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Robot-assisted gait training improves brachial–ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation

Randomized controlled trial

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Abstract

Objective: Brachial–ankle pulse wave velocity (baPWV) evaluates arterial stiffness and also predicts early outcome in stroke patients. The objectives of this study were to investigate arterial stiffness of subacute nonfunctional ambulatory stroke patients and to compare the effects of robot-assisted gait therapy (RAGT) combined with rehabilitation therapy (RT) on arterial stiffness and functional recovery with those of RT alone.

Method: The RAGT group (N=30) received 30 minutes of robot-assisted gait therapy and 30 minutes of conventional RT, and the control group (N=26) received 60 minutes of RT, 5 times a week for 4 weeks. baPWV was measured and calculated using an automated device. The patients also performed a symptom-limited graded exercise stress test using a bicycle ergometer, and parameters of cardiopulmonary fitness were recorded. Clinical outcome measures were categorized into 4 categories: activities of daily living, balance, ambulatory function, and paretic leg motor function and were evaluated before and after the 4-week intervention.

Results: Both groups exhibited significant functional recovery in all clinical outcome measures after the 4-week intervention. However, peak aerobic capacity, peak heart rate, exercise tolerance test duration, and baPWV improved only in the RAGT group, and the improvements in baPWV and peak aerobic capacity were more noticeable in the RAGT group than in the control group.

Conclusion: Robot-assisted gait therapy combined with conventional rehabilitation therapy represents an effective method for reversing arterial stiffness and improving peak aerobic capacity in subacute stroke patients with totally dependent ambulation. However, further large-scale studies with longer term follow-up periods are warranted to measure the effects of RAGT on secondary prevention after stroke.

Abbreviations: ADL = activities of daily living, ANOVA = analysis of variance, BBS = Berg balance scale, BMI = body mass index, BWS = body-weight support, baPWV = brachial–ankle pulse wave velocity, CV = cardiovascular, cfPWV = carotid–femoral PWV, DBP = diastolic blood pressure, ETT = exercise tolerance test, FAC = functional ambulation category, GF = guidance force, HR = heart rate, HTN = hypertension, FMA-LL = lower limb score in the Fugl–Meyer Assessment, NDT = neurodevelopmental techniques, VO_2 = oxygen consumption, HR_{peak} = peak heart rate, PT = physiotherapy, PWV = pulse wave velocity, RT = rehabilitation therapy, rpm = revolutions per minute, RAGT = robot-assisted gait therapy, RAGT+PT = RAGT in combination with physical therapy, SBP = systolic blood pressure, K-MBI = The Korean version of the Modified Barthel Index, W = watt.

Keywords: cardiopulmonary fitness, recovery of function, robot-assisted gait training, stroke, vascular stiffness

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1. Introduction

Stroke is a common cause of death worldwide,[1] and gait impairment after stroke can decrease functional independence, limit activities of daily living (ADL) and social participation, and reduce the quality of life.[2] Furthermore, stroke survivors remain at high risk for cardiovascular (CV)-related morbidity including recurrent stroke, myocardial infarction, and sudden cardiac death.[3,4] Recurrent strokes constitute 29% of all strokes in the United States of America,[5] and the cumulative 5-year recurrence rate for brain infarction is 42% for men and 24% for women.[6] Functional deficits after stroke may aggravate physical inactivity and lead to a deconditioned state, which might exacerbate CV fitness or decrease long-term prognosis.[7–9]

Therefore, task-oriented rehabilitation therapy for recovery of independent walking is a primary goal of poststroke rehabilitation. This type of therapy ranges from physical therapist-dependent mobility-related tasks that address key impairments and functional limitations to tasks employing specialized equipment using partial weight bearing treadmills, motorized aquatic treadmills, and novel robotic orthosis.

Atherosclerosis and arterial stiffness contribute significantly to the pathophysiology of CV diseases. Arterial stiffness is closely related to impaired arterial compliance and is an independent predictor of atherosclerosis, CV mortality, fatal and nonfatal coronary events, and fatal strokes.[10–12] Pulse wave velocity (PWV) is a marker of arterial stiffness.[13] Measurement of carotid–femoral PWV (cfPWV) is thought to represent central artery stiffness and to have prognostic value for development of CV-related morbidity and mortality.[14] On the other hand, brachial–ankle PWV (baPWV) has been developed as an alternative method for assessing arterial stiffness.[15] Measurement of baPWV records brachial and tibial artery waveforms via an automated method, does not require exposure of a femoral site, and has several other advantages including procedural simplicity and the short time required for measurement.[16] baPWV is related to the thickness of the intima media of carotid artery and aortic PWV[17,18] and is a significant and independent predictor of morbidity and mortality associated with CV diseases in patients on hemodialysis or those with acute coronary syndrome.[19,20] Furthermore, patients with acute stroke with higher cfPWV are at increased risk for poor long-term functional outcome, and baPWV and cfPWV are clinically related.[13,14] Also, a high baPWV is a predictive marker for ischemic stroke.[21]

Robot-assisted gait training (RAGT) is a safe, intensive, and task-specific repetitive practice that helps stroke patients with mild-to-severe motor impairments to reacquire motor coordination.[22] RAGT enables immobilized patients to practice gait-like movements at near-normal speed, and it can be performed with a gait training of more regular pattern, independently of manual efforts of physical therapists over a longer period of time than body-weight supported treadmill and conventional physiotherapy (PT).[23] A recent Cochrane Review reported that subacute stroke patients within the first 3 months who receive RAGT in combination with physical therapy (RAGT+PT) are more likely to achieve independent walking than patients who receive PT alone,[24] and Chang et al[25] reported that it improves peak oxygen consumption (VO_2) and paretic lower limb strength. Thus, this form of training can improve cardiopulmonary fitness as well as motor recovery in subacute stroke patients. However, few studies have investigated the effect of conventional rehabilitation therapy or RAGT+RT on arterial stiffness in subacute stroke patients or the relationship between arterial stiffness and clinical functional outcome in the subacute stroke phase. As most of the functional recovery after stroke is achieved within the first 6 months, task-specific training is most challenging in the subacute phase, which is defined as the period between 2 weeks and 6 months after stroke.[26]

Therefore, we sought to evaluate the correlation between functional outcome and arterial stiffness, determined by measuring baPWV, and to investigate the effects of RAGT+RT on arterial stiffness and functional recovery in subacute stroke patients with totally dependent ambulation.

2. Methods

2.1. Participants

Sixty patients admitted or transferred to the Department of Physical and Rehabilitation Medicine at Jeju National University Hospital were enrolled. All had experienced a first-onset cerebral stroke within the previous 3 months, involving cortical or subcortical areas, that had been confirmed clinically by computed tomography scans or magnetic resonance imaging.

Eligible patients who agreed to participate in this protocol were randomly allocated in a 1:1 ratio to 2 study groups: 30 patients were assigned to the RAGT group and the other 30 patients were assigned to the control group. To participate in the study, patients had to have hemiplegia after unilateral ischemic or hemorrhagic stroke. Inclusion criteria were as follows: clinical diagnosis of stroke <3 months after stroke onset, first-ever stroke, dependent ambulation with severe gait impairment (functional ambulation category [FAC] < 2), and sufficient cognition to understand procedures and provide informed consent.

Exclusion criteria were as follows: contraindications for RAGT therapy[23]; cerebellar or brainstem lesions that may affect autonomic or balance function; musculoskeletal disease involving the lower limbs, such as severe painful arthritis, osteoporosis, amputation, or joint contracture; and other concurrent neurological diseases (e.g., Parkinson disease, multiple sclerosis, etc.). The protocol was reviewed and approved by the Institutional Review Board of Jeju University hospital, and all subjects provided written informed consent before the selection procedure (JNUHIRB-1503010).

2.2. Intervention

All patients underwent conventional rehabilitation therapy consisting of a 30-minute physical therapy session and a 60-minute occupational therapy sessions, 5 times per week for 4 weeks. In addition, the RAGT group underwent a 30-minute session of gait training using exoskeletal robotic orthosis, whereas the control group underwent a 30-minute session of conventional physical therapy.

2.2.1. Conventional rehabilitation therapy. Physical therapy, conducted by physical therapists certified in neurodevelopmental techniques (NDT), was provided for balance and mobility. Depending on patients' functional status, training tasks consisted of sitting and standing balance training, active transfer, sit-to-stand training, and strengthening exercises. These tasks progressed to dynamic standing balance training and gait training assisted by a physical therapist. Occupational therapy consisted of stretching and strengthening exercises of upper extremity and task-oriented therapy for ADL, fine motor training, and sensorimotor recovery.

2.2.2. RAGT. The Lokomat (Hocoma AG, Volketswil, Zürich, Switzerland) is an exoskeletal robot-driven gait orthosis that can be controlled using a treadmill and a body-weight support (BWS) system (Video 1, http://links.lww.com/MD/B323). An exoskeletal robot system with harness was positioned on the patient's hip and knee joints to adjust joint movements depending on an individualized gait program; straps were used if the patient had insufficient foot clearance due to weak ankle dorsiflexion. A computer screen and virtual reality avatar allowed the patient and therapist to monitor treadmill speed, joint speed, joint angle, degree of power, and other gait-training parameters.

As motor function improved, levels of BWS, treadmill speed, and guidance force (GF) were adjusted: specifically, the level of BWS steadily decreased from 50% to 0%, GF decreased from 100% to 40%, and treadmill speed (starting at 1.2 km/h) increased by 0.2 to 0.4 km/h per session to a maximum of 2.6 km/h.

All parameters were individually adjusted during each session for the patients to take part in active gait performance and utilization of paretic hip and knee muscles, and patients could take part in active gait performance and utilization of paretic hip and knee muscles. Excluding time required for putting on equipment and operating the computer, actual training time was 30 minutes per session.

2.3. Outcome measures

baPWV and cardiopulmonary fitness were considered the primary outcomes. Secondary outcomes were clinical functional outcomes, including basic ADL function, balance, gait functions, and motor functions of the paretic lower limb. All assessments were performed at baseline and after the 4-week intervention. All outcome parameters were measured within 3 days before and after 20 sessions of training. A physiatrist (rehabilitation doctor) who remained blinded to each participant's group and treatment throughout the entire study analyzed the outcome measures of participants.

2.3.1. Primary outcomes: assessment of PWV and cardiorespiratory fitness. baPWV is measured noninvasively using an oscillometric method (VP-1000, Colin, Komaki, Japan). Caffeine or smoking was not permitted for at least 3 hours before the test; however, all medications such as antihypertensive agents, antithrombotic drugs, and statins were maintained during the assessment and intervention periods. The subject rested for at least 10 minutes in supine position,[17,27] and then oscillometric cuffs were placed at the mid-level of both arms and ankles; volume pulse and blood pressure were measured simultaneously. The distance between arms and ankles was estimated from the height of the patient. baPWV was calculated as the arm–ankle distance divided by the pulse time interval, and instantaneous systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the time of baPWV measurement were used for blood pressure analyses. For analysis, the average of values between the left and right sides was used.

Participants performed a symptom-limited graded exercise stress test using a bicycle ergometer (Ergoselect 600K, Ergoline GmbH, Lindenstraße, Berlin, Germany), which was supervised by a physiatrist and a physical therapist. A 12-lead electrocardiogram (Philips, Andover, MA) and expired-gas analysis using the breath-by-breath method and a portable telemetric system (Cosmed CPET, COSMED Inc., Pavona di Albano, Italy) were used. Patients were allowed 15 minutes of seated rest, after which resting heart rate, systolic blood pressure, and diastolic blood pressure were measured. The bicycle ergometer test was performed at a rate of 50 to 60 revolutions per minute (rpm).[28] The workload started at 10 watt (W) for 2 minutes and increased by 5 W every 2 minutes. VO_2 and respiratory exchange ratio (RER) were determined; the peak values of each of these parameters and peak heart rate (HR_{peak}) were taken as the average value during the last 30 seconds of each stage.[29] SBP and DBP were checked at rest, every 2 minutes during exercise, and every minute during recovery until the physician confirmed return to baseline. Resting and peak SBP and DBP values, resting and peak heart rate (HR) values, peak RER, and duration of exercise treadmill test (ETT) were recorded.

Tests were terminated upon detection of cardiorespiratory decompensation sign or gait instability, or on the patient's request. Achievement of maximal effort during the test was determined by the following criteria[29]: $RER \geq 1.0$, no increase in HR after an increase in workload, increase in $VO_2 < 1.5$ mL/kg/min after an increase in workload, $HR_{peak} > 95\%$ of age-predicted maximal HR, or volitional fatigue (decline in cycling rate <30 rpm).

2.3.2. Secondary outcomes: assessment of ADL, balance, motor functions of the paretic lower limb, and gait. The Korean version of the Modified Barthel Index (K-MBI) was used to assess performance in basic ADL.[30] Balance function was evaluated using the Berg balance scale (BBS), which measures a subject's balance function while performing common functional tasks in everyday life. Each BBS task is rated on a 5-point scale (0–4), with the maximum score of 56 indicating good balance.[31,32]

FAC was used to evaluate gait function and ambulation ability after stroke.[33]

Lower limb score in the Fugl–Meyer Assessment (FMA-LL) was used to assess motor function of both lower extremities including hip, knee, and ankle. FMA-LL is widely used for comprehensive clinical examination of leg function; the maximum FMA-LL score is 34 points.[34] The FMA-LL value of the paretic leg was assessed.

2.4. Statistical analysis

Simple descriptive statistics were used to characterize the samples and the distribution of variables. Data are presented as mean ± standard deviation for continuous variables including age, weight, height body mass index (BMI), and stroke duration, baPWV, and all parameters of cardiopulmonary fitness. χ^2 tests were used for categorical variables including lesion side, stroke type, underlying disease, and functional outcome measures (BBS, K-MBI, FAC, paretic lower limb score in the Fugl–Meyer Assessment [$FMA\text{-}LL_{paretic}$]). The Mann–Whitney U test was used for analysis of intergroup differences in the clinical outcome and the cardiopulmonary fitness parameters at baseline. The parameters of clinical outcome and cardiopulmonary fitness between pre- and post-4-week training were compared in each group by the Wilcoxon signed-rank test. Spearman correlation analysis was used to measure the correlation between baPWV and demographic and functional outcomes.

For comparisons of changes in outcome measures, repeated-measure analysis of variance (ANOVA) was used for parameters of functional outcome, arterial stiffness, and cardiopulmonary fitness according to time and type of therapy. Statistical analyses were performed using SPSS for Windows version 20 (IBM-SPSS Inc., Chicago, IL). A P value less than 0.05 was considered significant.

Table 1

General characteristics between 2 groups.

Characteristic	RAGT	Control	Intergroup *P*
Age, y	67.89 ± 14.96	63.2 ± 10.62	0.21
Gender (male:female)	17:13	15:11	0.41
Height, cm	162.81 ± 9.77	163.77 ± 9.88	0.74
Weight, kg	61.86 ± 13.34	65.98 ± 9.69	0.20
BMI, kg/m^2	23.33 ± 3.22	24.32 ± 3.24	0.29
Stroke duration, d	21.56 ± 7.98	18.10 ± 9.78	0.19
Lesion side (right/left)	10:20	12:14	0.41
Stroke type (ischemic/hemorrhage)	17:13	16:10	0.79
Underlying disease			
HTN (yes/no)	13:17	10:16	0.79
DM (yes/no)	14:16	11:15	0.44
Cardiac disease (yes/no)	8:22	12:14	0.17

All values were presented as mean ± standard deviation. BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, RAGT = robot-assisted gait training.

Table 2

Comparison of baseline functional outcome measures and arterial stiffness in RAGT and control groups.

Variable	RAGT	Control	Intergroup *P*
Activity of daily living			
K-MBI	25.54 ± 20.25	29.00 ± 17.05	0.623
Balance function			
BBS score	5.13 ± 4.39	7.61 ± 6.36	0.136
Ambulatory function			
FAC	0.10 ± 0.31	0.27 ± 0.46	0.201
Motor function of lower extremity			
FMA-LL$_{paretic}$	6.03 ± 3.67	8.67 ± 7.76	0.113
Arterial stiffness			
baPWV, m/s	17.68 ± 3.50	16.36 ± 3.17	0.143

baPWV = brachial–ankle pulse wave velocity, BBS = Berg balance scale, FAC = functional ambulatory category, FMA-LL$_{paretic}$ = paretic lower limb score in the Fugl–Meyer Assessment, K-MBI = The Korean version of modified Barthel index, RAGT = robot-assisted gait training.

3. Results

Sixty patients were screened for the study and equally randomized into 2 groups. Two patients in the control group refused to perform conventional rehabilitation therapy only, and another 2 patients in the control group dropped out during training. Consequently, 30 patients in the RAGT group and 26 patients in the control group completed training. We analyzed data from patients who completed the designated training.

General and demographic characteristics are presented in Table 1. Mean values of stroke duration were 21.56 ± 7.98 days in the RAGT group and 18.10 ± 9.78 days in the control group, which were comparable with subacute phase of stroke, and there were no intergroup differences in age, gender, weight, height, BMI, stroke type, lesion side, stroke duration, or underlying diseases such as hypertension (HTN), diabetes, and cardiac disease (Table 1).

3.1.1. Primary outcomes: assessment of PWV and cardiorespiratory fitness

Values and changes in measurements of baPWV in RAGT and control groups are summarized in Tables 2 and 3.

The RAGT group exhibited a significant reduction in baPWV after the 4-week intervention, whereas the control group did not (Table 3). Moreover, repeated-measure ANOVA revealed that participants in the RAGT group had less arterial stiffness than the control group after 4 weeks of intervention periods (Table 3, Fig. 1).

Baseline values reflecting arterial stiffness did not differ significantly between the groups. baPWV was positively correlated with age and negatively correlated with height, body weight, K-MBI, BBS, and FMA-LL$_{paretic}$ at baseline (Table 4).

In addition, clinical cardiorespiratory parameters before and after the intervention are listed in Tables 5 and 6. At baseline, clinical cardiorespiratory parameters did not differ significantly between the groups (Table 5).

Peak aerobic capacity (VO$_{2peak}$), HR$_{peak}$, and ETT duration were significantly increased in the RAGT group, whereas the control group did not exhibit any significant changes after 4 weeks (Table 6). Repeated-measure ANOVA revealed that participants in the RAGT had a higher peak aerobic capacity, as determined by measurements of peak VO$_{2peak}$, than the control group after 4 weeks of intervention ($P = 0.009$) (Table 6, Fig. 1). No significant interactions between other parameters reflecting CV response were observed between the groups.

Table 3

Improvement in Functional outcome and arterial stiffness after 4-week training in RAGT and control groups.

Variable	RAGT			Control			
	Pretraining	Post-training	Intragroup *P*	Pretraining	Post-training	Intragroup *P*	Intergroup *P*
Activity of daily living							
K-MBI	25.54 ± 20.25	55.92 ± 19.42	<0.001*	29.00 ± 17.05	60.94 ± 20.32	<0.001*	0.766
Balance function							
BBS score	5.13 ± 4.39	21.37 ± 13.24	<0.001*	7.61 ± 6.36	20.83 ± 13.69	<0.001*	0.392
Ambulatory function							
FAC	0.10 ± 0.31	1.33 ± 1.21	<0.001*	0.27 ± 0.46	1.95 ± 1.75	0.001†	0.277
Motor function of lower extremity							
FMA-LL$_{paretic}$	6.03 ± 3.67	13.43 ± 8.34	<0.001*	8.67 ± 7.76	16.14 ± 8.13	<0.001*	0.971
Arterial stiffness							
baPWV, m/s	17.68 ± 3.50	15.72 ± 2.92	0.003†	16.36 ± 3.17	16.42 ± 3.26	0.803	0.014†

All values were presented as mean ± standard deviation. baPWV = brachial–ankle pulse wave velocity, BBS = Berg balance scale, FAC = functional ambulatory category, FMA-LL$_{paretic}$ = paretic lower limb score in the Fugl–Meyer Assessment, K-MBI = The Korean version of modified Barthel index, RAGT = robot-assisted gait training.

* *P* value <0.01.

† *P* value <0.05.

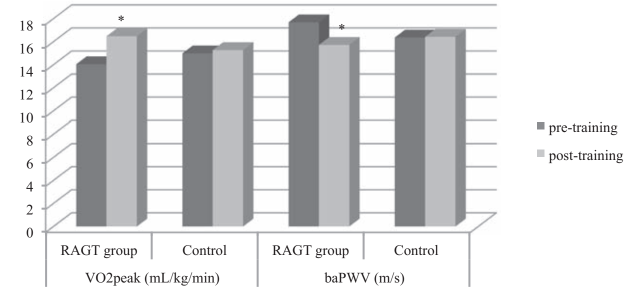

Figure 1. Peak aerobic capacity and arterial stiffness after a 4-week training in the robot-assisted gait training group and control group. Intergroup statistical differences are presented in the graph, *P value <0.05. baPWV = brachial–-ankle pulse wave velocity, RAGT = robot-assisted gait training, VO_{2peak} = peak aerobic capacity.

3.1.2. Secondary outcomes: assessment of ADL, balance, gait functions, and motor functions of the paretic lower limb

Baselines and changes in ADL, balance, gait, and motor functions of the paretic lower limb in RAGT and control groups are summarized in Tables 2 and 3. Baseline values did not differ significantly between the groups, and both groups exhibited significant improvements in all parameters, as measured by K-MBI, BBS, FAC, and $FMA\text{-}LL_{paretic}$. Repeated-measure ANOVA of all parameters did not reveal any statistical significance according to time between the 2 types of training.

4. Discussion

We compared the effects of robot-assisted gait training combined with rehabilitation therapy on arterial stiffness and cardiopulmonary fitness, as well as functional outcomes, with those of conventional rehabilitation therapy (RT) alone in subacute stroke patients with totally dependent ambulation. We found that RAGT + RT was better at improving arterial stiffness and peak aerobic capacity than conventional RT alone. These findings are of special interest because very little evidence is available regarding the effect of rehabilitation therapy on arterial stiffness, as measured by baPWV, in stroke patients.

The mean value of baPWV in the RAGT group improved from 17.68 ± 3.50 to 15.72 ± 2.92 m/s, a change of −1.97 ± 3.36 m/s, after a 4-week intervention with RAGT + RT, whereas the control group exhibited no significant change. To the best of our knowledge, no previous study has evaluated whether a change in arterial stiffness affects stroke morbidity or recurrence. However, a recent systematic review reported that the pooled relative risks of CV mortality and all-cause mortality for an increase in baPWV of 1 m/s are 1.13 (95% CI, 1.06–1.20) and 1.06 (95% CI, 1.02–1.10), respectively, corresponding to a risk increase of 13% ($Z = 3.96$, $P < 0.001$; $I^2 = 0.0\%$, $P = 0.941$) and 6% ($Z = 2.81$, $P = 0.005$; $I^2 = 0.0\%$, $P = 0.732$), respectively.[14] On the other hand, the Takashima study on the general Japanese population demonstrated that the adjusted hazard ratio for total stroke incidence after control for HTN and high arterial blood pressure was 1.72 (95% CI, 0.39–7.55) in a group with intermediate baPWV (14–17.9 m/s) and that the adjusted hazard ratio for stroke incidence with a 2-m/s increase in baPWV was 1.19 (95% CI, 1.01–1.41).[35] Although we did not assess the long-term effects of RAGT + RT on recurrence rate or morbidity and mortality after stroke, it seems likely that reduced arterial stiffness would reduce stroke recurrence or morbidity and mortality; however, further large-scale studies with long-term follow-up periods are necessary to test this prediction.

The underlying mechanisms by which RAGT + RT improves arterial stiffness remain undetermined, but growing evidence indicates that regular aerobic exercise such as walking or cycling reverses arterial stiffness in healthy adults.[35–40] Aerobic exercise promotes arterial remodeling, decreases sympathetic tone, and enhances endothelial function, thereby improving arterial distensibility.[37,41,42] Moreover, Chang et al[25] reported that 2-week RAGT had a positive impact on cardiopulmonary fitness and suggested RAGT as an effective method of aerobic exercise in stroke patients. In this study, the RAGT + RT group exhibited significant improvement in peak aerobic capacity and peak HR, and the total durations of ETT and improvement of peak aerobic capacity were greater than those in the RT group.

Stroke patients show low cardiovascular fitness[43] and the baseline mean VO_{2peak} value of our patients was 14–15 mL/kg/min, which was lower than that of subacute Korean stroke patients (19.7 mL/kg/min) who participated in our previous study,[44] but the FAC level was >3. Our value is comparable with the reference value of Chang et al, whose study participants were mainly FAC 0 or FAC 1. Thus, our

Table 4

Simple correlation analysis for the baPWV at baseline.

Variables	Correlation coefficient	P
Age	0.435	0.002*
Height	−0.445	0.001†
Weight	−0.386	0.006*
BMI	−0.174	0.227
K-MBI	−0.370	0.008*
BBS	−0.309	0.029*
FAC	−0.052	0.720
$FMA\text{-}LL_{paretic}$	−0.297	0.037*

All values were presented as mean ± standard deviation. baPWV = brachial–ankle pulse wave velocity, BBS = Berg balance scale, BMI = body mass index, FAC = functional ambulatory category, $FMA\text{-}LL_{paretic}$ = paretic lower limb score in the Fugl–Meyer Assessment, K-MBI = The Korean version of modified Barthel index.
* P value <0.05.
† P value <0.01.

Table 5

Comparison of baseline parameters of cardiopulmonary fitness in RAGT and control groups.

Variable	RAGT	Control	Intergroup P
VO_{2peak}, mL/kg/min	14.04 ± 3.33	14.98 ± 4.26	0.582
RER_{peak}	0.99 ± 0.12	1.00 ± 0.15	0.403
$HR_{resting}$	84.86 ± 9.9	86.17 ± 13.91	0.651
$SBP_{resting}$	118.36 ± 10.51	119.09 ± 13.83	0.856
$DBP_{resting}$	74.59 ± 6.99	76.65 ± 8.56	0.381
HR_{peak}	120.23 ± 14.88	117.96 ± 20.31	0.657
SBP_{peak}	154.36 ± 30.23	153.09 ± 27.92	0.955
DBP_{peak}	77.86 ± 8.88	79.39 ± 16.11	0.991
ETT duration	483.05 ± 263.56	509.83 ± 239.88	0.628

All values were presented as mean ± standard deviation. DBP_{peak} = peak diastolic blood pressure, $DBP_{resting}$ = resting diastolic blood pressure, ETT duration = exercise tolerance test duration, HR_{peak} = peak heart rate, $HR_{resting}$ = resting heart rate, RAGT = robot-assisted gait training, RER_{peak} = peak respiratory exchange ratio, SBP_{peak} = peak systolic blood pressure, $SBP_{resting}$ = resting systolic blood pressure, VO_{2peak} = peak aerobic capacity.
* P value <0.05.
† P value <0.01.

Table 6

Improvement in parameters of cardiopulmonary fitness after 4-week training in RAGT and control groups.

Variable	RAGT			Control			
	Pretraining	Post-training	Intragroup *P*	Pretraining	Post-training	Intragroup *P*	Intergroup *P*
VO_{2peak}, mL/kg/min	14.04±3.33	16.47±3.39	<0.001*	14.98±4.26	15.27±4.04	0.668	0.009†
RER_{peak}	0.99±0.12	0.96±0.06	0.285	1.00±0.15	0.99±0.10	0.642	0.645
$HR_{resting}$	84.86±9.9	83.73±10.53	0.285	86.17±13.91	85.04±13.51	0.535	0.996
$SBP_{resting}$	118.36±10.51	119.50±10.89	0.239	119.09±13.83	120.43±14.75	0.496	0.924
$DBP_{resting}$	74.59±6.99	75.05±9.83	0.78	76.65±8.56	73.65±14.75	0.267	0.274
HR_{peak}	120.23±14.88	130.1±16.53	0.01†	117.96±20.31	121.48±23.81	0.246	0.169
SBP_{peak}	154.36±30.23	160.45±31.45	0.276	153.09±27.92	153.35±21.67	0.964	0.462
DBP_{peak}	77.86±8.88	80.36±8.87	0.325	79.39±16.11	78.57±12.99	0.758	0.462
ETT duration	483.05±263.56	639.64±188.71	0.046†	509.83±239.88	566.04±230.06	0.196	0.235

All values were presented as mean±standard deviation. DBP_{peak} = peak diastolic blood pressure, $DBP_{resting}$ = resting diastolic blood pressure, ETT duration = exercise tolerance test duration, HR_{peak} = peak heart rate, $HR_{resting}$ = resting heart rate, RAGT = robot-assisted gait training, RER_{peak} = peak respiratory exchange ratio, SBP_{peak} = peak systolic blood pressure, $SBP_{resting}$ = resting systolic blood pressure, VO_{2peak} = peak aerobic capacity.

* P value <0.01.

† P value <0.05.

subjects performed effectively in the symptom-limited exercise stress test, suggesting that their estimated values are reliable.

However, we did not measure individual VO_2 during RAGT and could not confirm the amount of aerobic burden in RAGT. van Nunen et al[45] showed that VO_2 is 7.9±2.6 mL/min/kg at 50% BWS while walking at 1.7 km/h with GF set at 50%, which is the protocol that was used in our study and that has been usually applied in other RAGT studies. Considering these facts, the intensity of RAGT is thought to be about 50% to 55% of peak VO_2, which is comparable to the ACSM recommendation and sufficient to induce improvement in peak VO_2.

Therefore, our results confirmed the potential of RAGT as an effective aerobic exercise that could improve arterial stiffness and cardiopulmonary fitness. However, further studies of the aerobic burden of RAGT in subacute stroke patients should be conducted in the future.

By contrast, our conventional RT group only exhibited improvement in clinical functional outcomes and showed no sign of improvement in arterial stiffness. This might be explained by the fact that the conventional NDT program consists mainly of balance training as sitting and standing and strengthening exercise of paretic trunk and limb muscles at subacute phase in totally dependent stroke patients. In line with previous studies showing that resistance exercise training does not affect or reduce arterial stiffness,[46,47] a RT program consisting of balance and resistance training induced functional recovery only.

Furthermore, the baPWV of our patients (17.24±3.42 m/s) was much higher than 14.9±2.10 m/s, the reference value for healthy Koreans in their 60s.[48] This is to be expected for patients with stroke, who usually exhibit higher arterial stiffness than those who have not suffered stroke.[49] On the other hand, we measured baPWV of our participants at the subacute phase, with a mean duration of 19.97±8.83 days after stroke. Most studies showing significant prognostic value of arterial stiffness for early neurological deterioration and poor functional outcome made measurements during the acute phase of stroke, within 7 days postonset.[50–52]

However, during the acute phase of stroke, it is recommended to maintain a high blood pressure (BP), because a reduction in BP is associated with adverse clinical consequences. Accordingly, antihypertensive drugs are usually added at the subacute phase to prevent recurrent stroke. Antihypertensive drugs can also affect baPWV, which is most affected by instantaneous SBP. In addition, peripheral arteries are not altered significantly by the aging process or disease states,[53] and baPWV indicates vascular stiffness in both central and peripheral arteries.[35]

Therefore, although the baseline baPWV value of our participants was measured at the subacute phase, we tried to maintain antihypertensive drugs without alteration during the intervention period; consequently, most participants maintained stable resting SBPs and DBPs within the normal range. Although we did not determine the difference in baPWV between the acute and subacute phase, we believe that our measured baPWV value is relevant and sensitive to changes according to time and type of rehabilitation therapy. However, future studies should evaluate the difference in baPWV between the acute and subacute phases.

We also found that baPWV correlates with clinical functional outcome in subacute stroke patients. In clinical practice, most previous studies reported a relationship between arterial stiffness and clinical outcomes using modified Rankin Scale (mRS), which defines only 6 levels of disability and 1 level for death. Although mRS has been validated and is used universally to assess disability or dependency of stroke patients, all of our participants were mRS 5; therefore, in this study, mRS was insufficient to sensitively discriminate subtle changes or differences in disability.[54] Moreover, Kwon et al[55] reported that the Barthel Index at low ADL scores differentiates effectively between patients' mRS disability categories. Therefore, we used the K-MBI as a measure of basic daily functions and categorized the functional outcome into 4 parts: basic ADL (K-MBI), balance (BBS), ambulatory function, and motor function of the paretic lower limb. We found that baPWV is moderately correlated with balance and ADL function, and weakly correlated with motor functions of the paretic lower limb. However, we did not observe any relationship between baPWV and ambulatory functions. One possible explanation is that baseline motor function and ambulatory level were very low, and it was not possible to perform a satisfactory evaluation on subjects who were not able to walk independently.

This study had several study limitations. Most serious was the relatively small number of subjects evaluated, which was insufficient to generalize the effect of RAGT. Confirmation of our findings and identification of differences between the 2 types of therapy will require future studies with more participants. Second, the intervention duration was short, and we did not perform long-term follow-up; therefore, we cannot evaluate the long-term effect of RAGT on arterial stiffness and functional recovery. Third, we did not assess or monitor the aerobic burden of RAGT. Finally, we measured baPWV in subacute phase only, but could not compare it with the value during acute phase. Therefore, further large-scale studies with long-term follow-up periods are warranted to address this issue.

In conclusion, we demonstrated that 4 weeks of RAGT combined with rehabilitation therapy was better at improving arterial stiffness and peak aerobic capacity than 4 weeks of conventional rehabilitation therapy in subacute stroke patients with totally dependent ambulation, suggesting that RAGT represents an effective method of aerobic exercise for reversing arterial stiffness and improving peak aerobic capacity in these patients. However, further large-scale studies with longer term follow-up periods will be required to study the effects of RAGT on secondary prevention after stroke.

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