Journal of the Neurological Sciences 404 (2019) 11–15

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Acute stroke rehabilitation for gait training with cyborg type robot Hybrid Assistive Limb: A pilot study

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ARTICLE INFO

Keywords:
Robot-assisted rehabilitation
Acute stroke
Gait training
HAL
FIM
Measures

ABSTRACT

Robot-assisted gait training following acute stroke could allow patients with severe disability to receive a high dosage and intensity of gait training compared with conventional physical therapy (CP). However, given the limited data on gauging the efficacy of Hybrid Assistive Limb (HAL) on gait training in patients with acute stroke, we aimed to evaluate several outcome measures following gait training with HAL. Patients with first-ever stroke, who required a walking aid and were able to start gait training within 1 week of stroke onset were included in the current study. Patients were assigned to either the CP or HAL group. Outcome measures were collected at baseline, and at the 2nd (at 2–6 weeks), and 3rd (at 3–5 months) assessments. All patients underwent physical therapy until the 3rd assessment; patients in the HAL group underwent gait training using HAL until the 2nd assessment. Thirty-seven patients (19 from CP and 18 from HAL, median age = 69 years) completed the study. At the 2nd assessment, the total Functional Independence Measure (FIM) score was higher in the HAL group than in the CP group (90.1 vs. 79.0, p = 0.042). In conclusion, the FIM scale could be used to identify responsiveness to acute stroke rehabilitation using HAL.

1. Introduction

Minimizing physical impairment and facilitating functional recovery following stroke is the most important target of managing patients with acute stroke. There is accumulating evidence of enhanced plasticity, such as alterations of gene expression, inhibitory/excitatory synaptic input balance, and structural changes including synaptogenesis, which occur immediately after stroke [1–5]. Task-specific motor training that is initiated soon after stroke facilitates the reorganization of connections in a sensitive manner, which reportedly induces dramatic recovery if residual motor cortical areas are spared [6–8]. Thus, motion-focused training during the early phase of post-stroke may prove to be a promising intervention to increase the resolution of impairment in a proportional manner in patients with stroke.

There are still several challenges associated with making an acute stroke rehabilitation protocol. A very early rehabilitation trial (AVERT) demonstrated that a higher dose and very early mobilization within 24 h of stroke onset in acute strokes did not improve functional outcome at 3 months in patients with very early mobilization, compared to those who received usual care [9]. According to a meta-analysis, newly developed electromechanical-assisted training using various devices for walking, in combination with physical therapy, within 3 months after stroke improved independent walking compared with gait training without a device [10]. However, a device selection and rehabilitation

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https://doi.org/10.1016/j.jns.2019.07.012
Received 3 April 2019; Received in revised form 3 July 2019; Accepted 9 July 2019
Available online 10 July 2019

protocol to enhance recovery of function in patients with acute stroke has not yet been established.

A cyborg-type robot, Hybrid Assistive Limb (HAL), which is manufactured by Cyberdyne Inc., Tsukuba, Japan, is a promising robotic device using innovative technology cybernics, where man and machine are connected mechanically and electronically, is used in the system. A biped non-medical model of HAL, HAL-FL05, was chosen in the present clinical setting according to Japanese device regulation. Briefly, HAL can estimate and decode the wearer's motion intension of bilateral hips and knee joints in real time from bioelectrical signals, such as the wearer's motor unit potentials on the skin with joint angles and shoe force plate signals analyses. It can enhance the wearer's gait movement by means of appropriate actuator torque using four actuators on the bilateral hip and knee joints, as described in detail elsewhere [11]. In Japan, HAL was approved as a medical device for patients with eight rare neuromuscular diseases in 2015; however, it has not yet been approved for patients with acute stroke. Although there are reports on the safety or feasibility of the HAL system [12,13], and its beneficial effects on gait [14,15], its effectiveness on gait training following acute stroke has not yet been confirmed. Before a randomized controlled clinical trial to test the efficacy of HAL in patients with acute stroke can be conducted, appropriate outcome measures must first be established.

The aim of the present study was to evaluate several outcome measures following gait training, which was initiated within 1 week of acute stroke onset, to design a confirmatory clinical trial for gait training using HAL in the future.

2. Participants and methods

This was a single center, observational study. The present study was approved by the Institutional Research and Ethics Committee (M28-063-8) and registered with the UMIN clinical trial (ID: UMIN000024655). Written informed consent was obtained from all participants.

2.1. Participants

Patients with acute stroke admitted to the National Cerebral and Cardiovascular Center within 48 h of stroke onset from October 2016 to March 2018 were recruited to the present study. Inclusion criteria were as follows: (1) aged ≥ 20 and < 90 years old; (2) first-ever stroke; (3) required a walking aid (Functional Ambulation Categories; FAC [16] 0–2); (4) ability to start gait training within 1 week of stroke onset; and (5) fit in the robotic suit HAL (height, 150–180 cm; weight ≤ 80 kg). Major exclusion criteria were as follows: (1) communication difficulties due to impaired consciousness and/or cognitive dysfunction; (2) patients with aneurysmal subarachnoid hemorrhage; (3) difficulty in performing gait training exercises due to orthopedic disease; (4) serious hepatic/renal failure; and (5) gait impairment due to cerebral or muscle disorders other than acute stroke. Patients were quasi-randomly assigned to either the group undergoing gait training with conventional physical therapy (CP group) from October 2016 to January 2017 or to the group undergoing robot-assisted gait training using HAL combined with conventional physical therapy (HAL group) from February 2017 to May 2017. Patients were alternately allocated to either the CP or HAL groups between June 2017 and March 2018.

2.2. Gait training program

The gait training program in our hospital consisted of 1–3 sessions per day (20 min per session), 5 or 6 days a week for at least 1 week, but up to 6 weeks, according to the patients' achievements. In the CP group, gait training was performed by a physical therapist without using HAL for 3 weeks. In contrast, participants in the HAL group underwent gait training with HAL combined with physical therapy, which was conducted 3 days a week for 3 weeks, and conventional physical therapy, which was performed during another 2 or 3 days a week until transfer to a rehabilitation hospital. During HAL training, a mobile hoist (ROPOX ALL IN ONE™) was used to prevent falls and adjust the patient's posture. Two physical therapists oversaw each patient; one physical therapist monitored the HAL and patient's leg movement, while the other operated the mobile hoist to support the patient's gait appropriately (Fig. 1). After both groups completed training, all patients were discharged to a rehabilitation hospital to continue gait training until 3–5 months after the onset of the index stroke. In these hospitals, the patients underwent conventional physical therapy alone, for at least 3 sessions per day (20 min per session) but did not receive gait training with HAL.

Fig. 1. Gait training with Hybrid Assistive Limb (HAL).

2.3. Demographic data and outcome measures

We recorded baseline data, including demographic data, risk factors, and stroke subtype. Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) score [17].

The following outcome measures were also obtained: motor impairment assessed by Fugl-Meyer Assessment (FMA) [18,19]; walking ability assessed by FAC [16]; and independence in activities of daily living assessed by Functional Independence Measure (FIM) including the FIM total score, and motor (self-care, sphincter control, transfers, locomotion) and cognitive sub-scores (communication, social cognition) [20]. These outcome measures were collected three times during the study period, i.e., at registration as the 1st assessment, from 2 to 6 weeks after the stroke onset as the 2nd assessment (before transition to a rehabilitation hospital), and from 3 to 5 months after the onset as the 3rd assessment. All assessments in the HAL group were performed when the participants were not wearing the HAL. At the 3rd assessment, patients were asked to visit our hospital to follow up examinations of the motor assessment.

Further, we collected data associated with the amount of the rehabilitation. Adverse events included falls, symptom deterioration with NIHSS score ≥ 2, stroke recurrence, and the occurrence of cardiovascular events and infectious diseases until the 3rd assessment. Adverse events were assessed through the medical charts in our hospital or by querying this from the rehabilitation hospital. We analyzed data of patients who completed all three assessments.

2.4. Statistical analyses

The χ^2 test, Student's *t*-test, Mann-Whitney *U* test were used as appropriate to determine differences in clinical characteristics and outcome measures between the HAL and CP groups. Following the analysis of data from all the participants, we performed a post-hoc analysis on data from patients with severe lower limb motor impairment alone. This was defined as a value below the mean motor domain score of the lower extremity section in the FMA (FMA-LE) in all participants at baseline. All individual results were collected at each timepoint using an anonymous identification number assigned to each patient. We conducted a mixed-effect model for repeated measures using data from each patient as random intercepts to adjust for autocorrelation of individuals using the xtmixed command in the STATA software, version 14.2 (Stata Corp., College Station, TX, USA). All statistical tests were two-sided and statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS package (version 24. IBM Japan Corp., Tokyo, Japan) or STATA software.

3. Results

Of the 1038 patients who were admitted to our hospital within 48 h of stroke onset from October 2016 to March 2018, 47 patients (male, 28; age, 69 years in median) were enrolled in the present study. Among the 47 patients, 24 patients were assigned to the CP group, while 23 patients were assigned to the HAL group. No patient had falls, symptom deterioration, and stroke recurrence until the 3rd assessment after the onset of index stroke. Five patients in each group dropped out; data from the remaining 19 patients in the CP group and 18 patients in the HAL group were analyzed (Fig. 2).

There were no significant differences in patient characteristics between the two groups (Table 1). In the HAL group, the duration from stroke onset to the 2nd assessment was longer (median 25 vs. 20 days, $p < 0.001$) and the amount of rehabilitation by physical as well as occupational therapists per person until the 2nd assessment was higher, when compared with the CP group (physical therapists, median 730 vs. 500 min, $p = 0.002$; occupational therapists, median 510 vs. 280 min, $p = 0.004$). There were no other significantly different parameters in the amount of rehabilitation between the two groups (Table 1).

Significant improvements in all outcome measures at either 2nd or 3rd assessments compared to baseline assessment were demonstrated in both groups ($p < 0.001$). At the 2nd assessment, the predicted FIM total score in the HAL group was 90.1, which was higher than that in the CP group (79.0; $p = 0.042$); however, this difference disappeared at the 3rd assessment (Table 2). There were no significant differences in the FIM motor sub-score between the two groups at any of the three assessments. The FIM cognitive sub-scores in the HAL group at baseline and the 2nd assessment were higher than those in the CP group (Table 2). The social cognitive FIM sub-scores at the 1st or 2nd assessments were higher in the HAL group compared to the CP group; 1st assessment, median 17.7 vs. 15.2, $p = 0.012$; 2nd assessment, 20.3 vs. 17.8, $p = 0.017$. However, these differences were not significant at the 3rd assessment. There were no significant differences in the predicted score of FAC as well as FMA in each assessment between the two groups (Table 2).

Data from 23 patients whose mean value of FMA-LE under 20 underwent post-hoc analysis of severe motor impairment of lower limb; 11 patients were assigned to the CP group and 12 patients to the HAL group. FAC as well as the FIM motor sub-score at both the 2nd and 3rd assessments in the HAL group were significantly higher than those in the CP group (Table 3). At the 2nd and 3rd assessments, the transfers/locomotion FIM motor sub-scores were higher in the HAL group compared to the CP group; 2nd transfers score, median 12.0 vs. 8.7, $p = 0.007$; 3rd transfers score, median 18.7 vs.15.3, $p = 0.005$; 2nd locomotion score, median 6.3 vs. 3.5, $p = 0.009$; 3rd locomotion score, median 10.3 vs. 7.6, $p = 0.012$. Further, the FIM cognitive sub-scores in the HAL group at both the 1st and 2nd assessments were also significantly higher than those in the CP group (Table 3). In the FIM cognitive sub-scores, the communication/social cognitive sub-scores of the HAL group were higher compared to the CP group; 1st communication score, median 11.9 vs. 9.6, $p = 0.006$: 2nd communication score, median 13.1 vs. 11.3, $p = 0.034$; 1st social cognitive score, median 17.6 vs. 13.9, $p = 0.005$; 2nd social cognitive score, 20.3 vs. 17.2, $p = 0.017$. These differences were not significant at the 3rd assessment. In the FIM total score, the score at the 2nd assessment was significantly higher in the HAL group than that in the CP group (median 89.8 vs. 68.6 days, $p = 0.001$).

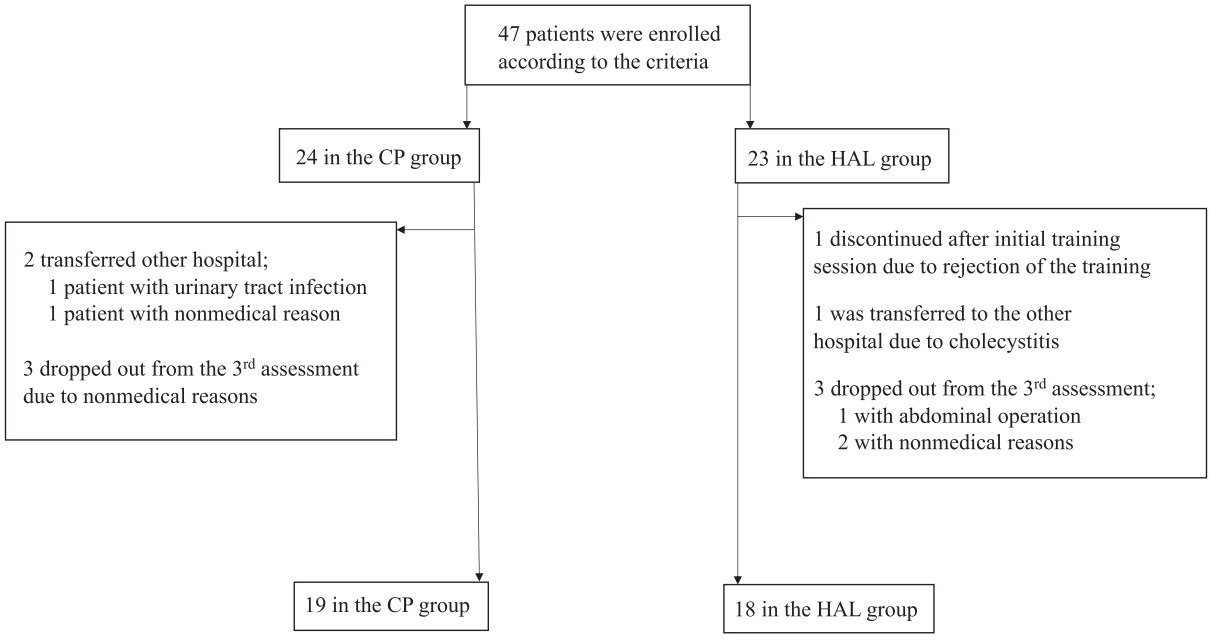

Fig. 2. Study profile.

Table 1
Demographic characteristics and variables indicated as the amount of rehabilitation.

	CP group (n = 19)	HAL group (n = 18)	P value
Age, years	69 (63–77)	69 (55–79)	0.773
Sex, F/M	7(37)/12(63)	2(11)/16(89)	0.124
Risk factors			
Smoking (none/past/current)	8(42)/5(26)/6(32)	9(50)/5(28)/4(22)	0.806
Alcohol drinking (none/current)	5(26)/14(74)	9(50)/9(50)	0.184
Hypertension	18 (95)	18 (100)	1.000
Dyslipidemia	7 (37)	10 (56)	0.330
Diabetes mellitus	3 (16)	6 (33)	0.269
Atrial fibrillation	3 (16)	2 (11)	1.000
History of ischemic heart disease	1 (5)	2 (11)	0.604
Stroke subtype			0.184
Ischemic	5 (26)	9 (50)	
Hemorrhagic	14 (74)	9 (50)	
NIHSS score	8(5–10)	7(4–9.25)	0.419
Thrombolytic therapy	3(16)	3 (17)	1.000
Days from stroke onset to the 1st assessment	5(4–7)	6(4–6)	0.975
Days from stroke onset to the 2nd assessment	20(16–22)	25(23–27)	< 0.001
Days from stroke onset to the 3rd assessment	96(93–121)	95(91–100)	0.330
Total amount of rehabilitation by physical therapists until the 2nd assessment (min)	500(480–680)	730(635–805)	0.002
Total amount of rehabilitation by occupational therapists until the 2nd assessment (min)	280(200–540)	510(440–850)	0.004
Total amount of rehabilitation by speech therapists until the 2nd assessment (min)	180(100–240)	250(115–460)	0.085
Total amount of rehabilitation by physical therapists until the 3rd assessment (min)	6080(4520–7260)	6100(4715–6660)	0.533

NIHSS score indicates National Institute of Health Stroke Scale. Age, NIHSS score, days from stroke onset to the initial gait training or the assessments, are median values and values in parentheses are interquartile ranges. Other values are numbers and values in parentheses are percentages of the number of patients.

Table 2
Summary of the results for the outcome measures.

Outcome measures	Ass.	CP group (n = 19)	HAL group (n = 18)	P value
FMA total score	1st	154.1 (138.4, 169.8)	152.7 (136.6, 168.8)	0.904
	2nd	170.8 (155.2, 186.5)	173.1 (157.0, 189.2)	0.847
	3rd	185.8 (170.2, 201.5)	179.9 (163.9, 196.0)	0.607
Lower extremity	1st	19.5 (16.4, 22.7)	16.8 (13.6, 20.0)	0.230
	2nd	23.3 (20.2, 26.5)	23.2 (20.0, 26.4)	0.967
	3rd	28.1 (24.9, 31.2)	26.7 (23.5, 29.9)	0.545
FAC	1st	1.05 (0.61, 1.50)	1.17 (0.71, 1.62)	0.725
	2nd	2.00 (1.56, 2.44)	2.44 (1.99, 2.90)	0.170
	3rd	3.53 (3.08, 3.97)	3.78 (3.32, 4.23)	0.437
FIM total score	1st	60.8 (53.3, 68.3)	63.9 (56.2, 71.6)	0.571
	2nd	79.0 (71.5, 86.4)	90.1 (82.4, 97.7)	0.042
	3rd	110.6 (103.2, 118.1)	113.9 (106.2, 121.6)	0.551
Motor sub-score	1st	35.0 (29.0, 41.0)	34.3 (28.2, 40.4)	0.868
	2nd	48.8 (42.9, 54.8)	56.7 (50.6, 62.9)	0.071
	3rd	77.6 (71.6, 83.5)	79.9 (73.8, 86.1)	0.587
Cognitive sub-score	1st	25.8 (23.7, 27.9)	29.6 (27.5, 31.8)	0.012
	2nd	30.1 (28.0, 32.2)	33.3 (31.2, 35.5)	0.034
	3rd	33.1 (31.1, 35.1)	33.9 (31.8, 36.1)	0.559

All values are predicted values and values in parentheses are 95% confidence interval.
Ass., assessment time point; 1st, 1st assessment; 2nd, 2nd assessment; 3rd, 3rd assessment., FMA, Fugl-Meyer Assessment; FAC, Functional Ambulation Categories; FIM, Functional independence Measures.

Table 3
Summary of the results for outcome measures in the subgroup of patients with severe walking disability.

Outcome measures	Ass.	CP group (n = 11)	HAL group (n = 12)	p
FMA total score	1st	137.7 (117.6, 157.9)	140.8 (121.6, 160.1)	0.827
	2nd	152.8 (132.7, 172.9)	162.3 (143.0, 181.5)	0.507
	3rd	165.3 (145.2, 185.4)	170.9 (151.7, 190.2)	0.691
Lower extremity	1st	14.4 (10.9, 17.8)	12.0 (8.7, 15.3)	0.329
	2nd	18.6 (15.1, 22.0)	20.8 (17.5, 24.0)	0.362
	3rd	25.4 (21.9, 28.8)	25.0 (21.7, 28.3)	0.881
FAC	1st	0.91 (0.40, 1.42)	1.17 (0.68, 1.66)	0.475
	2nd	1.55 (1.04, 2.06)	2.42 (1.93, 2.91)	0.016
	3rd	2.64 (2.13, 3.15)	3.75 (3.26, 4.24)	0.002
FIM total score	1st	54.4 (45.2, 63.5)	63.9 (55.2, 72.7)	0.139
	2nd	68.6 (59.4, 77.7)	89.8 (81.0, 98.5)	0.001
	3rd	101.3 (92.1, 110.4)	113.8 (105.0, 122.5)	0.053
Motor sub-score	1st	30.9 (23.7, 38.1)	34.4 (27.5, 41.3)	0.492
	2nd	40.1 (32.9, 47.3)	56.3 (49.4, 63.2)	0.001
	3rd	69.6 (62.4, 76.9)	79.9 (73.0, 86.8)	0.044
Cognitive sub-score	1st	23.5 (20.7, 26.2)	29.5 (26.9, 32.2)	0.002
	2nd	28.5 (25.7, 31.2)	33.4 (30.8, 36.1)	0.011
	3rd	31.6 (28.9, 34.4)	33.8 (31.2, 36.5)	0.261

All values are predicted values and values in parentheses are 95% confidence interval.
Ass., assessment time point; 1st, 1st assessment; 2nd, 2nd assessment; 3rd, 3rd assessment., FMA, Fugl-Meyer Assessment; FAC, Functional Ambulation Categories; FIM, Functional independence Measures.

4. Discussion

These results showed that the FIM score was sufficient to demonstrated significant changes due to gait training using HAL in acute stroke rehabilitation. In patients with severe motor impairment of the lower limb, the FAC score was also useful to measure the efficacy of HAL. Moreover, at the 2nd assessment, the FIM score improved in patients who received a higher dose-intensive gait training combined with HAL compared with those who received physical therapy without HAL, especially in patients with severe lower limb motor impairments.

In all patients, the predicted total score of FIM, but not FAC or FMA, at the 2nd assessment in the HAL group was higher than that at the 2nd assessment in the CP group. The FIM score is a tool of assessment of a patient's independence, describing the burden of care and the need for help to conduct the optimal level of functioning [20]. The FAC describes how much human support the patient requires when walking [16]. The FMA scale was developed as an instrument for measuring sensorimotor stroke recovery, based on concept of sequential stage of motor recovery patients with hemiplegic stroke [18,19]. The improvement in walking and functional independency at either the 2nd or the 3rd assessments compared to baseline levels in the present study demonstrated the spontaneous biological recovery post-stroke due to underlying physiological processes. These processes should be assessed by the FMA, FAC, and FIM scales. In addition to the improvement of motor recovery, achieving better activities of daily living or

independent walking in the HAL group, which are well described by the FIM or FAC, could be attributed to the patients' motivation aroused by robot-assisted rehabilitation since psychological features may affect the outcomes of patients undergoing robot-assisted rehabilitation [21–23]. In the present study, the higher social cognitive score at baseline of the HAL group could have affected the better physical and social function outcomes of this group at the 2nd and 3rd assessments.

In all patients, the significant improvement in the total FIM score in the HAL group could not be observed until the 3rd assessment due to the ceiling effect of the FIM score. Conversely, patients with severe walking disability in the HAL group demonstrated improvement in walking independency compared to the CP group at either the 2nd or the 3rd assessments. These findings in the HAL group could be attributed to the reduction of the ceiling effect in patients with severe walking disability, or by a more beneficial effect of the gait training with HAL for patients with a severe walking disability. Indeed, gait training with HAL that is targeted at patients with severe walking disability should be part of the training rationale because HAL enables patients with severe disability to receive a higher dosage and intensity of gait training compared with conventional physical therapy. The transfer or locomotion FIM motor sub-scores of patients with severe walking disability were higher in the HAL group compared to the CP group at both the 2nd and 3rd assessments. Since functional independency could be induced by gait training, in a dose-dependent manner, patients in the HAL group may start walking independency in relatively short periods compared with conventional physical therapy.

Several limitations in the current study must be noted. Given the observational study design of the present study, we could not control the total amount of rehabilitation training time until the 2nd assessment or FIM cognitive sub-score at baseline. Longer PT and OT training time until the 2nd assessment for patients with HAL group or higher score of FIM cognitive sub-score at baseline in the HAL group could have affected the independency of daily living at the 2nd and 3rd assessments. Still, compared to the CP group with severe walking disability, the HAL group did show improvement of FAC as well as FIM at the 2nd or 3rd assessments. Patients were randomized according to the alternate allocation, and the effect of confounding factors might not be balanced between the two groups.

In conclusion, both the FIM and FAC scores could be used to monitor clinical changes in response to acute stroke rehabilitation using HAL. It may be rational to conduct acute stroke rehabilitation using HAL targeted for patients with severe walking disability. A randomized trial would be needed to clarify the effect of HAL especially on patients with severe walking disability.

Source of funding

This study was supported by the Intramural Research Fund of the National Cerebral and Cardiovascular Center (29-3-1).

Disclosures

None.

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