Adapted Low Intensity Ergometer Aerobic Training for Early and Severely Impaired Stroke Survivors: A Pilot Randomized Controlled Trial to Explore Its Feasibility and Efficacy

Zun Wang, MS[1)a], Lei Wang, MD[1)a], Hongjuan Fan, MS[1)], Wenjun Jiang MS, PT[2)], Sheng Wang, MS, PT[3)], Zhaohua Gu MS, PT[3)], Tong Wang, PhD[3)*]

[1)] Rehabilitation Therapy Department, The Second Medical School of Nanjing University of Traditional Chinese Medicine, China
[2)] Department of Rehabilitation Medicine, Affiliated Hospital of Jiangsu University, China
[3)] Department of Rehabilitation Medicine, The First Affiliated Hospital of Nanjing Medical University: Nanjing 210029, China

Abstract. [Purpose] To evaluate the feasibility and efficacy of adapted low intensity ergometer aerobic training for early and severely impaired stroke survivors. [Subjects] The subjects were forty-eight early stroke survivors. [Methods] Eligible subjects were recruited and randomly assigned to an experimental group and a control group. Both groups participated in comprehensive rehabilitation training. Low intensity aerobic training was only performed by the experimental group. Outcome measures were the Fugl-Meyer motor score, Barthel index, exercise test time, peak heart rate, plasma glucose level and serum lipid profiles. [Results] Patients in the experimental group finished 88.6% of the total aerobic training sessions prescribed. In compliant participants (adherence≥80%), aerobic training significantly improved the Barthel index (from 40.1±21.1 to 79.2±14.2), Fugl-Meyer motor score (from 26.4±19.4 to 45.4±12.7), exercise test time (from 12.2±3.62 min to 13.9±3.6 min), 2-hour glucose level (from 9.22±1.16 mmol/L to 7.21±1.36 mmol/L) and homeostasis model of assessment for insulin resistence index (from 1.72±1.01 to 1.28±0.88). [Conclusion] Preliminary findings suggest that early and severely impaired stroke patients may benefit from low intensity ergometer aerobic training.
Key words: Aerobic training, Early and severely impaired stroke hemiplegia, Feasibility and efficacy

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INTRODUCTION

Low fitness levels and poor cardiovascular disease risks are highly prevalent among stroke survivors[1–3].Low fitness levels are closely related with vascular disease morbidity and mortality[4–6]. Aerobic training plays a significant role in improving fitness levels and cardiovascular risks among stroke survivors[7–10]. However, motor function limitations and safety concerns preclude very early and weak stroke patients from aerobic training. Previous studies have mainly focused on non-disabled stroke patients and it is still unclear whether severely affected stroke survivors could perform aerobic exercise training at levels requisite to produce aerobic gains. Therefore, it is necessary to explore the application of aerobic training across a broader range of stroke course and disability levels[11].

This study was designed to explore the feasibility and efficacy of aerobic training for very early and weak stroke survivors. The hypothesis was that low-intensity ergometer aerobic training would be well-tolerated by severely impaired stroke survivors to improve their functional levels and cardiovascular risks.

SUBJECTS AND METHODS

Subjects were recruited from the Rehabilitation Center of the First Affiliated Hospital of Nanjing Medical University in eastern China. They were hospitalized throughout the intervention period. This trial was approved by the hospital ethics committee in accordance with the Declarations of Helsinki revised in 1983. The purpose, nature, and potential risks of the trial were fully explained to the subjects who were free to withdraw anytime if they or their relatives request. All subjects gave their written, informed consent before participating in this study.

Subjects were included in the study if they were two weeks post stroke; six weeks within stroke onset; 45 to 75 years of age; unable to walk with any walk aid; severely

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[a]Both as first authors, contributed equally to this study and paper.
*Corresponding author. Tong Wang (E-mail: wangtong60621@163.com)

impaired with the affected leg scored 3 or less on the 7-point Chedoke-McMaster Stroke Assessment scale[12]; cardiovascular stable as determined by 12-lead ECG; had no orthopedic disease that might have precluded ergometer exercise training; were not taking medicines that might have significantly altered heart rate; and were able to understand the purpose and content of the study. The exclusion criteria were: signs and symptoms of subarachnoid hemorrhage; transient ischemic attack and those with severe cerebral edema; O2 dependence; angina; unstable cardiac condition; peripheral arterial occlusive disease; abnormal high fever; high blood pressure over 200/110 mmHg; dementia; aphasia operationally defined as incapacity to follow 2-point commands; untreated major depression or other medical conditions that precluded participation in exercise training.

Both the exercise test and aerobic training were conducted using the same ergometer (Monark, Sweden). Before aerobic training, the adapted symptom-limited graded exercise test was performed. Participates sat on a wheelchair which was firmly immobilized. Their feet were fixed to the pedals by soft belts. Ergometer power output was increased by 2.5 W every 3 minute until exhaustion based on patients maximal tolerance. Our prior study has proved the feasibility of aerobic exercise for severely impaired stroke patients and in this study, ten eligible subjects were tested twice at entry to the present program. As a result, they all finished the test at the same workload and for the same reason (test-retest percentage agreement =100%). Peak heart rate was defined as the highest observed during the exercise test and it was used to calculate the targeted heart rate for aerobic training. Subjects were excluded from the study if they could not produce enough power output (less than 5W) during adapted exercise test.

Eligible subjects were randomly allocated to an experimental group and a control group. The sealed envelope and block sampling method was used to achieve equal numbers in each group. A researcher unaware of the study performed the randomization procedure. The investigators were not blinded to group assignment, however, all the involved therapists and outcome assessors were blinded with respect to the baseline data and group assignment.

Both groups exercised five days per week for six weeks. Every training day, they received a comprehensive rehabilitation training program including three 40-minute sessions of physical training, two 15-minute sessions of occupational training, one 30-minute session of acupuncture or traditional Chinese manipulation and one 30-minute session of physical agent therapy. Physical training was mainly composed of stretch, balance, range of motion, gait training based on Bobath technique. Strength training was added when necessary. However, the amount of strength training was strictly controlled because it may have had negative effects on spasticity. One 40-minute session of physical training was replaced by low intensity ergometer aerobic training three days per week in the experimental group. Prior studies have demonstrated that routine rehabilitation training for severely compromised stroke survivors provides little aerobic stimuli[1, 7].

Low-intensity ergometer aerobic training was based on the peak heart rate. The targeted aerobic training intensity was calculated using the Karvonen equation[13, 14].
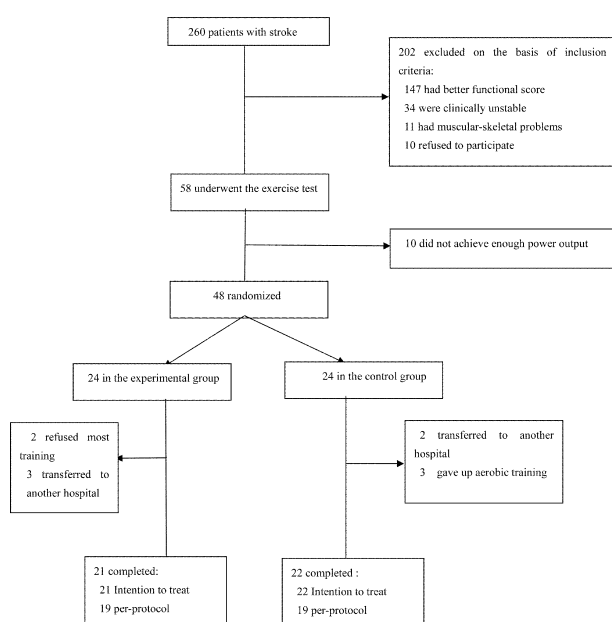
Target Heart Rate =
$$\text{(peak HR in the exercise test} - \text{resting HR)} \times 50\text{--}70\% + \text{resting HR}$$

Every aerobic training session consisted of five minutes warm-up, thirty minutes targeted intensity training and five minutes cool down period. Two breaks of less than thirty minutes were allowed per 30-minute training session. One additional therapist helped to correct patients performing wrong compensatory actions, keep them in good posture, verbally encourage the use of the affected leg and to monitor the training intensity to ensure the treatment fidelity. The first week of aerobic training was also supervised by a doctor experienced in cardiology. The resistance of the ergometer was adjusted to achieve the targeted heart rate level. A cardiac monitor or heart rate belt will be used and the resistance was progressively increased to ensure that the heart rate was always within the target zone.

The demographic properties of the participants such as age, sex and body weight were recorded. Data of the time interval between admission and stroke onset, type of stroke, and lesion site were collected from medical records. The actual number of aerobic training sessions finished by participants in the experimental group was recorded. Only aerobic training sessions with targeted intensity training times of 30 minutes reached was defined as finished one and short breaks of less than two minutes were allowed twice per session. In the first week, subjects' blood pressure and heart rate at rest, 15 and 30 minutes during training and 5 minutes post training were recorded using a cardiac monitor (Dash 4000). All patients were also evaluated before and after the intervention using the tests described above: Exercise test: The adapted exercise test was conducted to record peak heart rate and exercise test time; The Fugl-Meyer motor assessment and Barthel index: These two tools were used to accessed the motor function score and abilities of daily living respectively; The Oral Glucose Tolerance Test (OGTT): After 12 hours of overnight fast, patients underwent the standard OGTT to measure fasting glucose, fasting insulin, two-hour glucose level and the homeostasis model assessment-insulin resistance index (HOMA-IR) [HOMA-IR = insulin (μU/mL)$\times$ glucose (mmol/L)/22.5]. An intravenous catheter was inserted to facilitate blood sampling and 75g glucose were ingested at the beginning of the test; Serum lipids profiles: Blood samples obtained by venipuncture following overnight fasting. Serum for total triglycerides were assayed. HDL cholesterol was determined in plasma, and LDL cholesterol was calculated using the Friedewald equation.

Data were entered onto the Statistical Package for the Social Sciences (SPSS) version 12. All the datas were expressed in terms of mean±SD. To explore the effectiveness of aerobic training, a 2-way repeated-measures analysis of variance was used after confirming the normality of the data distribution by Kolmogorov-Smirnov test to examine the effects of time and intervention on the Fugl-Meyer motor score, Barthel index, exercise test time, peak heart

Fig. 1. Flow diagram of the study

Table 1. Clinical characteristics of both groups at start of the intervention

	Experimental group	Control group
N	24	24
Age (years)	57±6.8	55±11.5
Sex (F, female ; M, male)	F:6, M:18	F:7, M:17
Weight (Kg)	70.7±12.1	74.6±9.3
Interval (days)	30±10.2	36±12.1
Type of stroke		
Ischaemia	13	12
Hemorrhage	11	12
Site of stroke		
Cortex	5	6
Subcortical	13	11
Brainstem	3	5
Mixed	3	2
Affected side	6=left, 18=right	7=left, 17=right
History of hypertension	14	13
Exercise test time (min)	12.2±3.6	11.5±4.2
Peak heart rate in exercise test (beats/min)	123.9±18.6	116±11.1

rate, fasting glucose, fasting insulin, 2-hour plasma glucose, HOMA-IR and serum lipid profiles (Total triglycerides, HDL cholesterol, LDL cholesterol) respectively. When main effects were detected, student t test with the Bonferroni correction was performed as a post hoc test. P-value of <0.05 was considered significant. Primary analysis compared the effects of aerobic training on all outcome measures according to intention to treat analysis. Secondary (per protocol) analysis was performed based on participant compliance with the exercise program (defined as attending ≥ 80% of sessions).

RESULTS

Over four years and nine months, 48 eligible subjects were randomized (Fig. 1). Before the intervention, the average peak heart rate in the exercise test was 120.9±13.5 beats/min for all the subjects (experimental group: 123.9±18.6 beats/min, control group: 116±11.1 beats/min), much lower than age-predicted maximal heart rate (220-age:220−56=164 times/min) (p<0.05), but similar to their age-predicted submaximal heart rate (195-age:195−56=139 times/min) (p>0.05). The exercise test duration was 11.9±3.3 min (experimental group: 12.2±3.6 min, control group: 11.5±4.2 min). No adverse event occurred during the exercise tests.

There were 24 subjects in the experimental and control group. The demographic and clinical features were comparable between the two groups (Table 1). During the intervention period, there were no changes in medication for all the subjects for the addition of anti-hypertensive drugs for three subjects (2 with angiotensin receptor blockers and 1 with angiotensin-converting enzyme inhibitor agent).

Each subject in the experimental group was prescribed 18 aerobic training sessions (3 times × 6 weeks) in total.

Two of 24 patients (8.3%) were transferred to another hospital for reasons unrelated to exercise training (one was transferred to a hospital in his home city and another was transferred to the surgery department of a bigger hospital for deep vein because of thrombosis).Three patients (12.5%) gave up aerobic training for psychological reasons (give up due to discomfort or unpleasant feelings) after they had finished 9, 6 and 6 sessions respectively. Twelve patients (50%) missed one to three sessions for various reasons but finished all the other sessions (defined as compliant since they finished ≥ 80% of sessions). Seven patients (29.2%) finished all the aerobic training sessions prescribed. All subjects could adhere to routine rehabilitation training except those transferred to other hospitals.

Two patients transferred to another hospitals were excluded from the evaluation of aerobic training feasibility. The other 22 patients in the aerobic training group finished 351 (88.6%) of the total 396 (22 patients ×18 sessions) aerobic training sessions prescribed. If the three patients who gave up aerobic training were also excluded, 19 patients finished 330 (96.5%) of the total 342 (19 patients ×18 sessions) aerobic training sessions prescribed.

Twelve aerobic training sessions (342 prescribed ones minus 330 actual finished ones) were missed by compliant patients. Six sessions were missed because of general fatigue, 2 sessions were missed because of pain or discomfort in the affected leg (pain or discomfort in muscle or knee), and patients refused to do 2 sessions for psychological reasons (didn't want to do). In addition, 3 patients also reported affected leg discomfort several times during ergometer aerobic training, which did not affect their daily life or adherence to the training schedule.

No other adverse event occured during the aerobic train-

Table 2. Average (S±SD) heart rate and blood pressure responses to aerobic training of all the subjects in the experimental group (N:24 subjects×3 days=72)

	At rest	15 min	30 min	5 min after the end of training
Systolic blood pressure (mmHg)	125.2±11.4	158.3±20.1	159.1±22.3	129.3± 14.1
Diastolic blood pressure (mmHg)	80.2±11.3	90.1±10.3	93.1±10.4	81.3±8.7
Heart rate (times/min)	80.2±7.5	106.2±13.1	113.2±14.5	85.1±8.8

Table 3. Average (S±SD) heart rate and blood pressure responses to aerobic training of those with both hypertension and hemorrhagic stroke in the experimental group (N:8 subjects×3 days=24)

	At rest	15 min	30 min	5 min after the end of training
Systolic blood pressure (mmHg)	129.6±13.8	162.6±21.5	157.8±20.2	130.5± 14.9
Diastolic blood pressure (mmHg)	82.6±11.0	92.2±11.2	91.8±12.8	82.8±10.9
Heart rate (beats/min)	82.6±8.9	108.6±14.2	111.9±17.1	86.3±9.1

ing or intervention period. Systolic blood pressure and heart rate rose significantly during aerobic training but both return to rest levels within 5 minutes after training (Table 2, 3). Signs of ventricular premature contraction were occasionally seen in two patients' ECGs (electrocardiograms) during aerobic training. However, they all showed normal ECGs after aerobic training.

In the intention to treat analysis, the experimental group displayed significantly greater improvements in the Fugl-Meyer Motor Score and Barthel index ($p<0.05$) than the control group. No difference was found in other outcomes in both the between and within group comparison (Table 4).

Per-protocol analysis was subsequently performed. Significant increases in the Fugl-Meyer Motor Score and Barthel index were found in both groups ($p<0.05$) while the experimental group manifested greater changes ($p<0.05$). The between group comparison also indicated that the aerobic training improved the exercise test time, 2-hour blood glucose level and HOMA-IR in the experimental group ($p<0.05$). No change was found in peak heart rate, fasting glucose, fasting insulin, total triglycerides, HDL cholesterol and LDL cholesterol in both the within and between group comparisons in the per-protocol analysis ($p>0.0$) (Table 5).

DISCUSSION

This study demonstrated that adapted low intensity aerobic training is feasible and effective for extremely early and weak stroke survivors. Our results may provide additional support for the use of aerobic training for stroke survivors across a wide spectrum of disease course and functional levels.

Compared with previous studies, subjects in this study had unique features of early stroke course and low functional levels. Several adaptations to the aerobic training regime were made accordingly. First, the intensity was lower. We set the intensity according to outcomes in the adapted exercise test, in which the output power was increased by 2.5 W every three minutes. Second, less than two minutes rest

were allowed twice per session. Third, subjects' feet were firmly fixed to the ergometer pedals. Lastly, aerobic training was supervised by an therapist. As a result, most aerobic training sessions could be tolerated. Our preliminary results may be meaningful as an initial step in establishing an aerobic training modality for early and weak stroke survivors. However, many patients were precluded from the training due to clinical safety concerns. Some aerobic training sessions were missed by subjects and their reasons for absence were mainly general fatigue, local discomfort in the unaffected leg as well as psychological issues. Accordingly, much works is needed to make aerobic training more acceptable to such subjects. Improvement of aerobic training equipment such as the introduction of an ergometer combined with functional electrical stimulation[15], specific measures to target pain or discomfort in muscle, bone, or joint as well as more intense education and encouragement should be considered in future trials.

Subjects with several functional and vascular disease risks were included in the study to explore the efficacy of aerobic training. The preliminary results demonstrate that it may result in aerobic gains which promote functional, fitness and reduce vascular disease risk factors of compliant patients. Changes in the exercise test and OGTT results indicate that peripheral adaptations may be largely responsible for the training effects, since there were improvements in muscle property and insulin sensitivity[16–19]. The underlying molecular changes needs to be further explored. Previous studies have shown that aerobic training is effective in improving the fitness levels of stroke patients[7–10, 20–22]. Our training intensity was much lower because of our subjects' functional limitation. The intensity of aerobic training is a meaningful research theme. Several studies have indicated that high intensity intermittent aerobic training may be more effective in improving fitness levels[23], and it also is feasible for stroke patients. Our initial results imply that high intensity aerobic training may not be necessary for stroke patients. However, future investigations are needed to determine the most suitable aerobic training intensity for

Table 4. Mean scores before and after intervention of both groups (Intention to treat analysis)

Outcome	Experimental group (n=21)		Control group (n=22)	
	Pre	Post	Pre	Post
Fugl-Meyer Motor Score	25.2±17.1	40.2±10.2*Δ	23.8±16.1	31.2±11.2*
Barthel index	42.2±23.1	71.1±15.1*Δ	41.2±19.7	55.0±13.2*
Exercise test (min)	11.1±1.9	11.2±2.6	11.5±4.2	11.3±3.9
Peak heart rate	124.1±15.8	122.2±12.4	116±11.1	115.4±14.1
Fasting insulin (μU/mL)	8.41±1.78	7.99±1.02	8.67±1.03	8.57±1.19
Fasting glucose	5.12±0.31	5.11±0.49	5.12±0.81	5.12±0.31
2-hour blood glucose	9.21±1.11	8.98±1.15	9.08±2.06	9.12±1.02
HOMA-IR	1.75±1.03	1.56±0.89	1.54±0.99	1.52±0.84
Total triglycerides	1.45±0.13	1.49±0.15	1.43±0.36	1.46±0.11
HDL cholesterol	1.06±0.29	1.08±0.14	1.05±0.19	1.01±0.19
LDL cholesterol	2.51±0.42	2.61±0.56	2.61±0.55	2.58±0.56

Values in table are means±SD
*$p < 0.05$ within group comparison
Δ $p < 0.05$ between group comparison

Table 5. Mean scores before and after intervention of both groups (per -protocol analysis)

Outcome	Experimental group (n=19)		Control group (n=19)	
	Pre	Post	Pre	Post
Fugl-Meyer Motor Score	26.4±19.4	45.4±12.7*Δ	23.8±16.1	30.9±12.9*
Barthel index	40.1±21.1	79.2±14.2*Δ	41.2±19.7	58.0±15.1*
Exercise test (min)	12.2±3.6	13.8±3.6*Δ	11.5±4.2	11.8±4.3
Peak heart rate	122.9±18.6	124.3±15.9	116±11.1	118.4±14.9
Fasting insulin (μU/mL)	8.44±2.01	7.47±1.01	8.67±1.03	8.47±1.12
Fasting glucose	5.09±0.34	4.99±0.43	5.12±0.81	5.11±0.21
2-hour blood glucose	9.22±1.16	7.21±1.36*Δ	9.08±2.06	9.11±1.12
HOMA-IR	1.72±1.01	1.28±0.88*Δ	1.54±0.99	1.51±0.94
Total triglycerides	1.41±0.12	1.34±0.15	1.43±0.36	1.51±0.07
HDL cholesterol	1.01±0.13	1.04±0.12	1.05±0.19	1.02±0.13
LDL cholesterol	2.53±0.41	2.53±0.66	2.61±0.55	2.57±0.46

Values in table are means±SD
*$p < 0.05$ within group comparison
Δ $p < 0.05$ between group comparison

stroke survivors at each stage and functional level.

Only compliant patients showed improvements in exercise test time and OGTT results. This may indicate that training effectiveness is based on aerobic training compliance. Our study had several limitations. The sample size was small. It was determined by the number of subjects enrolled for training rather than power analysis. Besides, there was a large variation in subjects' basic characteristics including gender and type of disease. Moreover, many subjects were excluded because they did not meet the inclusion criteria or for medical reasons. This selection bias may affect the generalizability of our findings to population-based samples. There was also a significant drop out rate. In clinical setting, it is possible that patients may have deduced which group they were in and the outcome observers may not have been totally blind. There was also a significant difference between 1 or 2 and 3 on the 7-point Chedoke-McMaster Stroke Assessment scale. Future stud-

ies should divide subjects into subgroups based on this scale to further explore the effects of aerobic training. Regarding the final results, there may have been several influencing factors. First, the rehabilitation training program was individualized. The individual content of rehabilitation program may have influenced the result. Training modalities other than low intensity aerobic training, such as strength training also may have contributed to fitness gains. Second, for the weak subjects, a longer exercise test time may have been possible through familiarization with the equipment. We tried to overcome these influencing factors by enforcing the same training volume in total and for each training modality and the training program was quite similar since all the patients were at the same stage of motor recovery and disease course.

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