Role of walking-exercise therapy after stroke

Globas, C; Macko, R F; Luft, A R
Role of walking-exercise therapy after stroke

Abstract

Stroke commonly leads to reduced mobility, which leads to deconditioning and a worsening of vascular risk factors, such as diabetes. The worsened risk profile leads to further strokes and disability—a vicious cycle for the stroke survivor. Exercise (walking) therapy may break this cycle by providing adequate stimuli for improving gait through plastic adaptation in the brain and through increasing fitness. Randomized, controlled data demonstrate the efficacy for gains in fitness and walking speed, the latter being related to lasting changes in activation patterns of the brainstem and cerebellum. Diabetes and muscle inflammation can also be improved by aerobic exercise training. The scope of this review summarizes these data and identifies unresolved issues related to optimization, intensity and maintenance of therapy effects. Exercise should be an integral part of every rehabilitation program.
Role of exercise walking therapy after stroke

Christoph Globas, Robert Bosch Krankenhaus, Stuttgart, Germany, tel +49 (711) 81013 119, cglobas@web.de

Richard F. Macko, Department of Neurology, University of Maryland and Baltimore Veteran Affairs Medical Center, Baltimore, MD, USA, tel +1 (410) 605-7063, fax +1 (410) 605-7937, rmacko@grecc.umaryland.edu

Andreas R. Luft, Department of Neurology, University of Zurich, Switzerland

Short title: Exercise after stroke

Correspondence:

Andreas R. Luft
Department of Neurology
University of Zurich
Frauenklinikstr. 26
8091 Zurich, Switzerland
Tel: +41 44 255 5500
Fax: +41 44 244 4507
aluft@jhu.edu

Abstract

Stroke commonly leads to reduced mobility which leads to deconditioning and a worsening of vascular risk factors such as diabetes. The worsened risk profile leads to further strokes and disability – a vicious circle for the stroke survivor. Exercise (walking) therapy may break this circle by providing adequate stimuli for improving gait through plastic adaptation in the brain and through increasing fitness. Randomized controlled data demonstrates its efficacy for gains in fitness and walking speed, the latter being related to lasting changes in activation patterns of brainstem and cerebellum. Diabetes and muscle inflammation can also be improved by aerobic exercise training. The scope of this review it to summarize these data and identify unresolved
issues related to optimization, intensity and maintenance of therapy effects. But already now exercise should be an integral part of every rehabilitation program.

**Keywords**: exercise, rehabilitation, stroke, fitness, motor skill learning

**Introduction**

Stroke is one of the most common diseases in neurology, the third leading cause of death in developed countries and together with brain trauma the prominent reason for adult disability. According to WHO statistics the incidence of stroke worldwide is as high as all malignant neoplasms together. The prevalence of stroke-related disability is twice as high as the prevalence of cardiac insufficiency [1]. Therefore, stroke and its sequelae are a major health and financial burden.

At least 80% of stroke survivors are left with motor function deficits and around 50% with impaired mobility with about 25% being wheel-chair bound three months after stroke [2,3]. Impaired mobility leads to cardiorespiratory deconditioning which promotes obesity thereby promoting diabetes and worsening lipid/cholesterol profiles. The latter two are important risk factors for stroke and vascular dementia [4]. Even in patients without elevated cardio-/cerebrovascular risk before the onset of disability, such as spinal cord injured subjects, being immobile increases this risk [5]. Cerebrovascular risk causes further stroke-like events thereby potentiating disability. This leads into a vicious circle that propogates the loss of functional independence and recurrent atherosclerotic events (Figure 1).

Adding walking exercise sufficient to increase cardiorespiratory fitness to rehabilitation programs may not only improve walking but also break the metabolic/risk factor cycle. Most contemporary neurorehabilitation programs consisting of physical and occupational therapy are insufficient stimuli to increase fitness [6] and exercise therapy is underused in many neurorehabilitation hospitals. To date several randomized controlled trials have demonstrated the efficacy of exercise rehabilitation for improving fitness and mobility [7,8].

The scope here is to review the available information on efficacy as measured by improvements in walking and fitness. Open questions remain and are related to optimization of therapy protocols in non-responders to standard therapy, e.g., by using
higher intensities, and how to maintain therapy benefits when the formal program ended.

**Figure 1.** The vicious circle for the stroke survivor.

**Fitness and activity in stroke survivors**

The amount of daily physical activity correlates with cardiovascular fitness levels [9-13]. Inactivity (deconditioning) leads to reduced aerobic capacity as measured by the oxygen consumption (VO$_2$) during peak exercise [14]. In stroke survivors, VO$_2$ peak is approximately 50-70% of age- and gender-matched sedentary healthy individuals, (Figure 2) [15,16]. Part of this fitness deficit may already be present before the stroke because when tested in the acute phase even patients with minimal to moderate deficits have low peak VO$_2$ [15,16] – in line with the notion that fitness deficits are related to increased cerebrovascular risk [17,18]. Low levels of physical activity before the stroke have been associated with worsened outcome after two years [19].

Subsequently, mobility and motor deficits produce an additional decline in aerobic fitness [20] with severe consequences – fitness becomes the major limitation to mobility.
beyond locomotor deficits given that hemiparetic gait requires 55%-100% more energy than normal gait [21].

Activities of daily living (ADL) typically require an aerobic capacity (peak VO2) of 20 mL/kg/min for adults aged 65-97 years [22]. Most stroke survivors do not meet this level (Figure 2) [23]. Therefore, therapies to enhance aerobic capacity have the potential to benefit ADL function and independent living.

![Figure 2](image)

**Figure 2.** Aerobic fitness deficits in stroke survivors as a function of age as compared with healthy individuals.

**Exercise protocols**

Exercise protocols are well characterized in healthy individuals but it is unknown whether they are equally effective and safe after stroke. The American College of Sports Medicine has published guidelines for exercise protocols that effectively improve VO2 in healthy [24]. This improvement is related to frequency and intensity of training. For healthy adults the recommended exercise to maintain cardiorespiratory fitness, body composition, muscular strength, endurance and flexibility is 3-5 days per week 20-60
min of exercise at 55%-90% of the maximum age-adjusted heart rate. Exercise may be continuous or intermittent as long as bouts last a minimum of 10 min [25,26].

Concern for safety was the main reason for not prescribing exercise for stroke survivors in the past. With the appropriate screening for medical and particularly cardiac contraindications exercise can be considered safe for stroke survivors if conducted under experienced supervision [27,28]. The minimal or optimal training intensity that is necessary to reverse the cardiovascular and muscular deconditioning effects, remains unknown [6,23,28]. Stroke survivors with very low fitness may already profit from low-intensity training as it has already been shown for healthy individuals [29,30]. Controlled studies in stroke survivors show that 3 to 6 months moderate aerobic intensity treadmill training, consisting initially of as little as 2-3 min of walking interspersed with rest periods of similar duration produces significant gains in fitness and economy of hemiparetic gait, regardless of age and number of years elapsed since the initial stroke event [31].

The optimal exercise intensities and training modalities to improve both fitness and mobility function after stroke are not yet established. In terms of improving daily functioning, repetitive task specific training, i.e. walking, either over-ground or on a treadmill, might provide the best stimulus to enhance motor recovery apart from fitness gains [32]. Typically, protocols use intensities to reach a heart rate goal of 50% and 80% of the heart rate reserve determined by the formula of Karvonen (training HR = %\((HR_{max} - HR_{rest})\)). Low-weight bearing activities might be preferred in stroke survivors with reduced ability to bear weight on the paretic leg [33] and increased osteoporosis [34], because they are supposed to produce less injuries [35]. In these patients treadmill training with partial body-weight support [36] or water-based exercise programs may be considered [37]. Robotic devices to optimize the dynamics of the trained motor activity are promising developments but have so far failed to show a clear advantage over non-robotic training.

**Efficacy of exercise**

Aerobic exercise training in stroke survivors demonstrated clear benefits for aerobic capacity and walking velocity as reported by a meta-analysis of seven randomized controlled trials on a total of 480 subjects. Exercise intensity and duration used in these
studies ranged between 50% and 80% of heart rate reserve performed for 20-40 min for 3-5 days week. During the early stage after stroke exercise tended to produce greater fitness gains as compared with chronic subjects [38-40]. This finding may be related a certain degree of spontaneous recovery [39]. It may also indicate that subjects are more responsive to training stimuli during the acute phase in which the brain is in a state more susceptible to the plastic changes that mediate functional gains [41]. No randomized study has so far shown clear improvements in activities of daily living or quality of life.

An aerobic exercise program that improved fitness by 15% lead to an improvement in indices of insulin sensitivity and glucose tolerance [42]. In oral glucose tolerance tests, the insulin secretion was reduced by 24% while the glucose response was 14% lower. Fifty-eight percent of those stroke patients with abnormal glucose tolerance or type 2 diabetes mellitus at baseline improved (reversed) their clinical status based on glucose levels 120 min after glucose intake within a oral glucose tolerance test. Similarly, lipid profile may be positively affected by exercise training [43].

A Cochrane review on exercise training in 2004 covering 12 trials reported evidence for a positive effect of task-related walk training on mobility but concluded that more research is necessary to identify the optimal training mode and intensity [44]. A Cochrane review of 15 trials testing treadmill training with and without body-weight support and other walking interventions reported no significant advantage of either intervention on walking speed and dependence [45].

One trial demonstrated high improvements in peak VO2 (22.5%) after water-based exercise [37]. Training was performed at 80% heart rate reserve, which may account for the observed level of improvement. It seems promising to compare efficacy and adverse events, such as injuries, of land- and water-based programs in the future.

The available studies reported only few adverse events related to exercise therapy. Recurrent stroke risk in a group of 50 patients undergoing exercise training over 6 months was comparable to the risks in the general post-stroke population [46]. Pang et al. reported five falls in a group of 32 individuals undergoing 19 weeks of a fitness, balance and mobility program (1 hr, three times per week), but no fall resulted in injury [47].
In conclusion, the evidence available to date supports the use of exercise programs post stroke if they are conducted in sufficient intensity to produce fitness gains. However, further controlled clinical trials are necessary to identify the optimal regimen or combination therapy to improve cardiometabolic health, motor function, and quality of the stroke survivor's daily life.

**Effects of exercise therapy on brain and muscle**

Exercise therapy has multimodal effects on various organs as well as on body composition.

1. Likely related to its task-repetitive nature, aerobic treadmill exercise induces modifications in brain networks controlling the paretic limb after stroke. Six months of aerobic treadmill exercise increased activation of brainstem and cerebellum during movement of the paretic knee measured by blood oxygen level dependent signal changes (BOLD) in functional MRI scans [8]. Changes of BOLD signal are correlated with increased neuronal activity. These subcortical brain areas with increased activation after the training in this study are known as locomotor control centers in humans and animals [48]. Recruiting these centers may mediate recovery of gait as suggested by a positive correlation between activation change in cerebellum and increase in gait velocity [8]. Therefore, repetitive treadmill-walking therapy may be an adequate stimulus to trigger CNS plasticity that enables more efficient locomotion. Because aerobic treadmill exercise also improves cardiovascular fitness, it may be optimally suited to benefit home-based mobility function and independency in daily life. Whether stroke survivors make use of this ability may depend on additional psychosocial and behavioral factors that are so far not well understood, but may be modifiable using social learning models to enhance habitual physical activity and exercise behaviors that influence long-term health outcomes after stroke [49].

2. Apart from the brain and the cardiorespiratory system, the muscle is a third target organ influenced by aerobic exercise training. Lean tissue mass reduction correlates with neurological disability and poor fitness levels in chronic stroke survivors [50]. The paretic muscle has approximately 25% higher content of fat as compared with the nonparetic muscle [51]. Higher intramuscular fat is associated with insulin
resistance and diabetes [50]. These changes in skeletal muscle may also worsen fitness and the CVD risk profile.

Paretic muscle also shows an abnormal composition: there is a loss of type I muscle fibers as well as fiber atrophy, and reduced oxidative capacity [52-54]. Skeletal muscle contains fibers expressing different myosin heavy chain (MHC) isoforms. Which phenotype is developed, depends on the pattern in use. Slow (type I) MHC fibers have increased oxidative metabolism, are more resistant to fatigue, and have higher sensitivity to insulin-mediated glucose uptake. Fast (type II) MHC fibers, in turn, can be used for rapid and powerful movements. These fibers fatigue easily and are less sensitive to insulin [55]. After stroke, there is a major shift to fast MHC fiber type [20,54,56]. Therefore, stroke survivors are supposed to fatigue more rapidly and to be more resistant to insulin response [57,58]. These muscular changes are likely to contribute to metabolic syndrome and increased vascular risk, e.g., impaired glucose tolerance leads to a 2- to 3-fold increased risk for recurrent cerebrovascular events [59].

Treadmill aerobic exercise has been shown to reduce glucose intolerance and reduce diabetes rates [42] and may induce major alterations of muscle composition that underlie improved systemic metabolic health profiles for stroke survivors [50].

**Conclusion**

Low aerobic capacity, in addition to mobility impairment, are key factors contributing to post-stroke disability. Accordingly, VO2peak, as a measure of cardiorespiratory fitness, is approximately 50% of age-matched healthy subjects in stroke survivors [60]. VO2peak levels are strongly related to functional performance in the elderly. Additionally, hemiparetic gait also requires 1.5 to 2-fold increased energy exertion, which is difficult for stroke survivors to sustain due to profound physical deconditioning and secondary metabolic abnormalities in hemiparetic leg muscle. Exercise training help to reverse these deficits by improving fitness and secondary cardiometabolic health. Due to their task repetitive nature walking exercise improves locomotion and possibly mobility. Aerobic walking should therefore be part of every neurorehabilitation program.
**Expert commentary**

Rehabilitation after stroke is a rapidly evolving field with contributions from basic and clinical science. The recognition that the brain has the capacity for restoration through plastic adaptation if adequately stimulated, offers a window to recovery of movement abilities. However, restoring movement is not sufficient in chronic stroke patients who have marked deficits in cardiorespiratory fitness. Exercise walking therapy could solve both problems by addressing walking in a repetitive manner and fitness if the therapy has sufficient intensity to increase heart rate about 60-80% of heart rate reserve. Using treadmills, exercise walking can safely be employed in disabled stroke survivors and randomized trials demonstrate the efficacy of this approach for walking velocity and fitness in comparison with conventional or no treatment. Open questions are how to maintain the benefits once an exercise program ended and how to optimize therapy protocols for patients who do not respond to standard treatment. Further basic and clinical investigations are needed.

**Five-year view**

In five years time we may know how to optimally employ exercise therapy in stroke survivors, that is the intensity, mode and application necessary to produce and maintain maximum gains in mobility and fitness. We may also have identified the predictors of therapy response to different training programs, which is considerably variable across individuals and the impact of exercise training on quality of life and activities of daily living.

**Key issues**

- Stroke survivors with chronic motor disability have substantial reductions in cardiorespiratory fitness.
- Aerobic exercise training can safely improve fitness and increase walking speed.
- Exercise therapy reduces diabetic profiles and stroke survivors thereby potentially affecting the risk for recurrent cerebrovascular events.
• Treadmill walking induces adaptations in brainstem and cerebellum that are related to improvements in walking speed indicating a potential causal relationship.
• Aerobic training modalities modify muscle composition thereby potentially producing its metabolic benefits.

**Literature**


