**Topic Line: Stroke**

# Effects of combined aerobic and resistance exercise on central arterial stiffness and gait velocity in patients with chronic post-stroke hemiparesis

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Running heading: Exercise and arterial stiffness in hemiparesis

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**Conflict of interest**

All authors report no conflict of interest.

**ABSTRACT**

**Objective:** We investigated the effects of combined aerobic and resistance exercise training on central arterial stiffness and gait velocity in patients with chronic post-stroke hemiparesis.

**Design:** Twenty-six patients with chronic post-stroke hemiparesis were randomly assigned to either the combined aerobic and resistance exercise group (n=14) or the control group (n=12). The exercise intervention group received a combined aerobic and resistance exercise training (one hour/day, three times/week for 16 weeks), while the control group received usual care. Central arterial stiffness was determined by pulse wave velocity (PWV) and augmentation index (AIx@75). Gait velocity was assessed using 6-minute walk test (6MWT), 10-meter walk test (10MWT), and the Timed Up and Go (TUG) test.

**Results:** Patients in the exercise intervention group had greater improvement of mean PWV ($p$<0.001), AIx@75 (p=0.048) and gait velocity (6MWT, $p$<0.001; 10MWT, $p$<0.001) than did patients in the control group. Patients in the exercise intervention group also had greater improvements in physical fitness component (grip strength, $p$<0.001; muscular strength of upper and lower limbs, $p$<0.027; flexibility, $p$<.001) when compared with control patients.

**Conclusions:** The combined aerobic and resistance exercise program significantly reduced central arterial stiffness and increased gait velocity in patients chronic post-stroke hemiparesis.

Keywords: Hemiparesis**,** Arterial stiffness, Gait velocity, Combined exercise

Increased central arterial stiffness is a risk marker for stroke and hypertension.[1,2] Stroke patients had greater central arterial stiffness when compared with age-matched healthy peers.[3] Elevated carotid-femoral pulse wave velocity (PWV), a gold standard of systemic arterial stiffness, is a strong predictor of cardiovascular disease and all-cause mortality and is associated with increased risk of micro-vascular brain damage in both older adults and high-risk populations.[4,5]

Several studies have shown an inverse association between gait velocity and arterial stiffness.[6,7] Moreover, aerobic capacity is positively associated with gait velocity in patients with chronic stroke.[8] Improvements in physical fitness, achieved by exercise, may increase gait velocity and reduce arterial stiffness in patients with chronic post-stroke hemiparesis.

Some investigators have previously reported that conventional aerobic exercise or resistance exercise is associated with arterial stiffness and gait velocity in symptomatic patients and healthy populations.[9,10] Recently, several studies have shown that combined aerobic and resistance exercise is more effective in improving health-related factors including cardiovascular risk factors, augmentation index, gait performance and physical fitness, compared with conventional exercise alone.[11-13] However, little is known about the effects of combined aerobic and resistance exercise on PWV, gait velocity and arterial function in patients with chronic post-stroke hemiparesis.[14] Therefore, the primary aim of the present study was to investigate the effects of combined aerobic and resistance exercise on central arterial stiffness and gait velocity in patients with chronic post-stroke hemiparesis. We hypothesized that the combined aerobic and resistance exercise would improve central arterial stiffness and gait velocity in patients with chronic post-stroke hemiparesis. We performed randomized controlled trial to determine the independent effect of moderate-intensity aerobic and resistance exercise intervention on central arterial stiffness and gait velocity in Korean patients with chronic post-stroke hemiparesis.

## METHODS

**Subjects** Thirty-five patients with chronic post-stroke hemiparesis were recruited from the Hanwoori Community Center (Seoul, Korea). Inclusion criteria were medical diagnosis as follows: (1) time since stroke > 12 months; (2) subjects without arrhythmia, orthopedic disorders, and other neurological diseases; (3) subjects who had a mini-mental state examination (MMSE) score > 24 point; (4) subjects who could walk 10 meters independently without assistance. Subjects with a history of transient ischemic attack without symptoms of hemiparesis were excluded from the study. We examined subjects' physical fitness using 6-minute walk test (6MWT) before the experiment and excluded five subjects with substantially low level of 6MWT (<15$^{th}$ percentile, < 0.28 m/s). We assumed these subjects could not perform the exercise program due to low fitness function. We had random drawings before the experiment: each subject had to draw a sealed envelope and was randomly assigned to either the exercise intervention group (n=15) or the control group (n=15). Four subjects were dropped out before the post-test: one subject in the exercise group and three in the control group. Thus, 14 subjects in the exercise group and 12 subjects in the control group completed the experiment (Figure 1). This study was single-blind; Examiners for all outcome variables were blinded to patient group assignment. All subjects signed informed consent for the clinical examination, and all experimental procedures were approved by the Public Institutional Review Board.

**Interventions** The combined aerobic and resistance exercise group performed a 60-minute combined exercise session three times/week for 16 weeks. The control group received unsystematic physical activities or played Korean chess at the identical time. The control group did not receive any exercise intervention. They were asked to continue their normal daily activities. Most of them performed very light physical activities such as slow cycling with a cycle ergometer, walking on the hallway, or playing Korean chess.

Each exercise intervention comprised a 5-min warm-up, a 10-min stretching exercise, a 20-min resistance exercise, a 20-min aerobic exercise, and a 5-min cool down (table 1). Subjects performed a standardized whole-body stretching and light walking during the warm-up and cool-down periods. The main stretching exercise included 10 stretching movements (shoulder flexion / extension, shoulder abduction / adduction, trunk flexion / extension, and hip flexion / extension, and hip abduction / adduction) with a 6-sec passive stretching, 3-sec muscular contractions, and a 2-sec relaxation.[15] Aerobic exercise included a 10-min fast-walking on a sloping way and another 10min walking in up-stairs. Exercise intensity was established at 50% to 60% of heart rate reserve (HRR) using the heart rate monitor system (RX800CX, Polar Finland) for 8 weeks and then increased to 60% to 70% of HRR for the remaining 8 weeks.[16] Resistance exercise was carried out using elastic resistance bands.[17] Subjects performed resistance exercise, which included lunges, squats, hip flexion / extension, hip abduction / adduction, knee flexion / extension, shoulder abduction / adduction, shoulder flexion / extension, and abdominal crunch / back extension. Exercise intensity was progressed from 10 to 15 repetitions with 2 to 3 sets for each motion for 8 weeks and then gradually increased the resistance levels of the elastic band for the remaining 8 weeks. Resistance exercise was performed a rating of perceived exertion of 11 to 16 (light to hard) using the Borg Scale.[18] The exercise program was supervised by a trained exercise rehabilitation specialist and physical therapist.

**Outcome measures** We measured anthropometry, arterial stiffness, gait velocity, and physical fitness component. We also collected patients' basic medical information including time since stroke, medication use (hypertension, diabetes, cardiovascular disease), and stroke classification (ischemic stroke and cerebral hemorrhage). Body height (cm), weight (kg) and body mass index ($kg/m^2$) were measured using multi-frequency impedance analysis (Inbody 3.0, Biospace, Korea) and an extensometer. Brachial arterial blood pressure was measured after 10-min of rest in the supine position using an automatic monitor (UA-711, Japan). Aortic blood pressure was automatically analyzed through the pulse wave detected at the radial artery using SphygmoCor (AtCor Medical, Sydney, Australia) with the generalized radial-aortic transfer function. Arterial stiffness, carotid-femoral pulse wave velocity (PWV) and augmentation index (AIx@75) were estimated with the guidelines recommended by the Clinical Application of Arterial Stiffness Task Force III.[19] The PWV was calculated by dividing the distance (D) between carotid artery and femoral artery by the time difference ($\Delta t$) between the two sites ($PWV = D/\Delta t$, m/s). The distance between carotid and femoral arteries was measured by a tape measure, and the D was subtracted by the distance between carotid artery and supra-sternal notch. The AIx@75 was derived from the aortic pressure waveform which automatically adjusted to a heart rate of 75 bpm. All subjects completed vascular function and BP measurements after abstaining from caffeine intake or food intake for ≥ 3 hours.

Gait velocity was determined by 6MWT, 10-meter walk test (10MWT), and the Timed Up and Go (TUG) test.[20,21] The 6MWT was used to measure walking speed, sub-maximal endurance, and balance for persons with stroke following guidelines suggested by the American Thoracic Society.[22,23] The 10MWT was used to measure walking in 10 meters with each marker of 0, 2, 8, and 10-meter. Subjects walked for a 10-m distance, and the time spent at the mid-range (6 meters) was measured.[24] The average of two measurements was used for analysis. The TUG test was measured as follows: each subject stands up from an armrest chair, walks to the marked point (3 meters away from the chair), turns around, walks back to the chair, and sits down again.[25] This process was measured twice, and the average of two measurements was used for analysis. We used a stopwatch to measure the gait velocity, which calculated gait speeds (m/s unit). We also measured physical fitness component (e.g., muscular strength, balance, and flexibility) as secondary outcomes. Muscular strength was measured by a grip dynamometer on the unaffected side of the arm (T.K.K. 5401, Japan). The 30-s chair-stand test (CS30) was used to measure muscular strength in both legs.[26] Flexibility was measured by the sit and reach test (cm) suggested by Rikli and Jones.[27] The functional reach test (FRT) was used to measure balance following procedures by Katz-Leurer et al.[28] All muscular strength, flexibility and balance tests were measured twice, and the average of two measurements was used for analysis. All outcomes data were blinded until final data entry for 16-weeks intervention was completed.

**Statistical analysis** All data are presented as means and standard deviation (mean ± SD) or percentage (%). An independent *t*-test and a chi-square test were used to compare baseline mean or frequency differences between the exercise intervention and control groups. General linear models were used to test changes in mean values from baseline to 16 weeks between exercise intervention and control groups after adjustment for age and gender. All statistical procedures were performed by SPSS (version 21.0, SPSS Inc, Chicago, IL, USA) with a significance level at 0.05.

## RESULTS

As shown in Table 2, there were no baseline differences in clinical and anthropometric variables, arterial stiffness indexes, gait velocity parameters, and physical fitness component between the intervention and control groups (all $p>0.05$). Table 3 shows changes in vascular parameters between exercise intervention and control groups. Patients with exercise intervention had a significant reduction in mean values of central diastolic blood pressure (cDBP) ($p = 0.027$), AIx@75 ($p = 0.048$), and PWV ($p<0.001$) than did patients with the control group after adjustment for age and gender. There were no statistical differences in peripheral systolic blood pressure (pSBP) ($p = 0.36$) and central systolic blood pressure (cSBP) ($p = 0.23$) between the exercise intervention and control groups, but peripheral diastolic blood pressure (pDBP) in the exercise intervention group had a slight reduction compared with the control group ($p = 0.053$). Table 4 shows that patients in the exercise intervention group had significant improvements in 6MWT ($p<0.001$) and 10MWT ($p<0.001$) compared with control patients. Patients with the exercise intervention group also had greater muscular strength of upper ($p = 0.001$) and lower limbs ($p = 0.027$), and flexibility ($p<0.001$) compared with patients with the control group. There was no statistical difference in the Timed Up and Go velocity ($p = 0.20$) between two groups while balance capacity was slightly improved in the exercise intervention group compared with the control group ($p=0.052$).

## DISCUSSION

Our major finding was that the combined aerobic and resistance exercise training was associated with greater reduction in central arterial stiffness (assessed by carotid-femoral PWV and AIx@75) and improvements in gait velocity (measured by 6MWT and 10MWT) in patients with chronic post-stroke hemiparesis. We also observed that patients in the exercise intervention group improved physical fitness component such as muscular strength, flexibility, and balance. To our knowledge, this is the first intervention study to show the beneficial effects of combined aerobic and resistance exercise program (moderate intensity) on the carotid-femoral PWV, gait velocity, and physical fitness component in patients with chronic post-stroke hemiparesis.

Our findings are consistent with those reported by Takatori et al.[14] in which Japanese stroke patients who underwent intensive rehabilitation program (both aerobic and anaerobic exercise) for 12 weeks reduced cardio-ankle vascular index (CAVI) compared with their control patients. However, Takatori et al.[14] showed no changes in gait velocity and physical fitness after the exercise intervention. They comprised 120-min exercise intervention/day (two times/week) for 12 weeks, whereas our study had 60-min exercise intervention/day (three times/week) for 16 weeks. We believe that a 120-min exercise intervention/day is too much exercise for the elderly stroke patients (>65 years of age), which may even reduce the beneficial effects of physical exercise. In fact, the American Heart Association recommended that stroke patients should exercise 20 to 60 min/session, three to five times/week, to improve cardiovascular disease and motor function.[18] Our study was designed accounting for appropriate exercise intensity as a light to moderate-intensity. We believe that increases in gait velocity and improves in physical fitness with an appropriate exercise duration, frequency, and intensity may play an important role in treating patients with arterial stiffness. Our findings are also consistent in the direction with results from other study populations.[29,30] Figueroa et al.[29] stated that combined aerobic and resistance exercise may reduce pulse wave velocity in postmenopausal women. Motl et al.[30] found that combined aerobic and resistance exercise improved walking mobility in patients with multiple sclerosis.

In our study, the combined aerobic and resistance exercise was effective to enhance arterial stiffness and gait velocity in patients who suffer from chronic post-stroke hemiparesis. It is plausible that the combined aerobic and resistance exercise program may lower central arterial stiffness by enhancing blood pressure in stroke patients. Several investigators have shown that the combined aerobic and resistance exercise training reduced brachial systolic and diastolic blood pressure about 6mmHg and 5mmHg, respectively, with a reduction in arterial stiffness.[29,31] Our study also shows that patients with the exercise intervention had reduced central diastolic blood pressure (2.9 mmHg) and central systolic blood pressure (4 mmHg) compared with control patients. Thus, we believe that the combined aerobic and resistance exercise may positively influence to lowering central blood pressure, which may lead to an eventual reduction in central arterial stiffness. Interestingly, central blood pressure is a better predictor of cardiovascular disease and all-cause mortality than did peripheral artery blood pressure as measured in the brachial artery.[32,33]

Second, it is also plausible that the combined aerobic and resistance exercise may reduce central arterial stiffness through improved endothelium-dependent vasodilation.[34,25] The combined aerobic and resistance exercise enhances endothelial function,[34] which may reduce the central arterial stiffness.[35] In fact, improved endothelial function is negatively associated with arterial stiffness.[34]

Our study also shows that patients in the exercise intervention significantly improved muscular strength, flexibility, 6MWT and 10MWT compared with the control counterparts. The 6MWT was related with cardiorespiratory fitness in patients with post-stroke hemiplegia.[36] Increases in blood flow by regular exercise may improve shear stress and eNOS (endothelial nitric oxide synthase), and elevated eNOS may improve endothelial function and endothelium-dependent vasodilation by secreting nitric oxide, a vasodilator substance.[37] Although our study did not measure nitric oxide directly, we believe that central arterial stiffness might be reduced due to enhanced physical fitness. Although It is not clear how the combined aerobic and resistance exercise improves gait velocity, the following points can be suggested based on the previous studies.[38-42] A fast gait velocity in persons with central nervous system disorders has a lower central blood pressure.[38] Elevated central blood pressure causes the reduction of cerebral vasomotor and cerebrovascular reactivity, resulting in cerebrovascular damage.[39,40] This cerebrovascular damage causes reduced perfusion of frontal-subcortical in the frontal lobe, an important section for motor skills,[41] which may eventually lead to decreased gait velocity. We assume that the combined aerobic and resistance exercise causes the reduction of central blood pressure, which then increases central blood perfusion, resulting an increased gait velocity. In addition, fast walking training on a sloping way and walking in up-stairs in exercise intervention group may affect an improvement of gait velocity directly. Moreover, the walking capacity of individuals with post-stroke hemiparesis is directly related to physical fitness component such as muscular strength, balance and cardiorespiratory fitness.[42] We believe that improved physical fitness following combined aerobic and resistance exercise may directly affect gait velocity.

Elevated central arterial stiffness causes excessive left ventricular load and influences on vascular tone in the vascular wall, which leads to an increased risk of cardiovascular disease.[43] Slow gait velocity is positively associated with cardiovascular disease events.[44] Especially for patients with post-stroke, increased aortic stiffening is related to stroke recurrence.[45] Gait velocity is the most-important physical ability for normal social activities as a basic means of transportation for patients with post-stroke.[46] Central arterial stiffness and gait velocity are highly correlated with the physical fitness component such as cardiorespiratory fitness and muscular strength.[36,47,48] Hence, clinicians should consider the importance of combined aerobic and resistance exercise program in the treatment of chronic post-stroke hemiparesis by reducing arterial stiffness and improving gait velocity.

This study has some limitations. The present study had a relatively small sample size and further studies with a large sample size are needed to confirm these results. This study was conducted on targeting chronic post-stroke hemiparesis who were able to walk. Thus, the results of this study cannot be applied to all individuals with the post-stroke hemiplegia. In addition, this study included only the combined exercise program (moderate intensity) as an intervention arm, so we are unable to compare with single aerobic or resistance and different intensity of other combined exercise programs. Despite these limitations, the strength of this study is that we first tested the effects of combined aerobic and resistance exercise on central arterial stiffness in Korean patients with chronic post-stroke hemiparesis. Stroke is one of the leading causes of death worldwide.[49] However, only a few studies have examined the effects of combined aerobic and resistance exercise on arterial stiffness.[14]

This study is meaningful because it suggests that combined aerobic and resistance exercise may reduce central arterial stiffness. Although the subjects of this study had no information on additional disease, no significant differences in the usage of drugs between exercise and control groups were noted before the study was performed.

In conclusion, our findings indicate that the combined aerobic and resistance exercise is effective in improving arterial stiffness and gait velocity in patients with chronic post-stroke hemiparesis. Clinicians should concern the importance of combined aerobic and resistance exercise program (moderate-intensity) in the treatment of chronic post-stroke hemiparesis.

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Figure legends.

**Figure 1** Flow diagram of the study.