Predictors of Response to Treadmill Exercise in Stroke Survivors

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Abstract

Background—Aerobic treadmill exercise (T-EX) therapy has been shown to benefit walking and cardiorespiratory fitness in stroke survivors with chronic gait impairment even long after their stroke. The response, however, varies between individuals.

Objective—The purpose of this post hoc analysis of 2 randomized controlled T-EX trials was to identify predictors for therapy response.

Methods—In all, 52 participants received T-EX for 3 (Germany) or 6 (United States) months. Improvements in overground walking velocity (10 m/6-min walk) and fitness (peak VO_2) were indicators of therapy response. Lesion location and volume were measured on T1-weighted magnetic resonance scans.

Results—T-EX significantly improved gait and fitness, with gains in 10-m walk tests ranging between +113% and −25% and peak VO_2 between −12% and 88%. Baseline walking impairments or fitness deficits were not predictive of therapy response; 10-m walk velocity improved more in those with subcortical rather than cortical lesions and in patients with smaller lesions. Improvements in 6-minute walk velocity were greater in those with more recent strokes and left-sided lesions. No variable other than training intensity, which was different between trials, predicted fitness gains.

Conclusions—Despite proving overall effectiveness, the response to T-EX varies markedly between individuals. Whereas intensity of aerobic training seems to be an important predictor of gains in cardiovascular fitness, lesion size and location as well as interval between stroke onset and therapy delivery likely affect therapy response. These findings may be used to guide the timing of training and identify subgroups of patients for whom training modalities could be optimized.

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Keywords

stroke; lesion; gait; rehabilitation; aerobic treadmill exercise

Introduction

Impaired gait after hemiparetic stroke contributes strongly to overall disability. Aerobic treadmill exercise (T-EX) has been successfully used to retrain gait and improve cardiorespiratory fitness at the same time, thereby, reducing the disability related to immobility. Several randomized controlled trials have demonstrated benefits on various outcome parameters in patients with chronic gait impairments.[1-4] Although group effects are significant, the individual response to T-EX is variable. The reasons for this variability are not known. Identifying predictors of therapy-related benefits will serve to select and adjust the intervention to the individual patient.

For other rehabilitative treatments, predictive parameters have been reported. Using functional magnetic resonance imaging,[5,6] transcranial magnetic stimulation,[7,8] or positron emission tomography,[9] it was shown that different brain areas undergo lasting changes after stroke and after rehabilitative interventions. These changes in brain activation are associated with the degree to which motor function recovers. Cramer and coworkers[10] suggested that lower baseline motor cortex activation predicts higher therapeutic benefit. Given that brain activation during hemiparetic movement depends on the location and size of the brain lesion,[6] it is conceivable that lesion geometry has prognostic value. Lesion geometry indeed explains part of the variability in acute deficits after stroke and of functional outcomes at 3 months.[11-15] However, some studies have failed to show such relationships.[10,16]

Age was also identified as a predictor of functional outcome in previous studies.[17,18] This may be explained by higher frequency of comorbidity, stroke-related complications,[14] and limited plasticity of the aging brain.[19] The objective here was to investigate the value of clinical, demographic, and lesion-related variables to predict the benefit provided by T-EX in chronically disabled stroke survivors.

Materials and Methods

Participants

This post hoc analysis combines data from 2 randomized controlled trials that were conducted by the same collaborative group of researchers. In the first trial, they compared 6 months of aerobic T-EX with stretching exercises of equal duration in Baltimore, Maryland.[2,20] In the second trial conducted in Stuttgart, Germany, they compared 3 months of T-EX to conventional care. Here, data for the 52 participants from the T-EX groups of both trials for whom structural imaging data were available are analyzed (Table 1).

Participants in both studies had suffered a first-ever ischemic stroke at least 6 months prior to enrollment. Exclusion criteria were heart failure, unstable angina, peripheral arterial occlusive disease, aphasia, dementia, untreated major depression, clinical and/or neuroimaging signs of stroke-independent neurological diseases (eg, Parkinsonian syndromes), patients already performing aerobic exercise training for >20 min/d and >1 d/wk, and other medical conditions precluding participation in exercise (for details see ACSM21). The trials were approved by the institutional review boards of the University of Maryland and the Johns Hopkins University (US trial) and the Ethics Committee of the University of Tübingen, Germany (German trial). All participants provided written informed consent.

Assessments of Gait Function and Cardiovascular Fitness

Participants were enrolled when capable of completing ≥3 consecutive minutes of treadmill walking at ≥0.1 m/s without personal or body weight support (use of hand rails was allowed) and without signs of myocardial ischemia or other contraindications to training. During a peak-effort T-EX test with open-circuit spiroergometry, cardiovascular fitness was determined by measuring VO_2 in (mL/kg body weight)/min according to the standards of the American Heart Association[21,22] under continuous monitoring of vital signs and ECG. For peak VO_2 testing, a modified Balke protocol (increase of treadmill incline every 2 minutes with constant speed) was applied—a procedure to assess cardiovascular fitness in stroke patients with a reliability of repeated measurements of heart rate, systolic blood pressure, oxygen consumption (VO_2 in L/min), VO_2 (mL/kg/min), respiratory exchange ratio, rate pressure product, and oxygen pulse.[23] Locomotor impairments were assessed by 2 widely used and well-characterized tests.[24,25] The time required to walk 10 m at fastest and comfortable paces was used to assess the ability to walk short distances typical for the home environment. The distance walked during 6 minutes was added to evaluate sustained walking capacity. To render both tests comparable to each other and to published reference data, the mean velocity was calculated for both walking tests and was used in further analyses. Functional assessments were conducted before and after the training period.

Training

The T-EX training goal was three 40-minute exercise sessions per week at an aerobic intensity of 60% in the US trial and 80% of heart rate reserve (HRR) in the German trial. Duration and intensity started at low values (10-20 minutes, 40%-50% HRR) and increased by approximately 5 minutes and 5% HRR. To reach the training intensity target, treadmill velocity was increased by 0.05 m/s every 1 to 2 weeks as tolerated. In the US trial, training was conducted for 6 months and in the German trial, for 3 months.

MRI Data Acquisition

In the US trial, structural MRI data were collected using a 1.5 T Philips scanner (Philips, Eindhoven, Netherlands) within 2 weeks of the start and end of the training. In the German trial, MRI data were acquired from a 3T scanner (Vision, Siemens, Erlangen, Germany). T1-weighted images (3D-MPRAGE sequence, resolution 1 mm^3) covering the entire brain were acquired to determine lesion location and size. Functional MRI data collected in the US trial are reported elsewhere.[2]

Image Analysis

Lesion location was first determined by visual inspection performed by 2 raters independently (ARL and BH for the US trial; JML and CG for the German trial). Lesions were stratified into cortical/subcortical white matter with or without basal ganglia involvement, referred to as *cortical* lesions and *subcortical* lesions. The latter were defined as lesions restricted to the region medial to the insula and inferior to the corpus callosum. Brainstem lesions were regarded as subcortical.

To determine lesion volume, binary lesion masks were produced by manually segmenting the lesion area on all consecutive sections displaying the lesion. Lesion area was defined on T1 images as all voxels isointense to CSF plus hypodense voxels at the boundary of the lesion core. Manual segmentation was performed using MRIcro.[26] All voxels defining the lesion (1 voxel = 1 mm^3) were counted using a Matlab script.

Statistical Analysis

The changes in functional assessments (10-m walk test, 6-minute walk test, and peak VO_2) were expressed as absolute change and change relative to baseline performance. Relative changes were analyzed because we expected patients with more impairment to show less absolute improvement as compared with patients with smaller deficits. General linear models were used to assess the effects of age, gender, stroke-onset to therapy-onset interval, and lesion volume, side, and location (cortical, subcortical) on the dependent variables. Dependent variables were either baseline performance or change of performance (absolute or relative to baseline) in fitness and walking tests. In the models investigating change variables, the baseline value of the respective change variable was added as a covariate. Independent variables were entered into the model in a stepwise fashion using a criterion of $P < .25$ and then removed if $P > .05$. After identifying significant predictors, 2-way interactions between them were first added to the model and then removed if their effect was insignificant ($P < .05$). The efficacy of T-EX to improve fitness and gait was tested using repeated-measures ANOVA models, one for each outcome parameter. All data are expressed as mean ± standard error of the mean.

Results

Baseline Functional Impairment

The patients enrolled in Germany walked faster at their self-selected pace at baseline and had better cardiovascular fitness (Table 2) compared with those in the US trial. Overground walking velocity as measured in the 6-minute walk test and velocity in the 10-m walk test was slower in women, in older participants, in those with larger lesions (for the 10-m walk test fastest pace), and at higher baseline NIHSS score (Table 3). For gait velocity derived from the 6-minute walk test, we found a higher negative correlation with NIHSS score among participants in the German trial than in the US trial. Low cardiorespiratory fitness was predicted by female gender, right-sided lesion, and high (indicating greater impairment) NIHSS score. No other interactions between trial and other independent variables were significant.

Exercise-Related Functional Gains

Treadmill training led to increased gait velocity as measured by the 10-m walk test (fastest pace 0.85 ± 0.06 to 0.96 ± 0.06 m/s, $P < .0001$; comfortable pace 0.67 ± 0.05 to 0.75 ± 0.05 m/s, $P = .0006$) and as measured during the 6-minute walk (0.70 ± 0.05 to 0.84 ± 0.06 m/s, $P < .0001$). T-EX also improved cardiorespiratory fitness (peak VO_2 17.9 0.94 to 21.7 ± 1.18 mL/kg/min, $P < .0001$). There were no significant correlations between gains in fitness and velocity ($P > .5$ for all gait tests). Absolute and relative gains in these outcome parameters are presented in Table 2.

Predictors of Exercise-Related Functional Gains

Relative improvements in 10-m walk velocities were higher in participants with smaller lesions (Table 3). Relative gains in 6-minute walk velocity were higher in participants with more recent stroke events. Relative improvement in fitness (peak VO_2) was higher in German than in US participants (Table 3).

Absolute changes in walking or fitness were not predicted by baseline walking velocities or fitness. Absolute improvement in gait velocity measured during the 10-m walk test (fastest or comfortable pace) was greater in participants with subcortical than with cortical lesions (Table 4). Whereas improvements in patients with subcortical lesions were significant for both comfortable and fastest walking velocity (fastest pace: gain = 0.13 ± 0.02 m/s, $P < .0001$; comfortable pace: gain = 0.09 ± 0.02 m/s, $P < .0001$), gains in participants with

cortical lesions failed to reach significance (fastest pace: gain = 0.05 ± 0.03 m/s, P = .08; comfortable pace: gain = 0.02 ± 0.02 m/s, P = .5). Participants with shorter stroke– therapy intervals and left-sided lesions showed greater improvement in 6-minute walk velocity (Table 4, Figure 1). Nevertheless, both left- and right-hemisphere-lesioned participants walked faster in the 6-minute walk test (left-hemisphere lesion: gain in velocity = 0.16 ± 0.02 m/s, P < .0001; right-hemisphere lesion: gain = 0.08 ± 0.02 m/s, P < .001). Predictive models explained between 10% and 33% of the variability in therapy response (r^2 values Table 4).

Discussion

This post hoc analysis of 2 trials on aerobic T-EX demonstrates that despite overall significant benefits, the response to T-EX varies between individuals. Predictors of greater benefit in walking parameters were subcortical and left-sided lesion location, smaller lesions, and shorter interval time between stroke onset and onset of treadmill training.

Previous studies have demonstrated a relationship between lesion location and size and stroke-related deficits or benefits of conventional rehabilitation.[11,12,14,15,27,28] Whereas in laboratory animals lesion volume predicts functional deficits,[27,29,30] findings are heterogeneous in humans. Saunders and colleagues[15] reported that for middle cerebral artery (MCA) territory infarctions, lesion volume is a prognostic outcome indicator. Other studies failed to show this relationship.[16,31] Chen et al12 reported critical lesion sizes for different brain areas: motor impairment was high when lesions were larger than 75 cm^3 for the cortex, 4 cm^3 for the corona radiata, 0.75 cm^3 for the internal capsule, 22 cm^3 for the putamen, and 12 cm^3 for the thalamus. This indicates that functional outcome depends not only on lesion size but also on a combination of lesion size and location. Dawes and coworkers31 reported a trend for a correlation between corticospinal tract lesion volume and walking performance after a partial body weight support treadmill training. Beloosesky and coworkers11 reported a correlation between lesion size and rehabilitation success for cortical infarcts. In our data set, lesion volume was an independent predictor in relative gains in 10-m walk gait velocity (independent of baseline deficit). For absolute improvement, lesion location (subcortical vs cortical) was an independent predictor, representing the same association as the association between lesion volume and relative gain because cortical strokes were substantially larger then subcortical strokes. Whereas patients with subcortical strokes showed significant improvements in the 10-m walk, patients with cortical strokes failed to achieve significant effects. We also found an association between improvement in gait velocity during the 6-minute walk (absolute gain) and lesioned hemisphere. Participants with left-sided lesions improved twice as much in gait velocity as those with right-sided ones; however, both subgroups benefited significantly. Although it has been shown that overall stroke outcomes at 3 months poststroke (modified Rankin scale) were similar for those with left- and right-sided lesions,[32] locomotion was reported to recover better in patients with recent (mean 52 days) left-hemisphere lesions using conventional rehabilitation techniques.33 This difference may be related to the fact that visuospatial or attention deficits are more prominent in participants with right-hemisphere infarction, and this could interfere with locomotion because these cognitive functions are required for locomotion.34 It is plausible that 6-minute walks have higher cognitive demands, for example, higher demands for navigation in space, than 10-m walks and might, therefore, be more sensitive to right-hemisphere damage.

Age has been reported to predict poor response to constraint-induced movement therapy,[35] but age was unrelated to the benefits conveyed by treadmill therapy here. Similarly, Luk and coworkers[36] found in 878 stroke survivors that, if corrected for disability before the stroke, age per se does not predict functional independence at the time of discharge from the

rehabilitation hospital. In the healthy elderly population, King and coworkers[37] report younger age and better health and physical function at baseline to be predictors of exercise benefits. The reason for not observing predictive effects of age here, especially on fitness gains, may be the smaller age span and younger mean age in our participant sample as compared with those in the study by King et al.

A longer time interval between stroke onset and beginning of treadmill therapy were associated with less improvement in gait velocity measured during the 6-minute walk (absolute and relative). It is noteworthy that this relationship does not reflect differences in the efficacy of interventions delivered in the acute versus the chronic period after stroke because both trials recruited chronic participants at more than 6 months after their stroke. Although it does not qualify the finding that training on a treadmill can improve walking even long after stroke, this observation stresses the need for continued rehabilitation beyond the commonly prescribed 3 to 6 weeks.

It has been reported that apart from lesion-related parameters, more severe neurological deficits predicted less improvement after therapy for the recovery of arm function.[38] A similar finding was reported for constraint-induced movement therapy.[20] Here, we did not find an association between baseline deficits and therapy response—that is, there was no effect of a baseline functional measure on its absolute change after therapy. However, certain predictors of response also predicted baseline function—that is, lesion volume for the 10-m walk velocity. Their predictive value may therefore be explained via their effect on baseline function. Participants in the German trial had higher fitness levels at baseline than US participants and showed greater improvements, but baseline fitness itself did not predict gains in fitness in the combined study sample. Thus, the effects on fitness gains are not likely to be explained by the differences in baseline values between trials, particularly as one would expect even greater benefits in an unfit patient. The effects could, however, be explained by higher training intensity in the German trial (mean HRR at the end of training was 76% for Germany and 58% for the United States). Apart from that, none of the investigated independent variables (age, gender, baseline walking, stroke–therapy interval, and lesion volume, side, and location [cortical, subcortical]) seemed to predict gains in cardiovascular fitness in the combined sample.

Despite identifying significant predictors here, predictive models explained at most 33% (for 6-minute walk velocity) of the variability in therapy effects. Other parameters, such as the degree of microvascular encephalopathy, brain atrophy, or mental factors such as motivation and ambition to achieve the training goals, were not evaluated here but may be important for predicting the response to T-EX.

The limitation of this study is the combination of 2 trials that were conducted in different populations and used different durations and intensities of T-EX. Because it is difficult to recruit large numbers of chronically disabled stroke survivors for prolonged training within a research study, we decided to pool the data despite these design differences. Trial (the United States, Germany) was a covariate in all analyses, and interaction terms were tested to identify differences between the data sets. As discussed above, the effect of trial was significant only in models predicting fitness gains. This may have been a confounder precluding an identification of predictors of fitness gains.

Conclusion

In summary, the present study provides further support for the efficacy of aerobic treadmill training in chronic stroke survivors. Walking benefits might be related to lesion characteristics, with participants with large and right-sided lesions improving the least.

Additionally, earlier intervention after the stroke may optimize treatment effects. These findings might be important to consider when prescribing exercise interventions after stroke but require further confirmation by randomized controlled trials.

Acknowledgments

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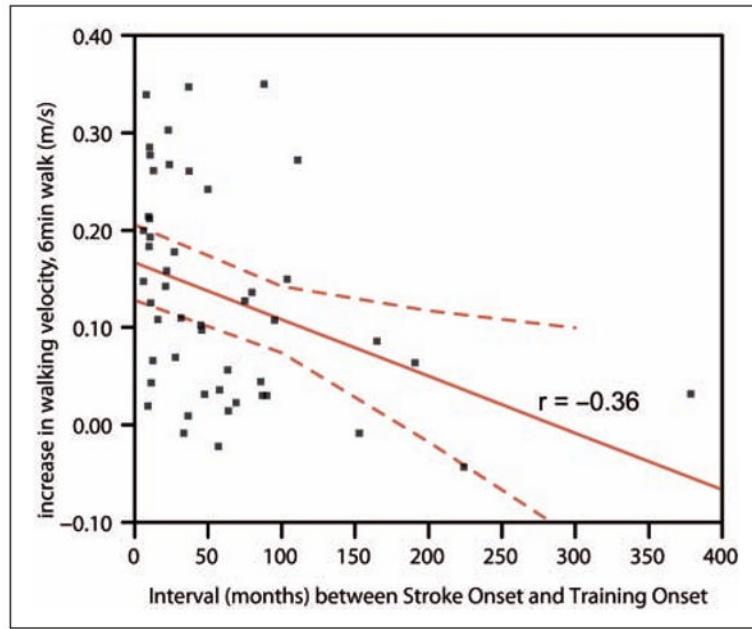
Figure 1. The absolute improvement in 6-minute walk velocity after treadmill exercise is greater in participants who were trained earlier after the stroke

Table 1
Demographic and Baseline Characteristics

	All (n = 52)	United States (n = 20)	Germany (n = 32)	$P_{\text{Difference}}$ (US vs German Trials)
Age (years), mean (SEM)	66.8 (1.1)	64.0 (2.1)	68.6 (1.1)	.055
Gender, Female (%)	18 (34.62)	12 (60)	6 (18.75)	.036[a]
Stroke therapy interval (months), mean (SEM)	59.00 (9.28)	60.06 (20.01)	58.34 (8.77)	.93
Stroke location, n (%)				
Brainstem	8 (15.38)	6 (30)	2 (6.24)	
Cortex	20 (38.46)	5 (25)	15 (46.88)	
Subcortical	24 (46.15)	9 (45)	15 (46.88)	
Right-sided stroke, n (%)	20 (38.46)	8 (40)	12 (37.5)	.86
Lesion volume (mm^3 SEM)	37421.54 (8065.83)	45775 (11484.75)	24056 (9717.42)	.16
NIHSS, mean (SEM)	4.08 (0.35)	3.67 (0.53)	4.31 (0.47)	.39

Abbreviations: SEM, standard error of the mean; NIHSS, National Institutes of Health Stroke Scale.

[a]Indicates significant differences between trials ($P < .05$).

Table 2

Baseline and Absolute (absCh) and Relative Changes (relCh) in Gait Performance and Fitness

	All (n = 52)			United States (n = 20)			Germany (n = 32)		
	Baseline	absCh	relCh	Baseline	absCh	relCh	Baseline	absCh	relCh
6-Minute walk velocity (m/s), mean (SEM)	0.704 (0.054)	0.127 (0.015)	0.198 (0.023)	0.585 (0.061)	0.115 (0.024)	0.206 (0.046)	0.778 (0.077)	0.135 (0.019)	0.194 (0.024)
6-Minute walk distance (m), mean (SEM)	253.25 (19.38)	45.90 (5.31)		210.6 (21.82)	41.35 (8.65)		279.91 (27.61)	48.75 (6.79)	
10-m Walk velocity (m/s), SSWS, mean (SEM)	0.672 (0.048)	0.059 (0.015)	0.133 (0.035)	0.558[a] (0.057)	0.075 (0.030)	0.217 (0.083)	0.739[a] (0.067)	0.0499 (0.017)	0.083 (0.024)
10-m Walk velocity (m/s), FCWS, mean (SEM)	0.852 (0.063)	0.100 (0.019)	0.156 (0.035)	0.748 (0.083)	0.126 (0.036)	0.25 (0.084)	0.914 (0.087)	0.084 (0.019)	0.100 (0.022)
Peak VO$_2$ (mL/kg/min), mean (SEM)	17.856 (0.944)	3.957 (0.527)	0.232 (0.030)	14.125[a] (1.214)	2.089[a] (0.510)	0.161 (0.039)	20.188[a] (1.167)	5.066[a] (0.720)	0.274 (0.041)

Abbreviations: SEM, standard error of the mean; SSWS, self-selected walking speed; FCWS, fast comfortable walking speed.

[a]Indicates significant differences between trials ($P < .05$).

Table 3

Predictors of Baseline Walking Impairment and Fitness

Dependent Variable	Predictors	Mean	SEM	r	P
10-m Walk velocity (m/s), comfortable	Trial (United States)	0.56	0.06		.009
	Trial (Germany)	0.74	0.07		
	NIHSS			−0.54	<.0001
10-m Walk velocity (m/s), fastest	Trial (United States)	0.75	0.09		.036
	Trial (Germany)	0.91	0.09		
	Gender (female)	0.69	0.07		.032
	Gender (male)	0.93	0.08		
	Age			−0.1	.012
	Lesion volume			−0.4	.023
	NIHSS			−0.5	.005
6-Minute walk velocity (m/s)	Gender (female)	0.56	0.06		.009
	Gender (male)	0.77	0.07		
	NIHSS (United States)			−0.14	<.0001
	NIHSS (Germany)			−0.69	
Peak VO$_2$ (mL/kg/min)	Trial (United States)	14.1	1.21		.013
	Trial (Germany)	20.2	1.17		
	Gender (female)	13.2	1.2		.0004
	Gender (male)	20.3	1.1		
	Stroke side (left)	19.7	1.2		.009
	Stroke side (right)	14.9	1.4		
	NIHSS			−0.28	.003

Abbreviations: SEM, standard error of the mean; NIHSS, National Institutes of Health Stroke Scale.

Table 4

Predictors of Therapy Response

Dependent Variable	Predictors	Mean	SEM	r	P	$r^2_{overall}$
Absolute gain in 10-m walk velocity (m/s), comfortable	Location (cortical)	0.015	0.021		.014	0.12
	Location (subcortical)	0.091	0.020			
Relative gain in 10-m walk velocity (m/s), comfortable	Lesion volume			−0.24	.0023	0.32
Absolute gain in 10-m walk velocity (m/s), fastest	Location (cortical)	0.047	0.025		.018	0.11
	Location (subcortical)	0.134	0.023			
Relative gain in 10-m walk velocity (m/s), fastest	Lesion volume			−0.24	.0035	0.27
Absolute gain in 6-minute walk velocity (m/s)	Stroke side (left)	0.16	0.02		.035	0.33
	Stroke side (right)	0.08	0.02			
	Stroke–Therapy interval			−0.36	.0088	
Relative gain in 6-minute walk velocity (m/s)	Stroke–Therapy interval			−0.31	.017	0.1
Absolute gain in peak VO$_2$ (mL/kg/min)	Trial (United States)	2.09	0.51		.005	0.15
	Trial (Germany)	5.07	0.72			
Relative gain in peak VO$_2$ (mL/kg/min)	Trial (United States)	0.16	0.04		.0312	0.15
	Trial (Germany)	0.27	0.04			

Abbreviations: SEM, standard error of the mean.