Treadmill Exercise Rehabilitation Improves Ambulatory Function and Cardiovascular Fitness in Patients With Chronic Stroke
A Randomized, Controlled Trial

Richard F. Macko, MD; Frederick M. Ivey, PhD; Larry W. Forrester, PhD; Daniel Hanley, MD; John D. Sorkin, MD, PhD; Leslie I. Katzel, MD, PhD; Kenneth H. Silver, MD; Andrew P. Goldberg, MD

Background and Purpose—Physical inactivity propagates disability after stroke through physical deconditioning and learned nonuse. We investigated whether treadmill aerobic training (T-AEX) is more effective than conventional rehabilitation to improve ambulatory function and cardiovascular fitness in patients with chronic stroke.

Methods—Sixty-one adults with chronic hemiparetic gait after ischemic stroke (>6 months) were randomized to 6 months (3×/week) progressive T-AEX or a reference rehabilitation program of stretching plus low-intensity walking (R-CONTROL). Peak exercise capacity (VO₂ peak), O₂ consumption during submaximal effort walking (economy of gait), timed walks, Walking Impairment Questionnaire (WIQ), and Rivermead Mobility Index (RMI) were measured before and after 3 and 6 months of training.

Results—Twenty-five patients completed T-AEX and 20 completed R-CONTROL. Only T-AEX increased cardiovascular fitness (17% versus 3%, 8% T-AEX versus R-CONTROL, P<0.005). Group-by-time analyses revealed T-AEX improved ambulatory performance on 6-minute walks (30% versus 11%, P<0.02) and mobility function indexed by WIQ distance scores (56% versus 12%, P<0.05). In the T-AEX group, increasing training velocity predicted improved VO₂ peak (r=0.43, P<0.05), but not walking function. In contrast, increasing training session duration predicted improved 6-minute walk (r=0.41, P<0.05), but not fitness gains.

Conclusions—T-AEX improves both functional mobility and cardiovascular fitness in patients with chronic stroke and is more effective than reference rehabilitation common to conventional care. Specific characteristics of training may determine the nature of exercise-mediated adaptations. (Stroke. 2005;36:2206-2211.)

Key Words: exercise ▪ hemiplegia ▪ rehabilitation ▪ stroke

Stroke is a leading cause of disability, resulting in chronic deficits that persistently impair function in approximately two thirds of cases. Conventional rehabilitation focuses on the subacute recovery period with therapy targeted across initial months toward improving basic mobility and activity of daily living skills. Most patients are discharged without complete recovery, often with no recourse beyond generic advice to stay active and continue stretching. This model is reinforced by studies showing recovery in ambulatory function plateaus within 11 weeks in 95% of individuals receiving conventional rehabilitation care. Although physical inactivity can propagate disability through deconditioning and learned nonuse after stroke, there are no evidence-based recommendations to promote regular therapeutic exercise in this population.

Based on animal studies and increasing clinical evidence that task-repetitive training can induce adaptive neuroplasticity, treadmill training has emerged as a strategy to promote locomotor recovery after stroke. However, efficacy of this modality is not established with a Cochrane Review reporting no significant effects from treadmill training. There are no randomized studies that establish whether exercise training can improve both functional mobility and aerobic fitness in the chronic phase of stroke.

We investigated T-AEX as a task-oriented modality to optimize locomotor relearning while providing cardiovascu-
lar conditioning in chronic stroke.\textsuperscript{11} Initial noncontrolled studies provide evidence that T-AEX improves fitness, leg strength, and gait while reducing spasticity and energy costs of hemiparetic ambulation.\textsuperscript{12–14} This randomized, controlled trial investigates the hypothesis that T-AEX is more effective than a rehabilitation regime including components of conventional care (R-CONTROL) to improve ambulatory function and cardiovascular fitness in chronic stroke.

**Materials and Methods**

Men or women \(\geq 45\) years of age with chronic (\(\geq 6\) months) hemiparetic gait after stroke were recruited from the Baltimore VA and University of Maryland Hospitals. The protocol was Institutional Review Board-approved and all patients provided written informed consent. Baseline evaluations included a medical history and examination, electrocardiogram, blood chemistry and counts, Mini Mental Status examination, Center for Epidemiological Studies Depression Scale, and a customized exercise stress test.\textsuperscript{15,16} Exclusion criteria included heart failure, unstable angina, peripheral arterial occlusive disease, aphasia, dementia, untreated major depression, and other medical conditions precluding participation in exercise.\textsuperscript{17,18}

**Exercise Testing**

A treadmill tolerance test was first performed to assess gait safety. Those completing \(\geq 3\) consecutive minutes treadmill walking at \(\geq 0.22 \text{ m/sec (} \geq 0.5\text{MPH)}\) proceeded to peak exercise testing.\textsuperscript{17} Subjects achieving adequate exercise intensities without signs of myocardial ischemia or other contraindications to training were enrolled.\textsuperscript{18} Exercise testing was performed to measure economy of gait and VO\(_2\) peak at baseline and after 3 and 6 months training.\textsuperscript{12} Economy of gait was calculated to estimate metabolic demands of hemiparetic ambulation.\textsuperscript{11} Measures of VO\(_2\) peak were used to index cardiovascular fitness.\textsuperscript{17}

**Ambulatory Performance Measures**

Timed 30-ft walks and 6-minute walks were performed at the 3 time points. Gait velocity during timed walks is an established metric of hemiplegic recovery,\textsuperscript{19} with 30-ft walks simulating short distances that typify home-based mobility. Six-minute walks were performed to assess sustainable walking capacity; an outcome representative of greater distances required for more sustained activity of daily living tasks.\textsuperscript{20}

**Functional Mobility**

Rivermead Mobility Index (RMI) and Walking Impairment Questionnaire (WIQ) were analyzed to examine effects of training on mobility. RMI includes 14 questions and an observation characterizing basic mobility.\textsuperscript{21} WIQ assessed effects of exercise on self-reported walking distance, speed, and stair climbing.\textsuperscript{22}

**Randomization and Blinding**

After baseline testing, volunteers were randomized to either T-AEX or R-CONTROL using a computer-based system. Because deficit severity and age affect stroke outcomes, stratified randomization was necessary to balance entry into groups.\textsuperscript{3} Accounting for attrition, enrollment of 30 per group was targeted to complete 21 per group. Preliminary power analysis based on pilot studies\textsuperscript{13} suggested that this number would result in sufficient power to detect between group differences in VO\(_2\) peak (0.80 power, \(\alpha=0.05\)). Questionnaires, surveys, and functional gait testing were conducted by blinded technicians unaware of treatment assignment under standardized conditions at a location (Geriatrics Research Education and Clinical Center) separate from the training site. As a result of staffing limitations and institutional safety regulations, treadmill exercise testing was conducted by the same staff under physician supervision (KFM) that provided medically supervised training. Hence, metabolic fitness tests were unblinded, but we attempted to minimize bias using scripted exercise testing protocols with defined physiological end points.\textsuperscript{11,18}

**Exercise Training**

T-AEX training target was 3-40-minute sessions per week at target aerobic intensity of 60% to 70% heart rate reserve (HRR).\textsuperscript{12,18} Training started at low intensity (40% to 50% HRR) for 10 to 20 minutes and increased approximately 5 minutes every 2 weeks as tolerated. Aerobic intensity was similarly progressed by 5% HRR every 2 weeks.

R-CONTROL provided matched duration exposure to staff implementing common components of conventional therapy. Subjects performed 13 supervised stretching movements lasting 35 minutes\textsuperscript{2} and 5-minute low-intensity treadmill walking at 30 to 40% HRR, approximating the aerobic stimulus of conventional rehabilitation.\textsuperscript{23} Hence, both groups were scheduled to receive 72 training sessions, equaling 48 hours of training across 6 months.

**Data Analyses**

Repeated-measures analysis of variance (ANOVA) was used to predict values of outcome variables across time. Each analysis controlled for serial autocorrelation using one of three correlation structures: unstructured, compound symmetry, or first-order autoregressive. Akaike's Information Criterion and Schwarz Bayesian Criterion were used to select among correlation structures. In cases in which group-by-time interaction was significant, within-group time point comparisons were made. Data are expressed as mean±standard error standard deviation. A 2-tailed \(P<0.05\) was considered significant. Data analysis includes calculation of VO\(_2\) peak was expressed in absolute terms (L/min), and corrected for body mass, and in (mL/kg/min). We compared between groups with an unstructured covariance matrix (SAS proc mixed). Regression and median split analyses examined whether clinical, demographic, or training parameters were related to the treatment response.

**Results**

Screening evaluations were performed on 111 subjects and 61 enrolled. Fifty were excluded at baseline for neurologic (n=23, 46%) or medical reasons (n=17, 34%), loss to follow up (n=7, 14%), or psychosocial factors (n=3, 6%). Neurologic exclusions included diagnosis of intracranial hemorrhage (n=5), severe deficits (n=4), deficits too mild (n=2), dementia (n=2), severe aphasia (n=3), depression (n=4), recurrent vertigo (n=1), and carotid stenosis (n=2). There were no significant differences in clinical or demographic characteristics between groups (Table 1).

**Training Data**

Twenty-five of 32 (78%) subjects completed 6 months T-AEX. Dropouts were the result of medical reasons unrelated to exercise (n=4) or compliance issues (n=3). Twenty of 29 (69%) R-CONTROL completed, with dropouts resulting from study-unrelated medical reasons (n=6) or compliance issues (n=3). Among the dropouts in T-AEX (n=7) and CONTROL (n=9), there were no baseline group differences in floor walking velocity (0.51±0.09 versus 0.58±0.1 m/s, \(P=0.60\)), VO\(_2\) peak (1.14±0.12 versus 1.22±0.12 L/min, \(P=0.60\)), 6-minute walk distance (600±120 versus 742±157 ft, \(P=0.50\)), WIQ distance (27±15 versus 35±12, \(P=0.70\)), RMI scores (10±1 versus 11±1, \(P=0.30\)), age (58±4 versus 65±3, years, \(P=0.15\)), gender ratio (6:3 versus 5:2, male:female), or hemispheric lesion location (4:5 versus 4:3, right:left). Fifteen T-AEX and 18 R-CONTROL were on antihypertensive medications, including 5 in each group on \(\beta\)-blockers. Dosage of \(\beta\)-blockers was...
TABLE 1. Clinical and Demographic Features of Patients Randomized to Treadmill and Control Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treadmill Exercise Group, n=32 (%)</th>
<th>Control Group, n=29 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>63±10</td>
<td>64±8</td>
</tr>
<tr>
<td>Gender, male:female</td>
<td>22:10</td>
<td>21:8</td>
</tr>
<tr>
<td>Race, black:white</td>
<td>20:12</td>
<td>15:14</td>
</tr>
<tr>
<td>Brain lesion side, right:left</td>
<td>18:14</td>
<td>13:16</td>
</tr>
<tr>
<td>Latency since stroke, mo</td>
<td>35±29</td>
<td>39±59</td>
</tr>
<tr>
<td>Coronal artery disease</td>
<td>7 (22)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (63)</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (41)</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>17 (53)</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>5 (16)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Ankle-foot orthoses</td>
<td>15 (47)</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Assistive device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (34)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Single-point cane</td>
<td>13 (40)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Quad cane</td>
<td>4 (13)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Walker</td>
<td>4 (13)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

unchanged throughout, except for discontinuation in one R-CONTROL.

Treadmill testing and training were well tolerated with no adverse events. Compliance was high with 84% attendance for T-AEX and 77% in R-CONTROL. In T-AEX, all training parameters showed progression, with initial mean aerobic intensity of 47±15% HRR, increasing to 58±14% HRR by 6 months (P=0.02). Training duration increased from baseline 12±6 minutes to 41±10 minutes by 6 months (P<0.0001). Training velocity increased from baseline 0.48±0.3 to 0.75±0.3 m/s by 6 months (P=0.012), a mean 56% increase. There was no change in body mass in either group.

Cardiovascular Fitness and Economy of Gait

Repeated-measures ANOVA revealed a significant group-by-time interaction for VO2 peak, indicating T-AEX was more effective in improving cardiovascular fitness levels (P<0.005, Figure 1). There was a 17% increase in VO2 peak (L/min) with T-AEX (P<0.001), which remained significant after adjusting for body mass (VO2 mL/kg/min, P=0.001; Table 2). Fitness gains were progressive and evenly distributed across 6-months (Figure 2). R-CONTROL group showed no change in VO2 peak. There was no significant group-by-time interaction for economy of gait. However, when the interaction term was dropped, within-groups analysis revealed both groups improved (Table 2).

Ambulatory Performance Capacity

There was a significant group-by-time interaction for 6-minute walk (P<0.01; Table 2), with T-AEX achieving nearly triple the gains of R-CONTROL in percentage terms (Figure 2). T-AEX increased 6-minute walk distance by 30% with most improvement (77%) occurring by 3 months (Figure 2). There was no group-by-time interaction for 30-ft timed walk, and within-groups analysis revealed improved 30-ft timed-walk velocities in both groups (Table 2).

TABLE 2. Effects of 6 Months T-AEX and R-CONTROL on Cardiovascular Fitness, Timed-Walk Performance, and Functional Mobility

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treadmill Group</th>
<th>Control Group</th>
<th>P, Group-by-Time Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Posttreatment</td>
<td>Baseline</td>
</tr>
<tr>
<td>Peak VO2, L/min</td>
<td>1.22±0.47</td>
<td>1.43±0.57†</td>
<td>1.25±0.36</td>
</tr>
<tr>
<td>Peak VO2, mL/kg/min</td>
<td>14.9±0.07</td>
<td>17.3±1†</td>
<td>14.7±1</td>
</tr>
<tr>
<td>Economy of gait, VO2 (mL/kg/min)</td>
<td>10.7±0.6</td>
<td>9.9±0.6*</td>
<td>10±0.5</td>
</tr>
<tr>
<td>6-min walk, ft</td>
<td>761±73</td>
<td>922±79†</td>
<td>848±10</td>
</tr>
<tr>
<td>30-ft walk usual pace, m/s</td>
<td>0.63±0.06</td>
<td>0.74±0.06*</td>
<td>0.67±0.07</td>
</tr>
<tr>
<td>30-ft walk fast pace, m/s</td>
<td>0.82±0.08</td>
<td>0.95±0.09*</td>
<td>0.9±0.10</td>
</tr>
<tr>
<td>Rivermead Mobility Index, patients</td>
<td>45±7</td>
<td>70±7†</td>
<td>50±7</td>
</tr>
</tbody>
</table>

*P<0.01 significance for time main effect after dropping group-by-time interaction.
†P<0.001 for significant improvement within T-AEX group.
Functional Mobility

Group-by-time analysis revealed only T-AEX improved WIQ–distance with 4-fold progressive improvement compared with R-CONTROL (Table 2, Figure 3). There were no differences between groups in WIQ speed or stair-climbing scores. Group-by-time analysis revealed no statistically significant improvements in RMI scores with T-AEX compared with R-CONTROL ($P=0.12$).

Determinants of the Response to T-AEX

There were no clinical or demographic factors that predicted a lack of T-AEX treatment response for any of the measured outcomes. Regression analyses showed no associations between increase in VO2 peak or 6-min walk and age at entry, latency since stroke, initial VO2 peak, or gait deficit severity ($P=0.12$). However, progression in selected treadmill training, parameters across 6 months were associated with key functional and fitness outcomes. Conversely, increase in treadmill training duration predicted improvements in 6-minute walk ($r=0.41$, $P<0.05$) but not change in VO2 peak ($r=0.19$, $P=0.34$). In contrast, increase in treadmill training velocity predicted gains in VO2 peak ($r=0.43$, $P<0.05$) but not change in 6-min walks ($r=0.17$, $P=0.46$).

Median split analyses according to degree of treadmill velocity progression within the T-AEX group revealed that subjects in the upper half of trainers experienced the greatest gains in VO2 peak (25%, $n=11$, $P<0.01$), whereas those in the bottom half of velocity progression did not reach a significant within-group fitness gain (9%, $n=12$, $P=NS$; Figure 4).

Discussion

We demonstrate for the first time in a randomized trial that T-AEX improves cardiovascular fitness and ambulatory function in chronic stroke. Although both R-CONTROL and T-AEX improved economy of gait and walking velocity over short distances, T-AEX was requisite to improve main outcomes of cardiovascular fitness, sustainable (6-min) ambulatory performance capacity, and the functional mobility measures. These findings demonstrate the physiological and functional benefits of task-oriented training administered according to a progressive aerobic exercise formula. The data
Further suggest that training prescriptions emphasizing velocity progression rather than longer duration will optimize gains in aerobic fitness compared with locomotor function, respectively.

The natural history of mobility recovery after stroke reveals a plateau within 3 to 6 months. Prospective studies report 95% of patients show no further recovery in ambulatory function beyond 11 weeks with conventional care. Current practice patterns for outpatient stroke rehabilitation typically include approximately 9 physical therapy sessions, ending within 28 to 140 days poststroke. Yet functional mobility declines in 43% within the year inpatient rehabilitation ends, with early therapy cessation predicting worsening. Randomized studies show delayed generic physiotherapy aimed at gait restoration increases 10-meter walk velocity 9% in patients with chronic stroke, whereas delayed entry controls become 12% slower, suggesting inactivity propagates mobility declines. Our participants had already completed all conventional physical therapy and were a mean 3 years poststroke, well beyond the expected therapeutic window for mobility recovery. However, the results show T-AEX improves fitness, reduces energy costs of hemiparetic gait, and increases ambulatory function even at this late stage. All of these outcomes may combine to improve activity of daily living function. We identify no clinical factors that predict lack of treatment response, including latency since stroke to at least 10 years. Hence, such exercise models have potential to generalize functional and cardiovascular health benefits across a broad spectrum of the chronic stroke population.

Cardiovascular fitness levels after stroke are only 50% of age-matched normals, energy demands of hemiparetic gait are elevated 1.5- to 2-fold, and patients with stroke often cannot maintain their preferred walking pace as a result of exercise intolerance. Randomized studies in patients with chronic stroke show that although 3 months aerobic exercise increases VO2 peak 8%, fitness levels decline 10% in delayed entry controls, revealing the expected relationship between inactivity and progressive deconditioning. Conventional rehabilitation does not systematically provide an adequate exercise stimulus. Cardiac monitoring reveals <3 min per physical therapy session reaches low aerobic intensity. Notably, our R-CONTROL group maintained fitness levels across 6 months and improved 30-ft floor walking and gait economy, which may enable activity of daily living tasks to be performed at a lower percent of peak exercise capacity. These gains may have resulted from the relatively active nature of the R-CONTROL rehabilitation program.

Post hoc analyses suggest specific characteristics of a T-AEX regimen may influence the nature of exercise-mediated adaptations. We found that the degree of progression in training session duration predicted improvements in 6-minute walk but not VO2 peak. This suggests “mass training,” indexed by greater repetition in longer training sessions, governs gains in locomotor control, consistent with animal studies in which task-repetitive sensorimotor stimuli are crucial to mediating neuroplasticity. Conversely, progression in T-AEX training velocity predicted fitness gains but not change in ambulatory function. Thus, cardiovascular adaptations after stroke may be contingent on advancing training velocity rather than HRR, the standard for defining exercise intensity in non-neurologic populations. In addition, the trajectory of fitness gains showed no plateau, suggesting that training beyond 6 months may produce further benefits. The features of exercise needed to optimize gains in aerobic fitness versus locomotor function require confirmation in prospective studies using differing progression strategies.

The small sample size and various design issues, including strict entry criterion, limit interpretation of this study. Only medically eligible subjects with mild–moderate gait deficits were enrolled, which may have selected a healthier and more mobile cohort not entirely representative of the general stroke population. The absence of blinding with respect to VO2 peak testing represents another potentially confounding limitation. Although it was impractical to completely blind testers to subject treatment assignment during treadmill aerobic testing as a result of personnel constraints, every effort was made to standardize protocols to minimize bias. Although a strength of our study is its randomized design, R-CONTROLs also improved, indicating even stretching plus low-intensity walking is beneficial. We had no usual care control group, which in chronic stroke typically includes no supervised exercise. Hence, no inferences can be made regarding effectiveness of T-AEX compared with conventional care. Finally, considering the relatively high study exclusion and dropout rates across 6 months, we do not know what proportion of community-dwelling patients with stroke could participate in or maintain longitudinal aerobic training.

Summary

In conclusion, T-AEX is superior to a reference control program and requisite to improving cardiovascular fitness and functional mobility. Specific features of the exercise prescription unique to neurologic patients may determine the nature of adaptations in motor function versus cardiovascular fitness. Further studies are needed to determine whether task-oriented exercise can improve long-term functional independence and cardiovascular health in chronic stroke.

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References


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