducing visible contractions [23].

RC slope and pMEPamp data collection

After the rMT of the motor cortex of the affected side was determined, the RC of MEP was measured 1 min later. The stimulation intensity was set to 100% of the rMT, increasing by 10% after every five stimuli. The TMS intensity was increased from 100 to 150% in 10% increments. This procedure was repeated for 1 min. Ten MEP samples were obtained at each stimulus intensity to construct recruitment curves. The linear RC slope, which reflects the neurophysiological intensity of cortical and corticospinal excitability, was then calculated. pMEPamp was recorded as the maximum MEP amplitude during RC measurement.

Central motor conduction time data collection

The CMCT values of healthy subjects were used as the reference standard for determining peripheral motor conduction time (PMCT). The coil was placed over the processus spinosus of the 7th cervical vertebra [24] The position of the coil was adjusted vertically. In this position, the end of the spinal nerve is suctioned and passed

through the intervertebral foramina. Peripheral motor latency (PML), which corresponds to PMCT from the intervertebral foramina to the muscle, can be calculated using the target muscle-evoked potential. CMCT is calculated by subtracting the shortest conduction time along the peripheral axon from the MEP latency recorded in the central motor cortex [21], [25] Same site was stimulated four times with 1.2 times the rMT, and the PML corresponding to the MEP with the shortest latency and highest amplitude was selected for calculation.

Secondary outcomes

6-min walk test data collection

We selected a long indoor corridor with limited people for 6-MWT data collection and marked the starting and turning points with colored ribbons on the ground. The patients were instructed to walk back and forth within the marked area for as long as possible. Using a timer, the total distance walked by the patient in 6 min was calculated and rounded off to the nearest meter.

Fugl–Meyer assessment lower extremity

FMA-LE is an impairment-based scale [26], which is used to measure lower limb motor function. This assessment tool consists of 17 items, with the highest score of 34. Each item is assessed using a three-point ordinal scale (0 = cannot perform, 1 = can perform partially, and 2 = can perform fully).

Functional ambulation classification

Walking ability was assessed using FAC [27], which evaluates lower limb function based on the ability to walk for 15 m.

Gait analysis

Gait analysis was conducted using a gait analyzer IDEEA3 (MINISUN) with a third-generation Intelligent Device (LLC, Fresno, CA, USA). Accordingly, the patients were instructed to walk on flat ground wearing recorder and heelless shoes. They were instructed to maintain a consistent speed as much as possible throughout a walking distance of at least 50 m. Thereafter, the recorder was removed, and the data was imported into the IDEEA software system and analyzed to obtain the target data, which included cadence, gait cycle time, and the support phase-to-swing phase ratio.

sEMG data collection

sEMG assessment (MyoMove, Northam Electric Co., Ltd., Shanghai, China) was conducted at 2048 Hz, with a magnification of 500× and a bandwidth of 5–500 Hz. According to the current international measurement method recommendations (http://www.seniam.org), [28] we selected the rectus femoris, biceps femoris, tibial anterior, and medial gastrocnemius of the affected lower limb as the targets [29] The reference electrodes were positioned on the lateral malleolus, and the active electrode was placed over each muscle belly. The electrodes were placed parallel to the muscle fibers and the centers of the two electrodes were separated by 2 cm. The electrodes were fixed using a flexible adhesive tape. After the sEMG signal appeared, we waited for 3 min until the signal was stable at < 15 μV and prepared for sEMG collection.

sEMG signal collection

The root mean square (RMS) and integral electromyography (iEMG) values for the rectus femoris, biceps femoris, tibialis anterior, and medial gastrocnemius were collected at different positions and movements.

Calculated co-contraction ratio

Muscle co-activation refers to the simultaneous activity of various muscles around the joint. Co-contraction ratio (CR) was calculated as the average of consecutive instantaneous activity of two muscle groups [30] We used the Main Project (EMG view 1.3, Laursen, Denmark) to analyze the data. sEMG signals with a stationary duration of 3 s were intercepted using the Main Project software, after which the iEMG and RMS for each muscle were exported. The iEMG of the antagonist muscles (rectus femoris and medial gastrocnemius) was expressed as a percentage of the total iEMG during maximum isometric contraction. The equation below was created based on the anatomical and functional roles of the two muscles, ranging 0–100%. [29] The results are the average of three measurements.

The calculation formula is as follows:

$$CR = \frac{\text{iEMG of antagonistic muscle}}{\text{iEMG of antagonistic muscle+}\atop\text{iEMG of agonist muscle}} \times 100\%$$

Sample size

According to our previous data, the effect size is at least 1.30 for neuroplasticity parameters, such as rMT, RC slope, pMEPamp, and CMCT. Considering the power of 80% and alpha value of 5% (two-tailed), each group will be at least 11 participants to detect the significance. The calculation is performed using PASS 2021 software (Kaysville, Utah, USA).

Statistical analysis

Continuous variables are presented as mean and standard deviation or medians and quantiles, whereas categorical variables are presented as frequencies and percentages. For baseline comparisons of continuous variables, t-tests were used to evaluate differences

between the two groups. For categorical variables, the χ^2 test, Fisher's exact test, or Mann–Whitney U test was used for intergroup comparisons. Generalized estimation equations were used to test the effects of the intervention, including time, group, and time × group interaction effects. Age, sex, height, weight, hemiplegic side, stroke type, days after stroke, education level, and Brunnstrom stage were considered as covariables. The Least Significant Difference.

adjustment was used for pairwise comparisons between different time points. Pearson correlation coefficient was used to determine the correlation between changes in the different outcomes. All statistical analyses were performed using SPSS (version 26.0), with $p < 0.05$ indicating statistical significance.

Results

Among the 60 potential participants screened, 25 satisfied the inclusion criteria (Fig. 2). Among these 25 participants, two participants withdrew consent in the treatment group and one withdrew consent in the control group. These participants were not included in the primary analysis. No adverse events were reported in either group. Current study adheres to CONSORT guidelines.

General information

Statistical analysis of all outcomes at baseline (T0) was performed using independent t-tests. Our results showed no significant differences in age, sex, weight, height, hemiplegic side, stroke type, onset time, degree of education, and Brunnstrom stage between the two groups ($p > 0.05$; Table 1). Similarly, no significant differences in rMT, pMEPamp, CMCT, RC slope, 6-MWT, FMA-LE, FAC, cadence, gait cycle time, support phase-to-swing phase ratio, RMS, CR of knee flexion, and ankle dorsiflexion were observed ($p > 0.05$; Table 1).

Outcomes

Primary outcome

As shown in Table 2, the rMT, pMEPamp, RC slope, and CMCT of the two groups improved significantly after 4 weeks of treatment (T2) compared with baseline ($p < 0.05$; Table 2). Compared with the control group, the treatment group showed a significant decrease in rMT and pMEPamp and an increase in the MEP RC slope ($p < 0.05$; Table 2). No significant difference in CMCT was found between the groups ($p > 0.05$; Table 2).

Secondary outcome

After 4 weeks of treatment, both the treatment and control groups showed improved 6-MWT, FAC, and FMA-LE; better cadence; shortened gait cycle time; increased support phase-to-swing phase ratio on the hemiplegic side; increased RMS of the rectus femoris, biceps femoris, tibialis anterior, and medial gastrocnemius; and reduced CR during knee flexion and ankle dorsiflexion ($p < 0.05$; Table 2). However, from baseline to 4 weeks after treatment, the treatment group was more effective in improving 6-MWT and reducing knee flexion CR than the control group ($p < 0.05$; Table 2). No significant differences in the other evaluation indicators were observed between the two groups ($p > 0.05$; Table 2).

Correlation analyses

Notably, the RC slope was positively correlated with the RMS of the tibialis anterior ($r = 0.524$; $p < 0.012$), biceps femoris ($r = 0.581$; $p < 0.005$), and medial gastrocnemius ($r = 0.595$; $p < 0.003$). rMT was negatively correlated with the 6-MWT ($r = -0.469$; $p < 0.028$), pMEPamp was positively correlated with the 6-MWT ($r = 0.437$; $p < 0.042$), and the RC slope was positively correlated with the 6-MWT ($r = 0.654$; $p < 0.001$). However, rMT was positively correlated with CR on ankle dorsiflexion ($r = 0.445$; $p < 0.038$), RC slope was negatively correlated with CR on ankle dorsiflexion ($r = -0.465$; $p < 0.029$), and pMEPamp was positively correlated with RMS of the medial gastrocnemius ($r = 0.492$; $p < 0.05$) (Fig. 3). The objective indicators of TMS and EMG were correlated with the improvement in lower limb walking ability.

Discussion

Improving lower limb motor function in patients with stroke is critical. Accordingly, motor function recovery has been associated with improvements in cortical excitability and corticospinal conduction [20] BEAR-H1 enables task-oriented and high-intensity walking training under relatively comfortable conditions in the early phase, which simulates weight loss during normal walking. This study showed that BEAR-H1 walking training improved neuroplasticity and lower limb motor function in patients with stroke.

Several studies have suggested that TMS parameters that are associated with motor function performance can be used to identify patients with neuroplasticity after a stroke [30] Increased rMT has been observed in the acute and subacute phases of stroke [31] Our results showed that although rMT decreased significantly in both groups after intervention, the decrease was more pronounced in the treatment group. Given that rMT reflects the stimulus intensity of nerve excitement, changes in its values may indicate the excitability of neuronal cell membranes in the motor cortex and neuroplasticity. Cortical excitability has also been associated with the potential for functional recovery in patients with chronic stroke [30] Related studies have reached similar conclusions, suggesting that improvements in motor function among patients with stroke are associated with increased cortical excitability in preserved motor pathways [32] Cortical

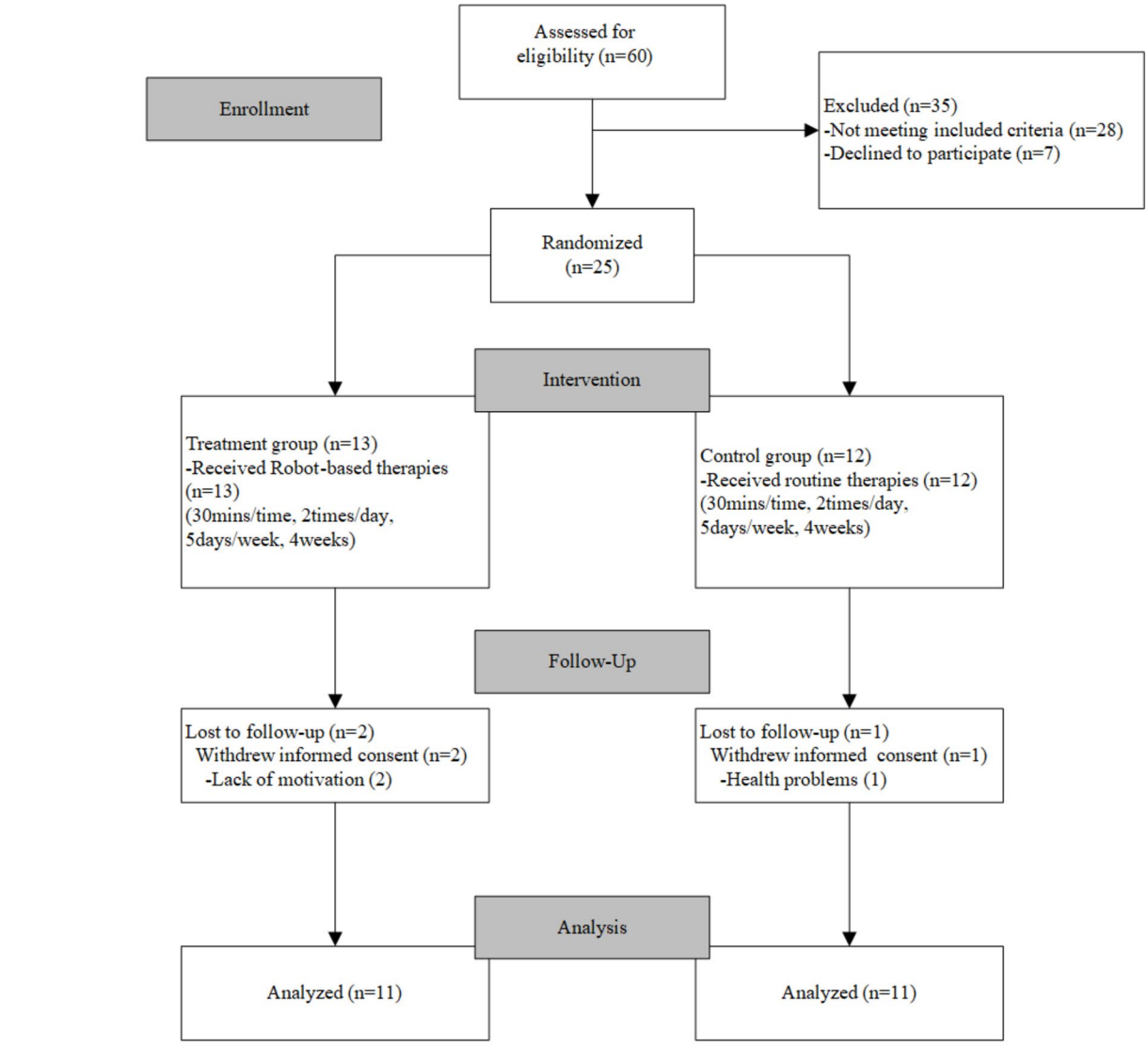

Fig. 2 Research Flowchart. **A**: Study Flow Chart CONSORT diagrame; **B**: Research timeline

Table 1 Baseline characteristics of patients

Characteristics	Group A (Treatment group) (*n* = 11)	Group B (Control group) (*n* = 11)	T/χ^2	*P* value
Mean age (SD), *yr*	48.64 (11.33)	51.55 (11.65)	0.393	0.698
Male, *n* (%)	9 (81.8)	7 (63.6)	0.326	0.568
Mean height (SD), m	1.72 (0.07)	1.66 (0.09)	0.130	0.897
Mean body weight (SD), *kg*	64.55 (10.34)	64.73 (8.63)	-1.278	0.214
Hemiplegia side, *n* (%)			0.987	0.320
Left	7 (63.6)	5 (45.5)		
Right	4 (36.4)	6 (54.5)		
Type of stroke, *n* (%)			0.987	0.320
Ischemia	7(63.6)	5 (45.5)		
Hemorrhage	4(36.4)	6 (54.5)		
Time since disease onset (SD), *day*	83.1 (48.1)	106.7 (50.8)	1.186	0.248
Degree of education, *n* (%)			3.134	0.371
Primary school and below	0 (0)	2 (18.2)		
Junior high school	3 (27.3)	4 (36.4)		
Senior high school	6 (54.5)	4 (36.4)		
College degree and above	2 (18.2)	1 (9.1)		
Stage of Brunnstrom, *n* (%)			1.754	0.625
II	0 (0)	1 (9.1)		
III	4 (36.4)	3 (27.3)		
IV	4 (36.4)	5 (45.5)		
V	3 (27.3)	2 (18.2)		
Mean rMT (SD), (%)	48.55(5.72)	52.55 (7.15)	17.989	0.263
Mean pMEPamp (SD), μv	499.44(63.88)	499.98 (105.83)	-0.384	0.705
Mean CMCT (SD), ms	8.35(1.07)	8.12 (1.75)	-0.097	0.924
Mean Curve slope (SD)	0.079 (0.012)	0.079 (0.007)	0.995	0.330
Mean Distance of 6-MWT (SD), *m*	101.00 (14.98)	82.18 (30.95)	-0.739	0.467
Mean Scores of FMA-LE (SD), (score)	22.18 (3.37)	22.91 (2.74)	0.383	0.705
Grade of FAC, *n* (%)			0.037	0.848
2	6 (54.5)	6 (54.5)		
3	5 (45.5)	5 (45.5)		
Mean cadence (SD), Step/min	34.64 (6.48)	30.99 (6.06)	-1.031	0.313
Mean Gait Cycle Time (SD), *S*	1.80 (0.38)	2.04 (0.59)	0.910	0.372
The ratio of support period to swing period	0.48 (0.15)	0.50(0.10)	0.537	0.597
RMS of Rectus Femoris (SD), μV	57.78 (16.67)	58.20 (35.71)	-0.024	0.981
RMS of Biceps Femoris (SD), μV	36.82 (18.50)	38.32 (25.92)	0.353	0.727
RMS of Tibialis Anterior (SD), μV	50.42 (21.17)	42.17 (27.85)	-0.575	0.571
RMS of Medial Gastrocnemius (SD), μV	47.64 (26.64)	42.57 (19.03)	-1.149	0.262
Mean CR of knee Flexion (SD), %	43.52 (8.59)	51.63 (10.57)	25.000	0.406
Mean CR of ankle dorsiflexion (SD), %	45.84 (12.25)	48.06 (14.07)	25.000	0.406

SD, standard deviation CMCT, central motor conduction time; pMEPamp, peak amplitude of motor evoked potential; rMT, resting motor threshold; 6-MWT, 6-min walk test; FMA-LE, Fugl-Meyer assessment lower extremity; FAC, functional ambulation category scale; CR, co-contraction ratio; RC, recruitment curve; RMS, root mean square

excitability is considered an objective method for measuring changes in neuroplasticity. One study showed that rMT measurements provide a reliable basis for the excitability of neuronal cell membranes, nerve conduction, and functional integrity of neuromuscular connections, [33] which is consistent with the findings of this study. Lower rMT values predict higher levels of motor function, which in turn is associated with increased cortical excitability (lower rMT values) [34] rMT results have a similar effect on the modulation of cortical excitability [35].

Although both groups showed significant improvements in the pMEPamp and RC slopes after intervention, these improvements were significant in the treatment group. pMEPamp and RC slope are considered reliable indicators of motor function, reflecting changes in the excitability state and neuroplasticity of the cortical motor area [22] Robot training mainly uses compensatory

Table 2 Primary and secondary outcomes

Outcome	Group A (Treatment group) ($n=11$)		Group B (Control group) ($n=11$)		Group-by-Time Interaction Effect[$]	Between-Group Difference in Change, Mean (95% CI)[‡]	*P* Value
	Mean	Change, Mean (95% CI)[†]	Mean	Change, Mean (95% CI)[†]			
Primary outcome							
Mean rMT (SD), %							
T0	48.55 (5.72)		52.55 (7.15)		< 0.001		
T1	45.18 (5.71)	−3.36 (− 3.94 to − 2.79)	50.09 (7.71)	−2.45 (− 3.09to − 1.82)		−4.91 (− 10.32 to 0.50)	0.075
T2	40.36 (5.45)	−8.18 (− 8.93 to − 7.43)	48.00 (7.43)	−4.55 (− 5.39to − 3.70)		−7.64 (− 12.82 to − 2.45)	**0.004**
Mean pMEPamp (SD), μV							
T0	499.43 (63.88)		499.98 (105.83)		*P* < 0.001		
T1	691.33 (152.35)	191.90 (128.60 to 255.20)	557.83 (133.84)	57.85 (35.64to80.07)		133.5 (19.24 to 247.76)	**0.022**
T2	849.48 (118.79)	350.05 (285.22 to 414.87)	597.50 (131.97)	97.52 (67.79to127.24)		251.9 (151.94to352.03)	**< 0.001**
Mean RC slope (SD)							
T0	0.079 (0.007)		0.079 (0.01)		*P* < 0.001		
T1	0.12 (0.02)	0.04 (0.03to0.05)	0.096 (0.02)	0.017 (0.012 to 0.02)		−0.02 (0.008to0.04)	**0.004**
T2	0.14 (0.02)	0.06 (0.05 to 0.07)	0.10 (0.02)	0.025 (0.02 to 0.03)		−0.03 (0.02to0.05)	**< 0.001**
Mean CMCT(SD), ms							
T0	8.35 (1.07)		8.12 (1.75)		*P* < 0.001		
T1	7.05 (0.95)	−1.30 (− 1.69 to − 0.91)	7.62 (1.71)	−0.49 (− 0.66 to − 0.32)		−0.57 (− 1.67 to 0.53)	**0.308**
T2	5.99 (1.32)	−2.36 (− 3.07 to − 1.66)	7.02 (1.82)	−1.10 (− 1.46 to − 0.74		−1.03 (− 2.29 to 2.15)	**0.112**
Secondary outcome							
Mean 6-MWT(SD), m							
T0	101.00 (14.98)		82.18 (30.95)		0.012		
T1	119.27 (30.08)	18.27 (7.68to28.87)	95.82 (29.16)	1.64 (0.62to2.65)		23.45 (− 0.15to − 3.98)	**0.051**
T2	153.27 (25.89)	45.45 (42.18to48.72)	118.55 (34.10)	24.36 (17.91to30.81)		−21.09 (− 29.35to47.06)	**0.011**
Mean FMA-LE(SD), (score)							
T0	22.18 (3.37)		22.91 (2.74)		0.026		
T1	24.18 (1.78)	2.00 (0.77to3.23)	24.18 (1.78)	1.27 (0.56to1.99)		0.00 (− 1.42to1.42)	1.000
T2	27.82 (2.96)	5.64 (4.34to6.93)	26.18 (2.09)	3.27 (1.96to4.58)		1.64 (− 0.41to3.68)	0.116
Grade of FAC(SD), n (%)							**0.026**
T0	2	6 (54.5%) -	6 (54.5%)	-	0.109	-	
	3	5 (45.5%) -	5 (45.5%)	-			
T1	2	3 (27.3%) -	1 (9.1%)	-	-	-	0.519
	3	7 (63.6%) -	9 (81.8%)	-			
	4	1 (9.1%) -	1 (9.1%)	-			
T2	2	2 (18.2%) -	0 (0%)	-	-	-	**0.040**
	3	5 (45.5%) -	2 (18.2%)	-			
	4	3 (27.3%) -	6 (64.5%)	-			
	5	1 (9.1%) -	3 (27.3%)	-			
Myoelectricity							
Mean CR of knee Flexion (SD),%							
T0	43.52 (8.59)		51.63 (10.57)		0.491		
T1	27.06 (7.66)	−0.15 (− 0.17to − 0.13)	37.59(9.16)	−0.15(− 0.17to − 0.13)		−0.09(− 0.16to − 0.03)	0.003
T2	17.05(5.77)	−0.25(− 0.28to − 0.22)	27.35(9.66)	−0.25(− 0.28to − 0.23)		−0.09(− 0.16to − 0.03)	**0.003**
Mean CR of ankle dorsiflexion (SD), %							
T0	45.84 (12.25)		48.06 (14.07)		0.087		
T1	28.81(8.78)	−0.15(− 0.18to − 0.12)	35.06(10.02)	−0.15(− 0.18to − 0.12)		−0.06(− 0.14to0.14)	0.115

Table 2 (continued)

Outcome	Group A (Treatment group) (*n* = 11)		Group B (Control group) (*n* = 11)		Group-by-Time Interaction Effect[$]	Between-Group Difference in Change, Mean (95% CI)[‡]	*P* Value
	Mean	Change, Mean (95% CI)[†]	Mean	Change, Mean (95% CI)[†]			
T2	15.00(3.40)	−0.27(−0.31to−0.23)	24.71(10.22)	−0.27(−0.31to−0.23)		−0.06(−0.14to0.14)	0.115
RMS of Rectus Femoris(SD),μV							
T0	57,78(16.67)		58.20(35.71)		0.014		
T1	72.71(13.50)	14.93(7.48to22.38)	66.16(33.07)	7.96(3.94to11.98)		6.55(−13.58to26.68)	0.524
T2	91.18(18.68)	33.40(26.51to40.30)	78.45(37.86)	20.25(14.67to18.43)		12.73(−11.05to36.52)	0.294
RMS of Biceps Femoris (SD), μV							
T0	36.82(18.50)		38.32(25.92)		0.001		
T1	51.16(23.31)	14.33(6.58to22.09	46.80(21.52)	8.48(4.62to12.34)		51.15(64.29to22.23)	0.633
T2	70.69(18.70)	33.87(28.77to38.96)	57.88(25.78)	19.57(14.20to24.93)		70.69(81.23to30.76)	0.162
RMS of Tibialis Anterior (SD), μV							
T0	50.42(21.17)		42.17(27.84)		$P < 0.001$		
T1	57.60(21.69)	7.18(−1.09to15.45)	56.91(25.27)	14.74(8.58to20.91)		0.68(−18.08to19.45)	0.943
T2	77.90(22.06)	27.48(15.45to31.28)	60.92(29.23)	18.75(14.49to23.01)		16.98(−3.65to37.61)	0.107
RMS of Medial Gastrocnemius (SD), μV,							
T0	47.64(26.64)		42.57(19.03)		0.010		
T1	57.36(21.77)	9.73(3.86to15.60)	47.14(22.10)	4.57(−0.88to10.02)		10.22(−7.25to27.70)	0.252
T2	76.19(24.82)	28.55(22.52to34.58)	59.00(21.47)	16.43(11.31to21.55)		17.18(−1.31to35.68)	0.069
Gait							
Mean cadence (SD), step/min							
T0	34.64(6.48)		30.99 (6.06)		0.014		
T2	41.82(7.00)	−7.18 (−7.81to−6.55)	37.04 (6.36)	−6.05 (−6.70to−5.39)		4.78 (−0.55to10.11)	0.079
Mean Gait Cycle Time (SD), S							
T0	1.80(0.38)		2.04(0.59)		0.579		
T2	1.48(0.27)	0.32(0.26to0.38)	1.68(0.41)	0.36(0.24to0.46)		−0.21 (−0.48to0.07)	0.143
the ratio of support period to swing period (SD)					0.006		
T0	0.48(0.15)		0.50(0.10)				
T2	0.61(0.15)	−0.13 (−0.15to−0.11)	0.59 (0.10)	−0.09 (−0.11to−0.08)		0.02 (−0.08to0.12)	0.724

SD: standard deviation; TMS: transcranial magnetic stimulation; BEAR-H1: Bilateral Exoskeletal assistive robot H1; rMT: resting motor threshold; RC slope: Slope of the recruitment curve; pMEPamp: the peak amplitude of motor evoked potential; CMCT: central motor conduction time; FMA-LE: Fugl-Meyer assessment lower extremity; FAC: functional ambulation category; 6-MWT:6-minute walking distance test; sEMG: surface electromyography; RF: rectus femoris; BF: biceps femoris; TA: tibialis anterior; MG: medial gastrocnemius; CR: co-contraction ratio

strategies to accomplish tasks and achieve treatment goals. The sensorimotor area of the cortex plays an important role in motor control [36] The increase in RC slope and MEP peak of the robot group in this study may indicate an enhancement of the corticospinal pathway connection in the brain. Motor function performance in patients with stroke depends on connections to a broader network of brain regions [37] The functional remodeling area can be located in the rear or front of the motor cortex, activating the primary motor cortex in the affected hemisphere (M1) [38] Therefore, this study was conducted to detect the M1 area excitability of patients with stroke via TMS. Robot-assisted training stimulates the relevant muscles of the lower limbs, which indirectly promotes changes in cortical motor excitability. Accurate visual and proprioceptive feedback is essential for motor skill learning. BEAR-H1 stimulates body's proprioceptors and promotes feedback from the sensory-motor neural pathway [39] Sensory input can affect motor cortex excitability in the target area. BEAR-H1 establishes repetitive, high-intensity, and sustainable sensory inputs to induce correct output from the patient and produce voluntary movements. Sensory input may be linked to brain plasticity in terms of motor recovery [40].

CMCT was obtained by subtracting the peripheral nerve component from the total latency obtained using TMS. CMCT reflects signal transmission time from the synapses of neurons in the cortex to the anterior horns of the spinal cord. For patients with stroke, a longer CMCT has been associated with worse recovery of motor limb function [41] Our findings suggest that the CMCT in the two groups was shorter after than before treatment,

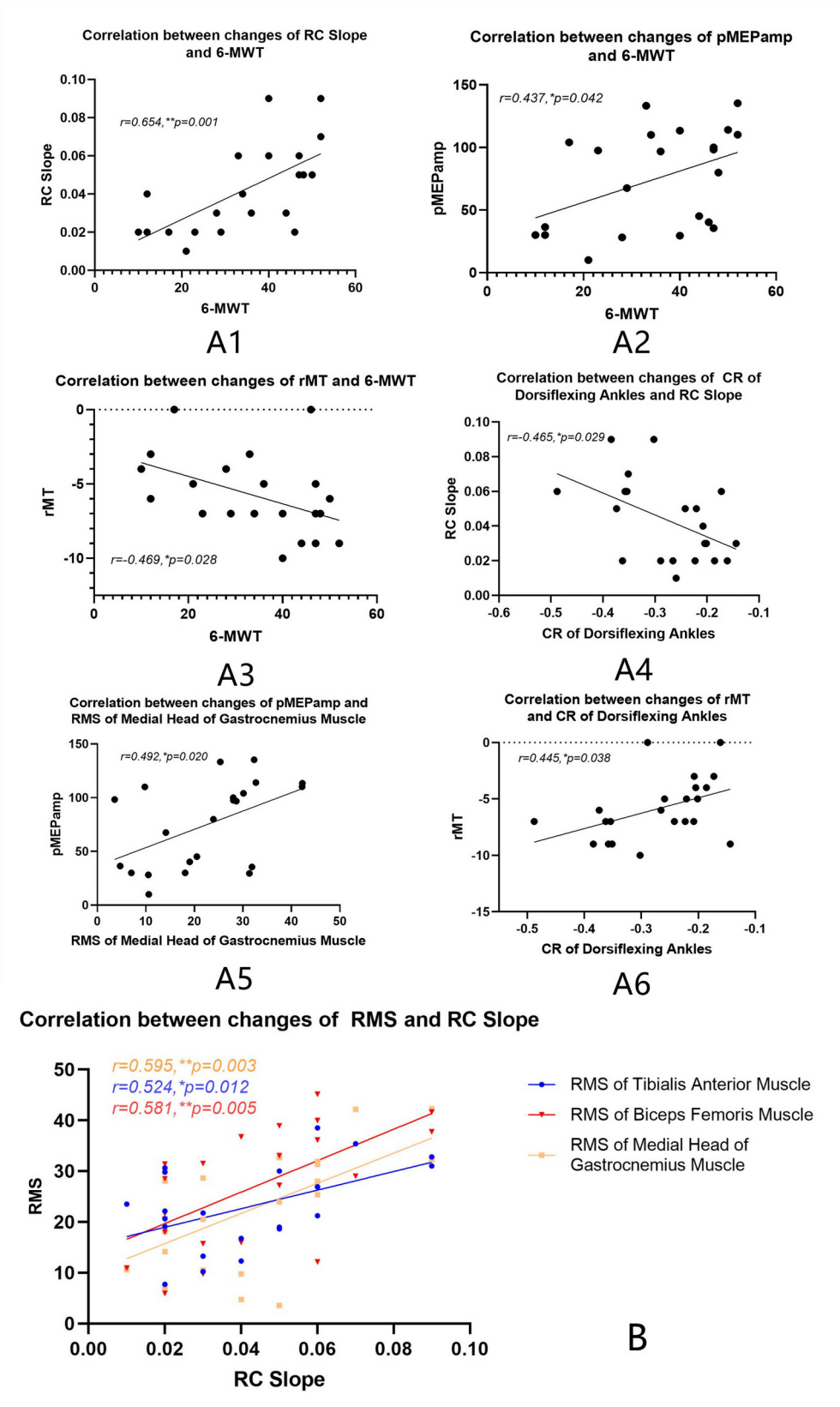

Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 Correlation analysis results between the primary indicators with 6-MWT and CR of ankle dorsiflexion. **A1**: 6-MWT correlated with RC slope ($R=0.654$); **A2**: 6-MWT correlated with pMEPamp ($R=0.437$); **A3**: 6-MWT correlated with rMT ($R=-0.469$); **A4**: CR of ankle dorsiflexion correlated with RC slope ($R=-0.465$); Fig. **A5**: RMS of Medial Gastrocnemius is correlated with pMEPamp ($R=0.492$); **A6**: CR of ankle dorsiflexion correlated with rMT ($R=0.445$); **B**: RC slope positively correlated with RMS of tibialis anterior ($R=0.524$), RC slope positively correlated with RMS of biceps femoris ($R=0.581$); RC slope positively correlated with RMS of the medial gastrocnemius ($R=0.595$)

which may directly indicate improved nerve conduction in the corticospinal tract of hemiplegic patients and indirectly indicate neuroplasticity changes, with similar trends observed for pMEPamp and RC slope. We speculate that the cerebral cortex becomes activated after treatment, thereby enhancing the excitability of the damaged corticospinal tract and ultimately improving the patient's lower limb motor function and walking ability.

Our robot training involved a complete walking mode that exercised each joint in lower limbs. Hemiplegic gait is characterized by abnormal cadence and gait cycle time. To prevent patients with stroke from falling while walking, the walking speed is slowed and the stride length is shortened. At baseline (T0), patients presented with a lower stance/swing ratio in the affected limb. Gait analysis data improved in both groups after 4 weeks of training. Hemiplegic gait always shows a reduction in the amplitude of motion and a lack of strength to move the limbs forward during the swing phase,42] which prolongs the swing time of the affected side and the support time of the unaffected side. Simultaneously, weakened balance and coordination ability significantly shorten the support time of the affected limb, [43] which in turn decreases the support period-to-swing period ratio on the affected side. The 6-MWT, which is a reliable indicator of lower limb muscle strength and physical walking capacity in patients with stroke, was primarily used to determine walking speed [44] Although both groups showed improvement in their 6-MWT after treatment, the improvement was significantly better in the treatment group. FAC and FMA-LE are usually selected to measure lower limb movement and walking ability in patients with stroke. Our study showed that both the treatment and control groups had improved FAC and FMA-LE, increased cadence, shortened gait cycle time, and increased support period-to-swing period ratio on the hemiplegic side, although no significant differences were observed between the two groups. Robot walking training may provide patients with symmetrical training patterns and stable balance, which play an important role in the recovery of lower limb motor function. Recently, a meta-analysis study revealed that robotic therapy is an effective strategy for promoting recovery of walking speed in patients [45].

As walking speed and distance increase, lower limb muscles require more muscular power to drive the legs forward. sEMG, which reflects motor unit recruitment and firing rates, can serve as an indicator of neuromuscular function recovery [46] This study focused on rectus femoris, biceps femoris, tibialis anterior, and medial gastrocnemius as the target muscles and measured changes in their EMG findings. Notably, our results revealed that both groups showed significant improvements in RMS, although no significant difference was observed between the two groups. These results are consistent with those of previous studies focusing on lower limb rehabilitation robot training [47] However, including the biceps femoris and medial gastrocnemius, related studies have concluded that the electric signal intensity of various muscles increases simultaneously during training, [48] which limits walking quality. Robot-assisted walking training reduces the co-activation of lower limb muscles and breaks the co-movement pattern. A correct walking pattern requires the interactive inhibition of active and antagonistic muscles during walking [49] We used CR as a reliable assessment metric. Walking requires combined neuromuscular movement. During walking, patients with stroke have increased CR in their lower limb muscles; increasing the value of CR increases the resistance value of joint movement [50] The CR of antagonistic muscle groups causes inefficient movement. We confirmed that CR in the two groups decreased significantly after treatment. Moreover, our findings showed that the treatment group was more effective in reducing knee flexion CR than the control group. The affected knee and ankle joints performed multiple repetitive flexion and extension movements with oscillation of the robotic exoskeleton, which promoted CR of the active and antagonistic muscles.

The rMT, pMEPamp, and RC slopes gradually improved with training. To understand the correlation between these indicators, we performed correlation matrix analysis for all primary and secondary outcome measures. Accordingly, we found that improvements in rMT, pMEPamp, and RC slope were significantly correlated with 6-MWT, CR on ankle dorsiflexion, and RMS of the tibialis anterior, biceps femoris, and medial gastrocnemius muscles. Therefore, we speculate that the mechanism by which BEAR-H1 training improves lower limb motor function in patients with stroke may be through improved corticospinal excitability, which is consistent with the TMS parameter values.

Limitation

The main limitation of this study is our inclusion of only subacute patients with stroke with certain walking abilities and the relatively small number of subjects meeting the inclusion criteria due to our strict inclusion and exclusion criteria. The study did not categorize the subjects into those with cerebral hemorrhage or infarction, which may have influenced the results. Future in-depth studies involving larger samples and multiple centers are necessary to investigate the effects of robotic training on the reconstruction of brain function in patients with stroke.

Conclusion

Our findings showed that BEAR-H1 training improved cerebral cortical excitability and corticospinal conduction in patients with stroke, which facilitated changes in neuroplasticity and significantly improved lower limb motor function in patients with stroke with hemiplegia. Correlation analysis revealed a significant correlation between changes in neuroplasticity and recovery of lower limb motor function in patients with stroke. We speculate that the mechanism by which BEAR-H1 training improves lower limb motor function in patients with stroke may be through improved cerebral cortical excitability and corticospinal conduction, which promote neuroplastic changes.

Supplementary Information

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Supplementary Material 1

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Author contributions

Study concept and design: Guozhi Huang and Tao Fan. Acquisition, analysis, or interpretation of data: Xue Zhang and Peng Zheng. Therapeutic intervention: Longlong He, Mingyang Wei and Zhangqi Peng. Scale evaluation: Xue Zhang and Ze Gong. Drafting of the manuscript: Peng Zheng. Critical revision of the manuscript: Tao Fan and Jing Zhou. Statistical analysis: Peihua Cao, Yu Shi and Shilin Li. Technical support: Qing Zeng and Pengcheng Lu. Study supervision: Yijin Zhao, Jihua Zou, Chenyu Xu and Rong Chen. Tao Fan and Peng Zheng contributed equally to this work and should be regarded as co-first authors.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethical approval and consent to participate

Studies involving human patients were reviewed and approved by the Institutional Ethics Committee of Zhujiang Hospital of Southern Medical University has approved our study (Reference Number: 2019-QX-004-01). Written informed consent was obtained from the individual or guardian participants.

Consent for publication

Not applicable.

Human and animal ethics

Not applicable.

Competing interests

The authors declare no competing interests.

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