Train the Vessel, Gain the Brain: Physical Activity and Vessel Function and the Impact on Stroke Prevention and Outcome in Cerebrovascular Disease

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Key Words

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Abstract

The burden of cerebrovascular disease (CVD) is huge and therapeutic options are limited. Physical activity is effective in preventing coronary heart and peripheral artery disease both experimentally and clinically. It is likely that the protective effects of exercise can be extended to both CVD and cognitive impairment. The pleiotropic protective and preventive mechanisms induced by physical activity include increased perfusion as well as mechanisms of collateral recruitment and neovascularization mediated by arterio- and angiogenesis. Physical activity increases the bioavailability of nitric oxide, bone marrow-derived CD34+ cells and growth factors, all of which promote neovascularization. Additionally, shear stress is discussed as a potential mechanism for vessel growth. Moreover, physical activity plays a role in endothelial function and cerebral autoregulation in small- and large-artery CVD. The vascular niche hypothesis highlights the complex interactions of neuro- and angiogenesis for regenerative and repair mechanisms in the human brain. Ex-

perimental and clinical studies demonstrate the positive impact of prior physical activity on stroke lesion size and on outcome after stroke. Clinical trials are necessary to further address the impact of physical activity on primary and secondary stroke prevention, outcome and cognitive function.

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Introduction

Physical activity reduces cardiovascular morbidity and mortality by modulation of ‘classical’ risk factors such as hypertension, diabetes and dyslipidemia [1, 2] (fig. 1). Shown to improve endothelial function in peripheral (PAD) and coronary artery disease (CAD) [3, 4], the effects of physical activity are likely mediated by increased bioavailability of nitric oxide (NO) and consecutive endothelium-dependent vasodilatation [5–7]. Moreover, exercise is a strong stimulus promoting neovascularization including arterio- and angiogenesis. Most pleiotropic effects of regular physical activity have been investigated either in healthy individuals or in PAD and CAD patients. So far, there is limited but growing evidence that physical activity might also play a preventive

Fig. 1. Pleiotropic effects of exercise and modulated cardiovascular risk factors [modified from 2].

role in small- and large-artery cerebrovascular disease (CVD) as well as in vascular and neurodegenerative dementia [8, 9].

In this review we will highlight the relationship between physical activity and CVD. We aim to illustrate the influence of exercise on endothelial function and neovascularization prior to stroke, the principles of collateral recruitment and the effects of exercise on cerebral hemodynamics. We will give an overview on the impact of exercise on stroke prevention and outcome and the influence of exercise on cognitive function. Finally, we will provide an outlook on future developments in research and on possible therapeutic options based on the vascular niche hypothesis.

Neovascularization in the Human Brain and Physical Activity

Various vascular mechanisms have been proposed to explain how exercise influences the maintenance, augmentation and/or improvement of cerebral blood flow

(CBF) and perfusion. All may crucially exert beneficial effects on stroke prevention and healthy human aging and are due to physical activity. The mechanisms include collateral recruitment and arterio-, vasculo- and angiogenesis.

CBF and Collateral Recruitment

In individuals with a functional stenosis of a large brain-supplying artery, cerebral autoregulation and regional CBF are often impaired [10]. Cerebral autoregulation is an essential intrinsic property in maintaining a constant CBF despite changes in cerebral perfusion pressure. CBF is kept constant in a range thought to be 50–60 ml/100 g/min [11] despite changes in mean arterial pressure by mechanoregulatory (blood pressure regulation) and chemoregulatory (PaCO₂) compensatory mechanisms, both leading to a myogenic response resulting either in vasodilatation or the constriction of smooth muscle cells in cerebral arteries and arterioles.

The extent of impairment of the cerebral autoregulation depends among other factors upon the degree of cerebral collateralization [10], which in turn also influences

the cerebrovascular reserve capacity (CRC) [12, 13]. The CRC refers to the brain's capacity to increase cerebral blood volume (CBV) and maintain a constant regional CBF in the face of low cerebral perfusion pressure. This can be quantified by PET, SPECT or Doppler ultrasound. It provides information as to whether arterioles are already maximally dilated (to maintain blood flow and metabolic needs in the poststenotic area) or if response to an increased demand is possible, for example, due to decreases in blood pressure [14]. A severely impaired CRC is associated with an increased risk of stroke or transient ischemic attack (TIA) in patients with high-grade carotid artery stenosis or occlusion [15].

The recruitment of existing collateral vessels within the circle of Willis is an endogenous protective mechanism by which sufficient blood supply can be maintained in 80% of all patients with high-grade extra- or intracranial stenosis or occlusion of brain-supplying arteries [for review, see 16]. For example, if unilateral carotid occlusion with a decrease in perfusion pressure occurs, inter-hemispheric 'cross-flow' via the anterior communicating artery may develop [17]. This is then associated with a reduced risk of internal hemodynamic watershed infarctions [18, 19]. Primary anastomoses are dependent upon the anatomic configuration of the circle of Willis. Consequently, the number of existing collaterals is inversely correlated with stroke risk [13]. Secondary collaterals independent of the circle of Willis develop under conditions of chronic ischemia or peripheral vessel occlusions via anastomoses of the internal and external carotid arteries, such as the ophthalmic artery or leptomeningeal arteries between the three intracranial vascular territories [16]. The extent of collateral circulation and the vasodilatory ability of the vasculature determine the CRC [12]. Exercise might improve CRC by inducing neovascular processes and, therefore, influence the risk of stroke or TIA (<http://clinicaltrials.gov/ct2/show/NCT00912561>).

Arteriogenesis – Outward Growth of Collateral Vessels

The adaptive reaction to an increase in diameter of collateral vessels in large-artery occlusive disease is referred to as arteriogenesis [20]. In rat models, the complex vascular mechanisms of arteriogenesis can be accelerated by different cyto- and chemokines. Several coronary and peripheral models of arteriogenesis have been developed to study the mechanisms that occur in preexisting arteriolar anastomosis-inducing mitosis in endothelial and smooth muscle cells [21]. Relevant cyto- and chemokines include monocyte chemoattractant protein 1 (MCP-1), granulocyte macrophage colony-stimulating factor (GM-CSF),

fibroblast growth factor-beta, and vascular endothelial growth factor (VEGF), which also modulate arteriogenesis in the brain [20, 22–24].

Though stimulation of arteriogenesis by cytokines is promising in animal models, randomized controlled trials in humans with application of cytokines as fibroblast growth factor [25, 26] or VEGF [27, 28] failed to improve clinical endpoints (e.g. angina score and walking distance in patients with CAD or PAD). Application of GM-CSF improved coronary collateralization as measured by invasive collateral flow index in CAD patients [29]. However, the START trial failed to demonstrate an improvement of the walking distance in PAD patients [30]. Additionally, in patients with stable CAD, a higher incidence of acute coronary syndrome was seen after subcutaneous application of GM-CSF [31]. The AXIS-1 trial demonstrated safety and tolerability of different dosages of G-CSF in patients with acute ischemic stroke but just recently it was reported that the phase II clinical trial (AXIS-2) with the G-CSF compound AX200 missed all primary and secondary endpoints [32].

Finally, arteriogenesis might be 'mechanically' stimulated by fluid shear stress due to an exercise-induced increase of CBF. Schierling et al. [33] demonstrated in a murine cerebral 3-vessel occlusion model that cerebral arteriogenesis is dependent on fluid shear stress. It is directly augmented by an increased blood flow due to an increase in the tangential forces exerted by the blood on the endothelial lining [34]. This exertion upon the endothelium then initiates a consecutive cascade of endothelial mechanisms including: (1) the expression of adhesion molecules like intracellular adhesion molecule (ICAM)-1 and (2) the upregulation of the endothelial NO synthase (eNOS) system and MCP-1. This in turn triggers an invasion of bone marrow-derived mononuclear cells and creates a complex cytokine environment and consecutive proliferation of endothelial and smooth muscle cells [34] (see fig. 2). In conclusion, arteriogenesis is a highly complex process based on a sophisticated interplay of different cytokines, enzymes, growth factors, cell types and populations, and direct stimulation of arteriogenesis might be a therapeutic approach in occlusive artery diseases [for review, see 35].

Angiogenesis, Postnatal Vasculogenesis and the Role of Endothelial Progenitor Cells

Angiogenesis (the sprouting of new capillaries from preexisting blood vessels) is thought to be the primary mechanism of new vessel formation in the adult [36]. In contrast, postnatal vasculogenesis signifies the forma-

Fig. 2. Angiogenesis, arteriogenesis and neurogenesis: exercise induces liberation of bone marrow-derived stem cells (stage A) circulating into the periphery. This is highly NO-dependent and caused by an upregulation of eNOS in stromal cells and leads to MMP-9 activation but is also enhanced by VEGF, angiopoietin-1, fibroblast growth factor, GM-CSF and pharmacological agents such as statins and erythropoietin [47, 50]. Exercise-induced shear stress (arrows, stage B) causes a cascade of mechanisms including the expression of intracellular adhesion molecule (ICAM)-1 and the upregulation of the eNOS system and MCP-1. This, in turn, triggers an invasion of bone marrow-derived mononuclear cells creating a complex cytokine environment and consecutive proliferation of endothelial and smooth muscle cells leading to an increase in diameter of an existing collateral artery (arteriogenesis) [34]. On a capillary level, EPCs are involved in the sprouting of existing capillaries and by the release of BDNF and VEGF (stage C), resulting in either recruitment of resident latent neuronal progenitors or neuroblast migration, thus facilitating neurogenesis.

tion of new vessels from endothelial progenitor cells (EPCs) [36]. While monocytes are considered prerequisites in the process of arteriogenesis [20], EPCs play an important role for angio- and vasculogenesis [37]. EPCs are bone marrow-derived stem cells and are distinct from mature endothelial cells in that they possess the potential to differentiate into endothelial cells. The definition of EPCs remains controversial [38]. In general, there are two main techniques to assess EPCs: flow cytometry (fluorescence-activated cell sorting, FACS) and in vitro assays as cell cultures. While FACS allows a detailed characterization of naive cells and different subpopulations, the technique is complex and susceptible to false-positive events, and a functional evaluation of the cell population is not possible. In contrast, cell cultures allow a functional evaluation of larger quantities of cultured

cells but, owing to the necessary culture medium supply and the unphysiological condition of cell cultures, physiological properties of these manipulated cells might be concealed. Usually, EPCs are phenotyped by a combination of markers specific for stem and endothelial cells with FACS. For example, typical combinations include the hematopoietic surface marker CD34 for hematopoietic cells, CD133 as a stem cell and VEGF receptor 2 (CD309) as an endothelial marker [39]. CD133 expression seems to be restricted to early EPCs and the surface antigen is lost during maturation to endothelial cells, which allows an identification of the maturation states of EPCs [40–42]. The number of EPCs seems to be associated with endothelial dysfunction [43] and has been found to be a better predictive risk factor for cardiovascular events than the combined Framingham score, un-

derlining the putative role of EPCs in vascular homeostasis and repair [44]. In the EPCAD study, the cumulative event survival increased stepwise across baseline EPC levels for the occurrence of a first major cardiovascular event [45]. Increased CD34+ counts have been found in patients with stenosis of carotid or middle cerebral artery and accelerated neovascularization characterized by moyamoya-like vessels. This has led to the conclusion that increased levels of bone marrow-derived CD34+ cells are correlated with neovascularization of the cerebral arterial circulation [46]. Therefore, EPCs might play an essential role in vascular regeneration, development and collateralization of the human brain. Even short-term exercise increases the number of circulating EPCs [47, 48] and a 4-week exercise program resulted in a lasting increment of circulating EPCs [49]. Exercise training also induces qualitative properties of EPCs by increasing expression of homing factor CXCR4, which might promote an improved integration of EPCs into endothelial networks [50].

The 'Vascular Niche of Neurogenesis' Hypothesis

According to the vascular niche hypothesis, regeneration and repair mechanisms can only proceed by adult neurogenesis in an angiogenic environment [51]. Adult neurogenesis is the process of generating new neurons that integrate into existing neuronal networks after fetal and early postnatal neurogenesis has ceased [52]. The findings from both experimental stroke and dementia studies underline the importance of a comprehensive consideration of the complex interactions between brain vasculature and neuronal function within the neurovascular unit [52]. Also antiangiogenic approaches in cancer contributed to the knowledge of mechanisms in the neurovascular unit, as recently reviewed by Carmeliet and Jain [53].

Endothelial cells release neurotrophic factors like brain-derived neurotrophic factor (BDNF) and VEGF [54], which stimulate the renewal of adult neuronal stem and progenitor cells and promote the production of neurons. In the adult brain, neurons and glia cells are generated throughout life in the subventricular zone, the posterior periventricular area and the subgranular zone of dentate gyrus in vitro and in the adult human brain [55, 56]. Available data in rodents show that under physiological conditions, neuroblasts from the subventricular zone migrate to the olfactory bulb [57]. Under ischemic conditions, neuroblasts migrate towards the ischemic boundary, where angiogenesis occurs and neuroblasts and cerebral vessels are linked together [58].

Endothelial cells also promote proliferation of neural progenitor cells and neuronal differentiation. Reciprocally, neural progenitor cells promote angiogenesis in vitro and VEGF seems to be a main growth factor facilitating this coupling [59], which also seems to occur in the human adult. Pereira et al. [60] showed in an MRI study that exercise increases CBV in the adult human dentate gyrus where exercise-induced neuro- and angiogenesis have been demonstrated in animals [37, 61–63].

Increased cortical CBV is correlated with angiogenesis in ischemia [64] and neoplastic processes such as gliomas [65]. In turn angiogenesis occurs in the vascular/neurogenic niche of the hippocampus [51]. Because of the correlation between CBV/angiogenesis and angiogenesis/neurogenesis, CBV measurement might be an indirect parameter for neurogenesis.

To conclude, the vascular niche hypothesis gives insights into the complex interactions of neuro- and angiogenesis [for review see 66] that can be influenced and stimulated by regular physical exercise. Exercise does not only strengthen muscle, it also strengthens the cerebral vasculoneuronal network.

Impact of Physical Activity on Stroke Outcome

Preclinical Evidence

Exercise has been shown to reduce infarction size and neurological deficits and to ameliorate brain injury after focal cerebral ischemia in a murine middle cerebral artery occlusion model [7]. This is attributed to increased expression and activity of eNOS, NO-dependent vasodilatation and regional CBF [7]. In addition, exercise inhibits injury due to inflammation by decreasing ICAM-1 expression and consecutive lower leukocyte accumulation in damaged brain and causes an overexpression of neurotrophins as BDNF in rats [67]. Early exercise after stroke might also be beneficial [68]. A subsequent study in a murine model revealed that voluntary exercise prior to acute cerebral ischemia increased levels of VEGF, which activates eNOS. Furthermore, exercise augmented the recruitment of EPCs into the ischemic region and increased the microvascular density and CBF both by angiogenesis and vasorelaxation, improving long-term recovery and regeneration [37, 69]. In conclusion, exercise promotes short- and long-term effects that increase cerebral perfusion and functional outcome by activation and expression of eNOS and EPCs after experimental ischemia in the mouse model.

Clinical Evidence

Individuals who were physically active prior to stroke have been shown to have less severe strokes and an improved stroke outcome [70, 71]. Light-to-moderate leisure-time activity was associated with an odds ratio of 4.18 (CI 1.55–11.26) for a lower severity of stroke upon hospital admission in 362 patients [70]. In addition, severity of stroke was lower in moderately active stroke patients, even though stroke size did not differ between low, moderate or high leisure-time physical activity levels [71]. Moreover, higher prestroke levels of physical activity are associated with an increased likelihood of good short-term (within 8 days) [70] and long-term (up to 2 years) [72] outcomes, measured by the NIHSS and modified Rankin Scale, respectively.

Exercise and Cognitive Function

The effects of exercise on healthy ageing and maintenance of cognitive function have been analyzed in a number of studies [73]. Cognitive impairment occurs more frequently in CVD patients than in age-matched controls [74]. It has been shown that endothelial dysfunction is associated with a high lesion load of white matter hyperintensities in MRI, underlining the importance of endothelial integrity and vasomotion in CVD [75]. There is a growing body of evidence suggesting that vascular and neurodegenerative dementias have common features that are crucially dependent upon the regulation of CBF on a microcirculatory level [76] and that exercise exerts beneficial effects on neurodegenerative dementia, vascular dementia and mild cognitive impairment [77, 78].

It is a matter of debate as to whether exercise might improve cognitive function in patients without known cognitive impairment [79]. It is known, however, that a sedentary lifestyle has a negative effect on neuronal plasticity and learning [80] and that aerobic fitness reduces brain tissue loss [81]. There are several hypotheses as to how exercise could influence executive control and alertness. First, exercise increases CBV [60] and CBF [7] – including in the dentate gyrus and hippocampus [82]. Second, the so-called ‘arousal hypothesis’ suggests that exercise induces an increase of catecholamines [83, 84] and thus increases arousal [85, 86]. Third, it is known that exercise upregulates neutrophils, in particular BDNF [87], facilitating dendritic branching and synaptic plasticity [88] (fig. 2). Flöel et al. [89] and Ruscheweyh et al. [90] showed that individuals with higher levels of physical activity had a better memory function and higher levels of neutrophils than G-CSF and BDNF, as well as increased

gray matter volume in cingulate and prefrontal areas. Finally, exercise improves mood and alleviates depression, which may in turn also affect cognitive function [91, 92].

During normal healthy aging CBF declines up to 50% [93–95] while cerebral autoregulation seems to be preserved [96]. Because no changes in regional CBF have been detected, it is assumed that this decrease reflects a global perfusion decrease associated with cerebral atrophy. Interestingly, Ainslie et al. [95] observed an increase of CBF velocity of the middle cerebral artery in endurance-trained men compared to individuals with a sedentary life style. This increase was persistent in all age groups and confirms the results of exercise-induced CBF increase in animal studies [7, 37]. One might speculate that this increase of CBF velocity reflects the lower cerebrovascular risk in physically active elderly as well as a protective mechanism against cerebral atrophy.

Physical Exercise in Primary Prevention of CVD

Several epidemiological cohort and case-control studies have addressed whether regular physical activity reduces the risk of stroke. Observational studies found associations between physical activity and stroke risk. The Honolulu Heart Study found that regular physical activity protected against hemorrhagic stroke incidence after examining over 7,500 Asian men for a 20-year period [97]. In the Oslo Study, leisure-time physical activity reduced the relative risk of stroke morbidity and mortality in middle-aged men [98]. Likewise, the incidence of all stroke subtypes was lower in physically active woman between the ages of 40 and 65 in the Nurses’ Health Study [99] and also in the Women’s Health Study [100], while women with low recreational physical activity showed a higher relative risk of stroke [101]. The Northern Manhattan Stroke Study found a protective effect of leisure-time activity (adjusted for vascular risk factors) for all stroke subtypes in Blacks, Whites and Hispanics over all age groups [102].

The Role of Exercise Intensity

It is not known whether there is an optimum of exercise intensity or a dose-response correlation of physical activity for stroke prevention. Linear [99, 103, 104], U-shaped [105, 106] and constant correlations for all activity levels [107] have been described. Two recent meta-analyses investigated the association of physical activity and stroke risk stratified by grade of activity [108, 109]. Both studies came to the conclusion that moderately intense exercise is sufficient to achieve a risk reduction for total stroke and

stroke subtypes. However, the influence of intensities or frequencies of exercise have rarely been investigated. Self-reported frequency and intensity with individual outcome measures such as sweat production [110] and dichotomization (active vs. inactive) or trichotomization (self-reported habitual low, moderate or high physical activity) [101] both in observational epidemiological and case-control studies limit the comparability between different studies. In British middle-aged men, the risk of heart attack was slightly increased in vigorously exercising men compared to those training at a moderate or moderate-to-vigorous level once weekly [111]. Furthermore, there is some evidence that frequent vigorous exercise is associated with an increased risk of atrial fibrillation [112], while light-to-moderate leisure-time activity and walking are associated with significantly lower atrial fibrillation incidence in older adults [113]. Recent data from the Northern Manhattan Stroke study suggest that moderate-to-high intensity physical activity was associated with a lower risk of ischemic stroke in men [114]. Grau et al. [115] pointed out that not only lifetime physical activity is associated with reduced odds of stroke or TIA. In that study, recently initiated exercise in individuals without a history of physical activity in young adulthood was also associated with reduced odds of stroke and TIA. Most patients exercised more than 2 but less than 7 h per week. The effects of training as they pertain to secondary stroke prevention, death, dependence and disability after stroke remain unclear [116]. Although secondary prevention programs for stroke patients exist, they are not as well studied or widely available as secondary prevention programs for cardiac patients [117].

Most clinical studies investigate the impact of endurance exercise activities such as cycling, walking or jogging on cardiovascular and stroke prevention. However, it was shown that even moderate-intensity resistance training is as effective as endurance sport for the prevention and treatment of high blood pressure [118]. Exercise and rehabilitation protocols tailored for specific stroke deficits in stroke survivors differ. Such training protocols mostly aim to improve the neurological motor deficit, but in addition it is shown that exercise in stroke survivors reduces stroke severity and improves stroke outcome [70–72].

Summary and Conclusions

There is growing evidence that physical activity prevents CVD and reduces cerebro- and cardiovascular morbidity and mortality. Exercise prior to stroke might improve stroke outcome and has been shown to improve

cognitive impairment in vascular and degenerative dementia. In contrast, secondary stroke prevention data are missing. The beneficial effects of exercise are multifaceted. First, exercise modulates cardiovascular risk factors. Second, exercise plays a role in the mediation of vascular and other endothelial effects. Apart from recruiting collateral vessels, physical activity can improve vessel collateralization by augmented arterio- and/or angiogenesis. The underlying physiological mechanisms for improved angiogenesis can be attributed to an increased phosphorylation of eNOS, elevated levels of bone marrow-derived CD34+ cells (e.g. EPCs) and subsequent endothelial or mechanical mechanisms leading to neovascularization and correction of endothelial dysfunction. According to the vascular niche hypothesis, neuronal regeneration is enhanced in the angiogenic environment – probably not only in the ischemic brain. No dedicated recommendations on the timing or dosage of physical activity can be given, but further randomized controlled trials should be encouraged.

In our view such trials should focus on the subacute phase weeks after stroke because the potential benefit of exercise in this phase can be assumed to be highest. Such trials should also investigate the right type and dosage of exercise intervention and the different levels of outcome (e.g. depression, activities of daily living) after an exercise intervention, as well as the surrogate parameters (e.g. CBF, endothelial markers) of the potential underlying vascular mechanisms.

However, in the end there is no doubt that, in general, exercise can be recommended as a nonpharmacological and noninvasive intervention in the primary and secondary prevention of stroke for the sustainment of cognitive function, and finally for the improvement of outcome and rehabilitation after stroke. Strain the muscles, train the vessels, and gain the brain!

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Disclosure Statement

The authors report no conflicts of interest.

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