Efficacy of Feedback-Controlled Robotics-Assisted Treadmill Exercise to Improve Cardiovascular Fitness Early After Stroke: A Randomized Controlled Pilot Trial

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Background and Purpose: Cardiovascular fitness is greatly reduced after stroke. Although individuals with mild to moderate impairments benefit from conventional cardiovascular exercise interventions, there is a lack of effective approaches for persons with severely impaired physical function. This randomized controlled pilot trial investigated efficacy and feasibility of feedback-controlled robotics-assisted treadmill exercise (FC-RATE) for cardiovascular rehabilitation in persons with severe impairments early after stroke.

Methods: Twenty individuals (age 61 ± 11 years; 52 ± 31 days poststroke) with severe motor limitations (Functional Ambulation Classification 0-2) were recruited for FC-RATE or conventional robotics-assisted treadmill exercise (RATE) (4 weeks, 3 × 30-minute sessions/wk). Outcome measures focused on peak cardiopulmonary performance parameters, training intensity, and feasibility, with examiners blinded to allocation.

Results: All 14 allocated participants (70% of recruited) completed the intervention (7/group, withdrawals unrelated to intervention), without serious adverse events occurring. Cardiovascular fitness increased significantly in both groups, with peak oxygen uptake increasing from 14.6 to 17.7 mL · kg^{-1} · min^{-1} (+17.8%) after 4 weeks (45.8%-55.7% of predicted maximal aerobic capacity; time effect $P = 0.01$; no group-time interaction). Training intensity (% heart rate reserve) was significantly higher for FC-RATE (40% ± 3%) than for conventional RATE (14% ± 2%) ($P = 0.001$).

Discussion and Conclusions: Substantive overall increases in the main cardiopulmonary performance parameters were observed, but there were no significant between-group differences when comparing FC-RATE and conventional RATE. Feedback-controlled robotics-assisted treadmill exercise significantly increased exercise intensity, but recommended intensity levels for cardiovascular training were not consistently achieved. Future research should focus on appropriate algorithms within advanced robotic systems to promote optimal cardiovascular stress.

Video abstract available for more insights from the authors (Supplemental Digital Content 1, http://links.lww.com/JNPT/A107).

Key words: *exercise therapy, exercise tolerance, robotics, stroke, subacute care, treadmill training*

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INTRODUCTION

Evidence suggests that individuals with stroke benefit from cardiovascular exercise interventions. Several prospective trials and meta-analyses investigating cardiovascular fitness interventions using leg cycle ergometry, treadmill training, and combined upper- and lower-limb ergometry demonstrated beneficial effects on cardiovascular fitness in subacute[1-12] and chronic stroke.[13-17] Furthermore, preliminary evidence exists for improved cerebral vasomotor reactivity,[18] subcortical neural network activation,[19] and enhanced cognitive function[20,21] after cardiovascular exercise poststroke. However, the main body of available research is focused on individuals with mild to moderate motor impairments. Unique challenges such as nonambulatory status, limited trunk control, poor postural control, and poor coordination of the affected limbs may restrict individuals with severe impairments from performing exercise on conventional devices. Recently, a total-body recumbent stepper to implement cardiovascular exercise in persons with severe motor limitations was proposed.[22,23] Considering that walking ability is one of the major goals of stroke rehabilitation, and given the importance of task-specific training in the early stages of recovery,[24,25] more functional rehabilitation strategies are sought to provide effective exercise interventions in populations with severe motor impairment.

A promising approach to overcome motor limitations while facilitating task-specific activity and cardiovascular stress is body weight-supported treadmill training. Research

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has shown that gait symmetry improves with increasing body weight support.[26] However, during walking with body weight support of more than 15%, vertical ground reaction forces and functional activity of antigravity muscles are decreased, which leads to substantially lower oxygen uptake levels during body weight-supported treadmill training compared with conventional treadmill exercise.[27,28] Because individuals with severe motor impairments need considerable guidance during walking with lower body weight support, the application of robotics-assisted treadmill exercise (RATE) might be of relevance in this context. The technology provides important features for neuromuscular and cardiovascular training (ie, assistive support during the gait trajectory for progressive body weight loading) and the opportunity to implement control strategies to facilitate participation and increase effort.

Studies on motor recovery after stroke have shown that RATE seems to facilitate similar outcomes compared with body weight-supported treadmill training.[29-31] However, individuals tend to minimize their effort during RATE because of the constant physical support of the actuated exoskeleton, defined as "slacking".[32] Metabolic cost and muscle activity patterns have been shown to be substantially lower during RATE compared with conventional body weight-supported treadmill training in persons with incomplete spinal cord injury.[33] Nevertheless, recent experimental research on cardiovascular responses in persons with severe hemiplegia significantly increased the metabolic cost during RATE.[34-36] The active stance phase, which produces body weight loading, might be responsible for the increase in exercise intensity, whereas gait speed and advanced force controllers (eg, guidance force) had only small effects on oxygen uptake.[34]

Optimal exercise intensity is a crucial factor for improving cardiovascular fitness. Recent guidelines for individuals with stroke recommend regular cardiovascular exercise at an intensity level of 40% to 70% heart rate reserve (55%-80% of heart rate maximum; rate of perceived exertion 11-14 [scale of 6-20]).[37] Although a first intervention study on RATE to improve cardiovascular fitness by decreasing body weight support yielded promising results in the subacute phase after stroke,[38] further research has shown that conventional RATE could not reach recommended cardiovascular exercise intensity in persons with severe hemiplegia.[35,36] Therefore, a novel protocol has been developed to control and direct active participation during RATE with the specific aim of provoking higher cardiopulmonary responses.[39] This incorporates biofeedback mechanisms, allowing the control of exercise intensity through the guidance of the individual's voluntary effort. The approach presented here provides control of exercise intensity during RATE by biofeedback and voluntary adaptation of the hip and knee forces by the individual. Initial studies demonstrated feasibility and reliability for feedback-controlled RATE (FC-RATE) to assess cardiovascular fitness and guide exercise intensity during cardiopulmonary exercise testing protocols soon after stroke.[40,41] The next logical step is to evaluate FC-RATE in a pilot-randomized controlled trial to assess the clinical efficacy and feasibility of the method for cardiovascular training and improving cardiovascular fitness during subacute stroke rehabilitation.[42] This is relevant for the further development of the concept and the design of future large-scale trials.

The aim of this study was to carry out a preliminary investigation of efficacy and feasibility of FC-RATE for improving cardiovascular fitness in persons with severe motor impairments early after stroke. We hypothesized that FC-RATE would reach a substantially higher cardiovascular training intensity compared with conventional RATE in a clinical setting, thus resulting in significantly increased cardiovascular fitness after a 4-week FC-RATE intervention. In addition, we expected to affirm feasibility by achieving predefined criteria.

METHODS

Design

This was a single-center, single-blind, randomized controlled pilot trial. The study protocol was published previously.[43] The Ethics Review Board of the Canton of Aargau in Switzerland approved all experimental procedures (Reference No. 2012/051).

Participants

Twenty participants with first-ever stroke were recruited by research staff at a neurological rehabilitation clinic in Switzerland between October 2012 and March 2014. Participants were presented to the responsible ward physician and a cardiologist to confirm eligibility. Inclusion criteria were (1) clinical diagnosis of a first-ever stroke, (2) less than 20 weeks poststroke, (3) older than 18 years, (4) Functional Ambulation Classification less than 3, and (5) ability to understand the procedures and provide informed consent. Exclusion criteria were (1) contraindications for cardiopulmonary exercise testing as outlined by the American College of Sports Medicine,[44] (2) contraindications for RATE according to the device manufacturer (eg, bone instability [osteoporosis], severely fixed contractures, and vascular disorders of the lower limbs), (3) concurrent neurological disease (eg, spinal cord injury, multiple sclerosis, and Parkinson disease), (4) concurrent pulmonary disease (eg, chronic obstructive pulmonary disease), and (5) a history of dementia. Individuals with any suspicion of these conditions were excluded. All participants provided written informed consent.

Randomization was performed using a computer-generated permuted 4-block allocation scheme. A researcher not otherwise associated with the study generated the list and sent it to the clinic pharmacy for safekeeping. The lead trial therapist contacted the pharmacy for assignment. A blinded examiner conducted all assessments and the randomization was concealed until the last postintervention assessment was performed and the data processing and acquisition was terminated.

Outcomes

The primary outcome of this study was efficacy, which was evaluated by cardiovascular fitness and training intensity. Peak cardiopulmonary performance was assessed by peak oxygen uptake ($V_{O_{2peak}}$), peak work rate (P_{peak}), peak ventilation rate (V_{Epeak}), peak respiratory rate (R_{fpeak}), peak heart rate (HR_{peak}), and respiratory exchange ratio (V_{CO_2}/V_{O_2}) at $V_{O_{2peak}}$ (RER_{peak}). Additional cardiovascular parameters included the gas exchange threshold and important derivatives such as O_2

cost of work ($\Delta V_{O_2}/\Delta P$), O_2 pulse at $V_{O_{2peak}}$ (O_{2pulse}), and V_E versus V_{CO_2} slope ($\Delta V_E/\Delta V_{CO_2}$). Continuous heart rate monitoring was used to evaluate the training intensity. The secondary outcome was feasibility, which was rated on the basis of predefined criteria.[45] Compliance focused on training attendance during the intervention phase (ie, the number of sessions completed) (defined to be ≥90%). The number of dropouts gave the attrition rate during the entire study (defined to be ≤10%). The occurrence of any serious adverse events gave information on the protocol's clinical safety (defined to be 100%). Successful data acquisition was assessed by reporting any loss of breath-by-breath, continuous heart rate, or mechanical work rate data (defined to be 100%).

Instrumentation

Robotics-assisted treadmill exercise was implemented using a robotic gait orthosis (Lokomat, Hocoma AG, Volketswil, Switzerland). The powered exoskeleton provides control of both legs, synchronized with an integrated treadmill (h/p/cosmos sports & medical GmbH, Traunstein, Germany) and a motor-driven body weight support system with real-time feedback control for body weight unloading (Lokolift, Hocoma AG, Volketswil, Switzerland). The feedback-control approach for exercise testing and experimental training was based on the work rate exerted on the exoskeleton by the participant calculated from the force, moment arm, and velocity data at the 4 active joints (hip and knee). The participant was instructed to vary the forces applied on the exoskeleton by volitional muscle activity and to keep the measured and visualized active work rate as close as possible to the target (Figure 1). Detailed information on FC-RATE can be found elsewhere.[40]

Pulmonary gas exchange and ventilatory measurements were carried out using breath-by-breath ergospirometry (MetaMax 3B, Cortex Biophysik GmbH, Leipzig, Germany). Heart rate was recorded by a heart rate belt (T31, Polar Electro, Kempele, Finland) and a receiver board (HRMI, Sparkfun, Boulder, CO). A software module for the overall procedure was programmed in LabVIEW (Version 2009, National Instruments, Austin, TX).[46]

Testing Procedure

Cardiovascular fitness was assessed using FC-RATE-based cardiopulmonary exercise testing. At study entry, all participants completed a familiarization session with the FC-RATE concept, starting with a trained physical therapists adjusting the robotic orthosis to provide a physiological gait pattern and ensuring the participants could walk comfortably. An initial test of decreasing body weight support continuously by 5% per minute was implemented to define the minimal possible body weight support level. After the first adjustments, participants were asked to perform a short constant load exercise test for 5 minutes (target work rate = 20 W) to practice using the feedback-control structure. Finally, the safety procedures for potential adverse events were explained in detail.

After a break of at least 24 hours, participants performed consecutive cardiopulmonary exercise testing with 48 to 72 hours between the trials. All sessions were controlled for time of day. Participants were instructed not to consume food, alcohol, nicotine, or caffeine at least 3 hours before testing.

Participants were asked at the beginning of the first exercise test to increase their maximal voluntary effort during FC-RATE within 30 seconds to define the maximal work rate for the subsequent tests. The progressive ramp was defined as a continuous slope aiming to reach the predefined maximal work rate in 10 minutes. All participants performed 2 tests at baseline (on separate days) and 1 test at postintervention. The

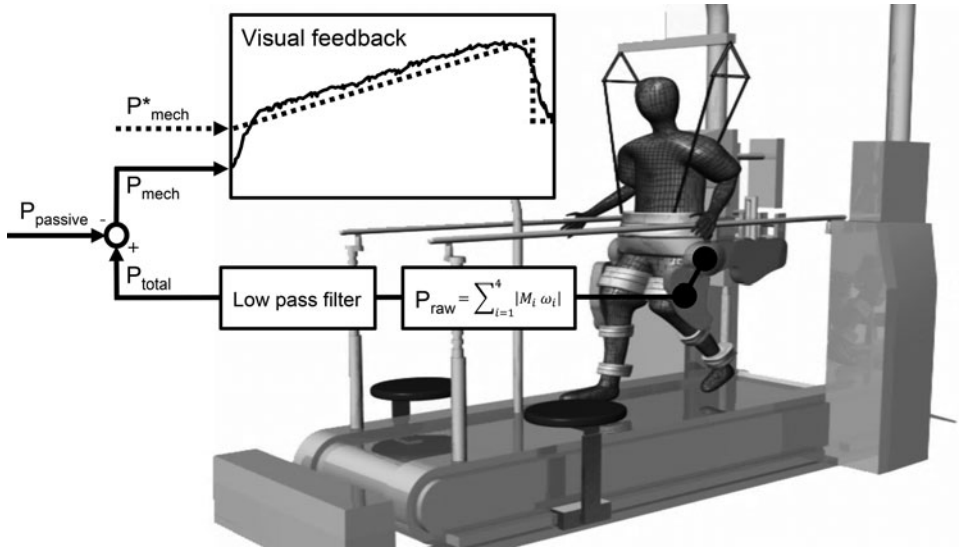

Figure 1. Feedback-controlled robotics-assisted treadmill exercise. Hip and knee joint forces and angles are measured in real time to allow calculation of the mechanical work rate (P_{mech}, solid line) and projection onto a screen in front of the person. Individual target work rate profiles (P^*_{mech}, dashed line) are used to guide exercise intensity during robotics-assisted walking. The passive mechanical work rate ($P_{passive}$) is evaluated before every session and subtracted from P_{mech}. M_i, moments of force; P_{raw}, raw mechanical work rate; P_{total}, total mechanical work rate; ω_i, angular velocity.

test protocol followed strict termination criteria and there was close adherence to established models for cardiopulmonary exercise testing according to international guidelines.[44,47] Detailed information on FC-RATE-based cardiopulmonary exercise testing can be found elsewhere.[41]

Intervention

Both groups were balanced in terms of exposure (3/wk, 30 min/session) over a period of 4 weeks (12 sessions). All training sessions were led by 1 of 2 experienced physical therapists, who were trained in the intervention protocols. The training intensity was monitored in both groups by continuous heart rate measurement and further confirmed by rating of perceived exertion on the Borg scale of 6 to 20.[48] Walking cadence was fixed at 60 steps/min for all sessions, and body weight support was individually adjusted within a range of ±10% to provide a physiological gait pattern.

The experimental group received progressive cardiovascular exercise using FC-RATE. The first training session was defined to start at 40% of P_{peak} (determined from a previous exercise test) to approach 40% of heart rate reserve (Borg scale approximately 11-14). The intensity was then adjusted on the basis of continuous heart rate data and rating of perceived exertion indications by modulating the target work rate in 5% increments for every subsequent session to reach the target intensity. The target heart rate was set at 40% to 70% of heart rate reserve.[37] The control group received conventional RATE, where therapists focused on gait quality only. All training sessions started with a 5-minute warm-up period while passively walking in the device, followed by 25 minutes of continuous FC-RATE at the target level (experimental) or 25 minutes of conventional RATE (control).

All participants received individually tailored conventional care, in addition to RATE or FC-RATE, including physiotherapy (4-5 sessions/wk, 30-60 min/session), occupational therapy (2-3 sessions/wk, 30-60 min/session), and individual speech and language therapy. Because of the severely impaired status of the participants, no specific aerobic exercise training was provided during conventional care.

Data Processing

Raw breath-by-breath data were processed using a zero phase shift moving average filter over 15 breaths.[49] Peak cardiopulmonary variables were defined as the maximal values in the final 30 seconds during incremental exercise. Of the 2 consecutive tests at baseline, the data set containing the highest $V_{O_{2peak}}$ was considered for analysis. Criteria for maximal aerobic capacity were (1) plateau in oxygen uptake, (2) respiratory exchange ratio 1.15 or more, and (3) peak heart rate within 10 beats per minute of the age-predicted heart rate maximum (adjusted for participants on β-blocker medications).[44] The identification of a V_{O_2} plateau was performed by plotting the slope and 95% confidence interval (CI) of the $\Delta V_{O_2}/\Delta P$ slope, where data points outside the extrapolated 95% CI were taken as evidence of plateauing or leveling off behavior.[50] The gas exchange threshold was estimated using the v-slope method.[51] Predicted maximal heart rate was defined as $208 - (0.7 \times \text{age})$,[52] but the formula was adjusted to 70% for participants on β-blocker medication.[53] Heart rate reserve was defined as predicted maximal heart rate − resting heart rate.[54] Data processing was performed using MATLAB (Version R2010a, MathWorks, Natick, MA) and LabVIEW (Version 2009, National Instruments, Austin, TX).

Statistical Analysis

Descriptive statistics were calculated on all outcome variables. For comparisons of baseline characteristics and training intensity between groups, a Mann-Whitney *U* test was applied for continuous and ordinal variables and an x^2 test for nominal variables. The analyses were based on the intention-to-treat approach. The F1-LD-F1 model by Brunner and Langer was used to test the median treatment effect, time effect, and the effect of the interaction by an analysis of variance-type test statistic (F_n).[55] The models were computed with the R 3.0.3 statistics program. All other statistical analyses were performed with SPSS (SPSS Inc, Chicago, IL).Because of the exploratory nature of the study, 2-sided *P* values ($P \leq 0.05$) were considered significant and no adjustment for multiple endpoints was performed.

RESULTS

Participants

The number of individuals screened, enrolled, randomized, and completing the trial is shown in Figure 2. There were no significant differences in baseline characteristics between the 2 groups (Table 1). No serious adverse events occurred during FC-RATE-based cardiopulmonary exercise testing. Thirteen participants (93%) completed the tests without symptomatic responses. The overall reason for test termination was inability to reach the target work rate because of generalized and/or leg fatigue.

One participant required a test termination per safety criteria because of high systolic blood pressure of more than 210 mmHG during the baseline assessments, which was considered an adverse event. The participant's results were considered valid because both exercise tests were terminated at very high exercise intensity. The responsible ward physician/surgeon admitted the participant to the intervention phase after careful medical evaluation. The high systolic blood pressure response in this participant was not observed during any of the training sessions, or during the postintervention assessment.

With respect to the 3 criteria for maximal aerobic capacity, 2 participants (14%) showed a plateau in V_{O_2}, 1 participant (7%) achieved an RER_{peak} value 1.15 or more, and 4 participants (29%) reached HR_{peak} within 10 beats per minute of the age-predicted heart rate maximum; 2 of these had an adjusted heart rate because of β-blocker medication. None of the participants reached more than 1 criterion for maximal aerobic capacity. No significant differences were found across cardiopulmonary performance parameters at baseline, except for $\Delta V_{O_2}/\Delta P$ ($P = 0.017$).

Efficacy

Peak cardiopulmonary performance showed no significant group-time interactions, but within-group analyses revealed that both groups improved over time ($V_{O_{2peak}}$ absolute, $P = 0.02$, effect size (ES) 0.38; $V_{O_{2peak}}$ relative, $P = 0.01$,

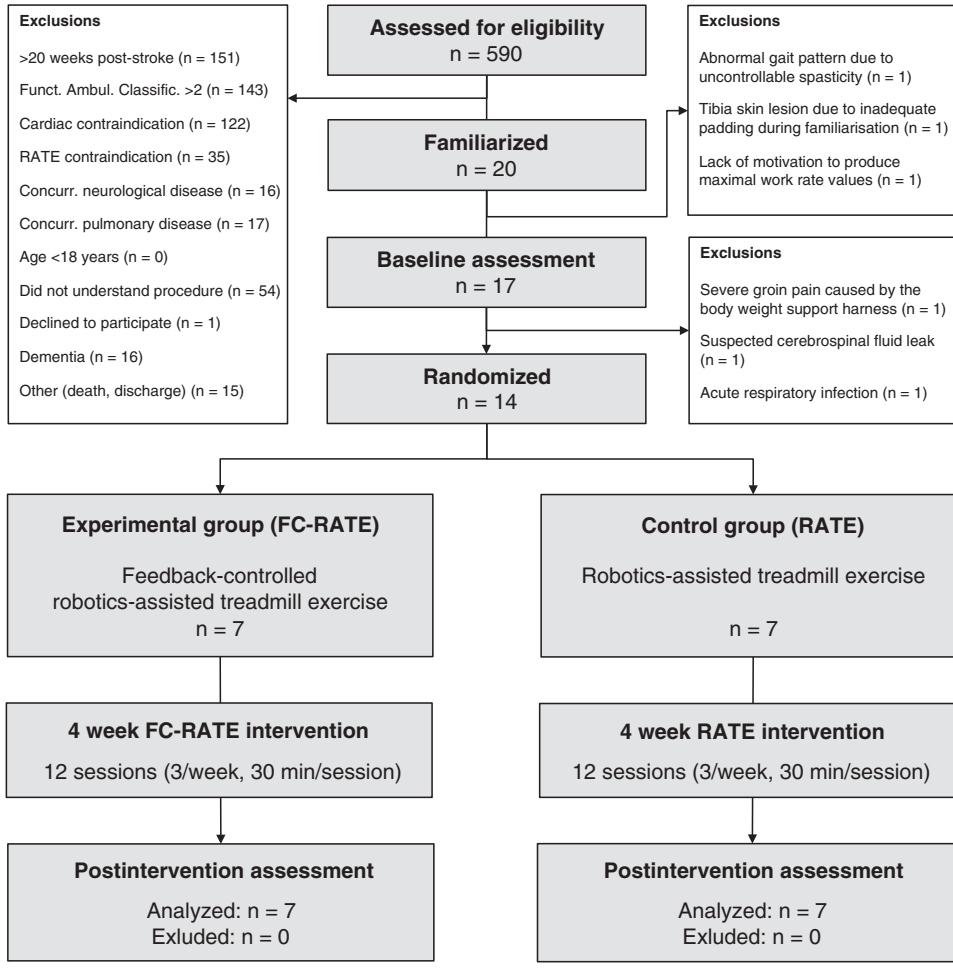

Figure 2. Study flowchart.

Table 1. Participant Characteristics at Baseline[a]

	Experimental Group		Control Group			
	FC-RATE (n = 7)		RATE (n = 7)		%	*P*
Men/women	3/4		6/1		64/36	0.27
Type of stroke: ischemic/hemorrhagic	5/2		7/0		86/14	0.46
Hemiparetic side: right/left	5/2		2/5		50/50	0.29
Medications: β-blockers/ACE inhibitors/both	1/3/1		3/7/3		29/71/29	
Comorbidities: Hypertension/dyslipidemia/adipositas/ diabetes mellitus	4/1/2/1		3/2/1/2		50/21/21/21	
Time poststroke, d	52 ± 42	32 (14-139)	45 ± 30	31 (21-92)		0.71
Age, y	57 ± 12	52 (44-77)	63 ± 13	58 (47-84)		0.32
BMI, kg/m^2	29 ± 6	26 (23-38)	26 ± 6	25 (19.5-37.9)		0.46
Functional Ambulation Classification (0-5)	1.0 ± 0.8	1 (0-2)	0.9 ± 1	1 (0-2)		0.82
Extended Barthel Index (0-64)	39 ± 9	42 (27-54)	47 ± 7	46 (39-55)		0.21
Body weight support during RATE, %	60 ± 10	63 (46-70)	60 ± 9	59 (50.0-76.9)		0.81
Walking speed during RATE, m/s	0.56 ± 0.04	0.56 (0.50-0.61)	0.58 ± 0.06	0.61 (0.50-0.64)		0.54
Resting heart rate, beats/min	78 ± 7	80 (68-85)	73 ± 8	72 (63-85)		0.46
Predicted maximal heart rate achieved, %	80 ± 9	77 (72-98)	83 ± 15	83 (63-107)		0.62
Predicted maximal oxygen uptake achieved, %	47 ± 24	38 (19-79)	51 ± 20	49 (23-76)		0.71

[a]Values are given in numbers (n) or mean ± standard deviation, median (min-max).

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; BMI, body mass index; FC-RATE, feedback-controlled robotics-assisted treadmill exercise; RATE, robotics-assisted treadmill exercise.

ES = 0.58; V_{Epeak}, $P = 0.001$, ES = 0.49; RER_{peak}, $P = 0.001$, ES = 0.82; O_{2pulse}, $P = 0.02$, ES = 0.29) (Table 2). No other significant differences in cardiovascular performance parameters were found. Overall, absolute V_{O2peak} increased from 1236 to 1477 mL · min^{-1} (48.2%-57.6% of predicted absolute V_{O2max}[56]), relative V_{O2peak} from 14.6 to 17.7 mL · kg^{-1} · min^{-1} (45.8%-55.7% of predicted relative V_{O2max}[56]), and HR_{peak} from 122 to 128 beats/min (80.7%-84.7% of predicted maximal heart rate[52]).

Training intensity over the 4-week intervention period (12 sessions) was significantly different between the groups (heart rate, $P = 0.002$; heart rate reserve, $P = 0.001$). For the experimental group, heart rate was (mean ± standard deviation) 110 ± 8 beats/min (95% CI, 103-116) and heart rate reserve was 40% ± 3% (95% CI, 37-42). For the control group, heart rate was 83 ± 13 beats/min (95% CI, 73-92) and heart rate reserve was 14% ± 2% (95% CI, 12-16). The course of training intensity for both groups is shown in Figure 3.

Feasibility

The compliance to the intervention protocol was 100%. All participants who completed the baseline assessment were able to complete the training protocol. However, several controllable and uncontrollable events led to an attrition rate of 30% during familiarization and baseline assessment. Of the 6 participants who dropped out, only 2 gave reasons on the basis of uncontrollable factors such as suspected cerebrospinal fluid leak and acute respiratory infection. The other 4 dropouts were caused by controllable factors. The gait pattern of 1 participant was disturbed by severe spasticity, which prevented a physiological gait pattern. One participant had a tibial skin lesion and another developed severe groin pain because of inappropriate padding. Furthermore, 1 participant was able to, but not motivated to, follow the target work rate, as described previously. Although 2 cardiopulmonary exercise tests in 1 participant were considered as adverse events, no serious adverse events occurred during the study protocol (100% clinical safety), and all data could be recorded continuously (100% successful data acquisition).

DISCUSSION

This study aimed to carry out a preliminary investigation on efficacy and feasibility of FC-RATE for improving cardiovascular fitness in persons with severe motor impairments early after stroke. We hypothesized that FC-RATE would reach a substantially higher cardiovascular training intensity compared with conventional RATE in a clinical setting, thus resulting in significantly increased cardiovascular fitness after a 4-week FC-RATE intervention. In addition, we expected to affirm feasibility by achieving predefined criteria.

Efficacy

The results demonstrated substantial and significant overall increases in cardiovascular fitness, but no significant between-group differences when comparing FC-RATE with conventional RATE in a 4-week cardiovascular exercise intervention early after stroke. Although the FC-RATE concept achieved a significantly higher training intensity compared with conventional RATE, the difference between the

Table 2. Feedback-Controlled Robotics-Assisted Treadmill Exercise-Based Cardiopulmonary Exercise Testing Results and Group, Time, and Interaction Effects

	Experimental Group (FC-RATE)				Control Group (RATE)				Statistics					
	Baseline		Postintervention		Baseline		Postintervention		Group		Time		Interaction	
	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	F_n	P	F_n	P	F_n	P
V_{O2peak}, absolute, mL · min^{-1}	1241 ± 642	1143 (602-2490)	1461 ± 683	1090 (679-2481)	1232 ± 669	1086 (460-2403)	1494 ± 672	1585 (629-2688)	0.02	0.90	5.80	0.02[a]	0.39	0.53
V_{O2peak}, relative, mL · kg^{-1} · min^{-1}	14.3 ± 4.9	15.9 (8.4-21.7)	17.5 ± 6.2	15.6 (10.6-26.9)	14.8 ± 5.6	15.3 (7.2-23.4)	18.0 ± 5.9	18.1 (9.4-25.9)	0.06	0.81	7.27	0.01[a]	0.13	0.72
P_{peak}, W	39.6 ± 32.9	21.2 (9.1-87.9)	52.0 ± 44.7	37.1 (5.7-143.4)	65.2 ± 31.3	70.6 (14.3-107.4)	67.6 ± 25.7	78.2 (13.5-91.5)	2.65	0.10	0.57	0.45	0.05	0.83
V_{Epeak}, L/min	43.1 ± 21.5	41.8 (17.6-82.8)	52.3 ± 23.6	47.4 (25.6-92.2)	36.5 ± 17.3	34.8 (15.7-70.5)	47.0 ± 21.0	47.5 (22.7-86.0)	0.25	0.62	10.85	0.001[a]	0.89	0.35
Rf_{peak}, L/min	39.7 ± 10.9	35.7 (27.0-54.7)	40.2 ± 6.0	40.5 (32.3-48.8)	32.3 ± 8.1	30.7 (22.7-45.4)	35.6 ± 12.7	30.5 (26.2-61.4)	2.77	0.10	0.88	0.35	0.00	1.00
HR_{peak}, beats/min	128 ± 9	129 (113-140)	136 ± 20	130 (115-161)	117 ± 20	108 (97-144)	121 ± 18	120 (99-150)	1.68	0.20	1.55	0.21	0.17	0.68
RER_{peak} (V_{CO2}/V_{O2})	0.91 ± 0.07	0.90 (0.79-0.99)	0.97 ± 0.08	0.94 (0.89-1.09)	0.91 ± 0.06	0.92 (0.84-1.00)	0.99 ± 0.14	0.96 (0.85-1.28)	0.05	0.82	10.53	0.001[a]	0.33	0.56

Abbreviations: F_n, analysis of variance-type statistic; HR_{peak}, peak heart rate; P_{peak}, peak work rate (power); Rf_{peak}, peak respiratory rate; RER_{peak}, peak respiratory exchange ratio; SD, standard deviation; V_{CO2}, carbon dioxide output; V_{Epeak}, peak ventilation rate; V_{O2peak}, peak oxygen uptake.
[a] Statistically significant: $P \leq 0.05$.

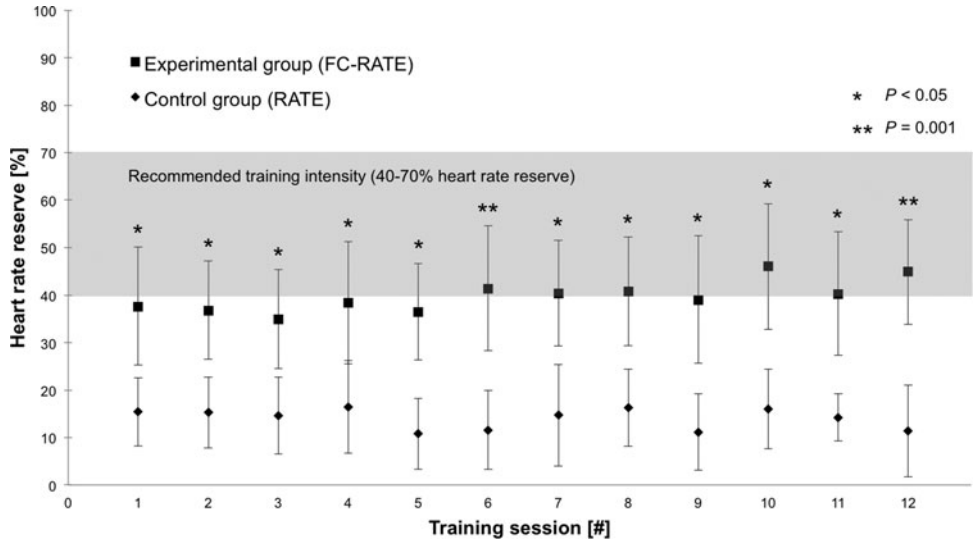

Figure 3. Training intensity given as heart rate reserve (predicted maximal heart rate − resting heart rate) during the 4-week intervention (12 sessions). Values represent mean ± 95% confidence intervals.

2 approaches was considered not to be clinically relevant. In detail, the experimental group did not consistently achieve the target range of 40% to 70% heart rate reserve.[37] Subanalyses revealed that only 3 of the 7 participants in the experimental group (42%) achieved at least 40% heart rate reserve during the intervention phase (44%, 47%, 66% vs 28%, 28%, 29%, 35% heart rate reserve). Thus, FC-RATE did not consistently achieve recommended intensity levels for cardiovascular training,[37] which highlights the need to further develop and optimize the effectiveness of this modality for training.

A major issue was the severely impaired status of the participants, which restricted exercise at higher target work rate values. This is underlined by the fact that the main reason for test termination during FC-RATE-based cardiopulmonary exercise testing was the inability to reach the target work rate because of generalized and/or leg fatigue. In addition, P_{peak} in the experimental group was much lower at both time points compared with the control group, although not statistically different. This finding might have led to further limitations for the experimental group to achieve higher intensity levels. Even so, the high demand of coordinated limb movement, in combination with the severe neurological impairment of the participants, is a challenge. The period of time where participants could apply mechanical forces was probably too short, despite the slow walking speed of 0.57 m/s. Individuals generally tend to exercise using the unaffected side more dominantly, which leads to deviations from the predefined physiological gait pattern and further challenges in bilateral limb coordination. A further issue might be the low cardiovascular fitness status of the participants. The fact that all participants presented with severe motor impairments, low cardiovascular fitness status and were not used to physical exercise training complicated the implementation of prolonged FC-RATE. The results clearly indicated a slow increase in mean training intensity over time for the experimental group (Figure 3).

However, it has been shown that even light to moderate exercise intensity is beneficial in deconditioned persons.[57] Feedback-controlled robotics-assisted treadmill exercise in its current form could, therefore, have potential for cardiovascular training. But the approach might have only limited power to promote significant between-group differences when compared with conventional RATE that has been shown to slightly increase exercise intensity.[34–36] Unfortunately, the present study protocol provided light training intensity for both groups and, thus, washed out potential between-group differences. It can be hypothesized that a longer intervention period and/or a comparison to conventional care (no RATE) would lead to significant differences in cardiovascular fitness, as FC-RATE has been shown to significantly increase exercise intensity to a moderate level.

A recent study that compared conventional RATE with standard care in a comparable sample found promising results, favoring RATE within only 2 weeks.[38] Unfortunately, the authors did not report the effective training intensity (eg, % heart rate reserve), which led to difficulties for comparisons. They guided the training intensity for the RATE group by decreasing body weight support from 40% to 0% and guidance force from 100% to 10%. Although the sample in this earlier study was not able to walk with body weight support of less than 40% because of severe motor limitations, their findings might be based on the comparison with a sedentary control group (conventional care), and the fact that the sample described was admitted earlier poststroke. Previously, the interval between stroke onset and intervention start as well as exercise intensity was shown to be predictive of training-induced gains in cardiovascular fitness.[58]

The protocol presented here evaluated the minimal body weight support at baseline, and adjustments during the intervention were only allowed within a range of ±10% to maintain a physiological gait pattern. Although a further decrease in body weight support was not feasible because of the low

motor function status of the included participants, the goal to substantially reduce body weight support remains important to optimally facilitate hemiparetic leg loading (activate relevant weight-bearing muscles).[59] Advanced orthoses along with sophisticated controllers might provide solutions to enable unilateral assist-as-needed support during RATE in the future.

Both groups improved their $V_{O_{2peak}}$, the accepted criterion for cardiovascular fitness, after the 4-week intervention. The mean overall increase in relative $V_{O_{2peak}}$ of 3.1 mL · kg^{-1} · min^{-1} (+17.8%, ES 0.58) is nearly clinically meaningful, considering that 3.5 mL · kg^{-1} · min^{-1} has been associated with significantly fewer coronary events such as coronary artery disease[60] and a 12% reduction in mortality in men with cardiac disease.[61] Individuals will generally profit from greater ability to engage in rehabilitation procedures at a lower percentage of their maximal exercise capacity. Considering the overall increase in $V_{O_{2peak}}$ of +17.8% within 4 weeks, this is a promising result related to the spontaneous recovery of $V_{O_{2peak}}$ of 16.9% in a 4-times longer period (20 weeks) reported in a comparable sample.[62] The significant time effect on $V_{E peak}$ (+19.9%), RER_{peak} (+7.2%), and O_2 pulse at $V_{O_{2peak}}$ (+11.6%) further underlines the improvement in exercise tolerance for both groups. Finally, the findings confirm the seriously compromised exercise capacity of individuals with severe impairments early after stroke, given the relative $V_{O_{2peak}}$ values at postintervention of 17.7 ± 5.8 mL · kg^{-1} · min^{-1}, which are 55.7% of predicted $V_{O_{2max}}$.[56]

Feasibility

Although the compliance to the intervention protocol was high, there was a dropout of 6 participants (30%) during familiarization and baseline assessment. Skin lesions and severe groin pain because of inappropriate padding are readily preventable by careful familiarization and padding procedures; however, abnormal gait patterns because of spasticity and lack of motivation are more difficult to control. Extended familiarization procedures, securing a careful padding of the limbs during all times, advances in harness design, and sophisticated work rate controllers are required to decrease attrition rates and improve motivation to elicit high target work rate levels in future trials.

The study demonstrated clinical safety and successful data acquisition. No serious adverse events occurred during FC-RATE-based cardiopulmonary exercise testing or during the intervention protocol. The strict eligibility criteria, designed to prevent adverse events in this pilot approach, led to the exclusion of a variety of individuals (97% of the initially screened population). For example, 21% were excluded because of cardiac contraindications for cardiopulmonary exercise testing. This large proportion of individuals with cardiac pathologies could profit from controlled cardiovascular exercise interventions. The number of individuals who cannot receive FC-RATE is rather small (ie, only 6% had contraindications for RATE), which underlines the potential impact of the concept.

Although the reliability of FC-RATE-based cardiopulmonary exercise testing has been demonstrated in a previous trial,[41] the ability to evaluate true maximal exercise capacity using this novel approach needs to be tested. The fact that only 50% of the participants reached some criterion for maximal aerobic capacity suggests that the results on cardiovascular fitness presented here must be considered as submaximal overall. It could be that the guidelines postulated for healthy people and individuals with chronic stroke may not be realistic for determination of true exercise capacity in persons with severe motor limitations early after stroke. Further research in populations with severe motor impairments needs to establish valid criteria for maximal exercise capacity.

The clinical effort associated with the feedback-control approach presented in this study is comparable with conventional RATE. Additional measurements at baseline, such as the evaluation of minimal body weight support, can be easily implemented in clinical routine. As a minimum, 2 experienced therapists are needed to perform FC-RATE-based cardiopulmonary exercise testing, and 1 trained therapist can implement the training. Although previous work proposed a total-body recumbent stepper to implement cardiovascular exercise testing in persons with severe motor limitations,[22,23] and FC-RATE might be considered as a very elaborate and costly endeavor, this is the first study that presents a task-specific training device for assessment of cardiovascular fitness and guidance of exercise intensity early after severe stroke.

Overall, the concept presented in this study is deemed feasible with a need for major modifications. Considering the complexity of implementing the procedure in a sample with severe motor impairments early after stroke and the lack of effective cardiovascular intervention strategies, the findings presented here are of high clinical importance. The study revealed major issues associated with the customization of RATE/FC-RATE and the consistent achievement of recommended intensity for prolonged training. Advances in body weight support systems and improved work rate controllers combined with appropriate visual and auditory feedback might provide solutions in the near future. For example, more degrees of freedom combined with individual joint control during the gait cycle would decrease body weight support to an absolute minimum, which in turn could increase exercise intensity in this population. Furthermore, the specific extensions of tasks (eg, robotics-assisted stair climbing) could further increase cardiovascular stress and, hence, facilitate task-specific training.

Limitations

The major limitation of the current study is the small sample size, which may render the results underpowered. However, considering our pilot approach and the difficulty to implement an intensive cardiovascular exercise intervention in this early stage after severe stroke, the sample of 20 individuals at the outset was a realistic group size to obtain first estimates.

The results presented here could be partly explained by spontaneous recovery, in addition to the training intervention, and must therefore be interpreted with caution. Although most of the exercise tests can be considered as submaximal, the overall increase in exercise capacity could have been influenced by the improved motor status of the participants.

The present study was not able to include a control group that received usual care only because of ethical considerations

(all included participants would have received RATE as usual care).

Although demonstrating early beneficial effects, despite the short training duration that has been reported in previous trials,[8,38] the training volume and frequency in the current study was below recommended levels for cardiovascular exercise.[57] The length of the inpatient stay restricted the training volume to a 4-week period, and the weekly course of in-house rehabilitation limited the training frequency. Optimal training volume and frequency should theoretically reach 5 sessions/wk for a minimum of 8 weeks.[37]

As this was a pilot trial, outcomes beyond basic cardiovascular fitness measures such as vascular risk factors, motor function, gait pattern, cognition, and well-being were not examined. Future trials need to establish deeper insight into the effects on cardiovascular health, motor recovery, cognition, and quality of life.

CONCLUSIONS

Substantial and significant overall increases in the main cardiopulmonary performance parameters were observed in both groups, but there were no significant between-group differences when comparing FC-RATE and conventional RATE. Feedback-controlled robotics-assisted treadmill exercise significantly increased exercise intensity in persons with severe impairments early after stroke, but the recommended intensity levels for cardiovascular training were not consistently achieved. Future research should focus on the development of appropriate algorithms within advanced robotic systems to promote optimal cardiovascular stress. This study is an important step toward the implementation of effective cardiovascular exercise along with task-specific training early after severe stroke.

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