Int J Clin Exp Med 2015;8(11):19859-19866
www.ijcem.com /ISSN:1940-5901/IJCEM0015380

Review Article

Physical exercise-induced protection on ischemic cardiovascular and cerebrovascular diseases

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Received August 13, 2015; Accepted October 12, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Physical exercise is any bodily activity to enhance or maintain physical fitness and overall health and wellness. A series of associated studies have demonstrated that physical exercise could alleviate the infarct volume, increase the collateral circulation, promote endothelial progenitor cells, improve cerebral blood flow after cardiovascular and cerebrovascular diseases. In this review, we summed up the protective effects of physical exercise on cerebral blood flow (CBF), vascular endothelium, vascular vasodilation, endothelial progenitor cells and collateral circulation. An awareness of the exercise intervention benefits for cardiovascular and cerebrovascular diseases may encourage more patients with cerebral infarction and myocardial infarction and people with high risk factors to accept exercise interventions for the prevention and treatment of cardiovascular and cerebrovascular diseases.

Keywords: Physical exercise, cerebral infarction, angiogenesis, myocardial infarction, cerebral blood vessels

Introduction

Physical exercises are generally divided into three types according to the overall effect on the human body: first, aerobic exercise refers to any physical activity involved with large muscle groups and results in your body to use more oxygen than resting, including long slow distance training, swimming, brisk walking, rowing, hiking and cycling; second, anaerobic exercise (also called strength or resistance training) can maintain, strengthen, and tone the muscles, as well as promote bone strength, balance, and coordination ability including weight training, eccentric training, lunges, pushups and bicep curls using dumbbells; third, flexibility exercises refers to stretch and lengthen the muscles of our body, which aims to reduce the risk of injury, including various limb and trunk stretching training.

Regular exercise training is proved to improve abnormal arterial blood pressure, decrease obesity, ameliorate glucose and lipid metabolic disorders and reduce the abnormal rheological properties of blood [1-3]. The long-term physical exercises in the elderly participants can improve the neural adjustment of lower leg muscles to promote efficient output of muscle strength. Additionally, it is well established that exercise training regulates endothelial function, partly through the activation of endothelial nitric oxide synthase (eNOS) [2]. Other benefits of exercise training included the down-regulation of blood viscosity, fibrinolysis [4] and plasma fibrinogen concentration, the increase of plasma tissue plasminogen activator activity and the promotion of HDL-cholesterol [5]. However, the protective effect of physical exercise on cerebral infarction and myocardial infarction are not explicit. Therefore, we summarize the protective effects of physical exercise on ischemic cardiovascular and cerebrovascular diseases, including the regulation of cerebral blood flow (CBF), vascular endothelium, vascular vasodilation, endothelial progenitor cells, collateral circulation and the related factors.

The protection of exercise on ischemic cerebrovascular diseases

The effect of exercise on CBF: Cerebral blood flow (CBF) is essential for human survival.

Cerebral vascular response to exercise is different from other peripheral vascular due to the small vascular bed of cerebral vasculature which is powerfully controlled by partial pressure of carbon dioxide in artery and cerebral autoregulation [6]. The traditional view on the total cerebral blood flow (CBF) is that CBF kept relatively constant and was mainly unaffected in different conditions, including exercise training. However, the subsequent research results demonstrate that high intensity exercise training could regulate the CBF and cerebral neuronal activity. Multiple factors are involved in the regulation of CBF increase caused by exercise, including the partial pressure of carbon dioxide, muscle mechanoreceptors, cardiac output, glucose uptake and neural innervation [7]. Promotion in exercise intensity up to nearly 60% of maximal oxygen uptake results in elevations in CBF, and then CBF went back to baseline values due to lower Pa(CO(2)) via hyperventilation-induced cerebral vasoconstriction, indicating that heavy exercise brought about CBF decreases in spite of the increase of cerebral metabolic demand [8].

For human studies, a previous study 20 years ago on human brains after stroke demonstrated that the angiogenesis was obvious in the penumbra in the infarcted hemispheres. Furthermore, the result of Spearman's p analysis showed that the increased blood vessel counts were significantly correlated with longer survival of stroke patients, indicating that angiogenesis might play a key role in the repair process after stroke [9]. Moderate to severe intensity exercise leads to only medium increases in cerebral blood flow (CBF) in spite of big increases in arterial blood pressure (ABP) and sympathetic activity. Animal studies indicate that the regulation of cerebral blood flow (CBF) during exercise is regulated not only by autonomic nervous system but also by cerebral autoregulation (CA) and the arterial baroreflex-regulated control of the systemic circulation [10]. Compared with conventional rehabilitation programs, treadmill aerobic training (T-AEX) is more effective in promoting cardiovascular fitness, improving ambulatory performance on 6-minute walks and increasing mobility function by Walking Impairment Questionnaire (WIQ) for patients with chronic stroke, demonstrating that the mode of exercise determined the effect of exercise-mediated adaptations [11]. The high-activity exercise significantly reduces vessel tortuosity and promotes small-diameter cerebral vessels in healthy elderly subjects, compared to low-activity exercise training, resulting in a vessel morphologic pattern analogou to that of younger subjects. This study might partially explain the reason why aerobic activity could improve cerebral vasculature anatomy [12].

For animal studies, as for the effect of exercise on cerebral blood flow in dogs, there are not significant changes of total CBF during the treadmill exercise in moderate intensity. However, there is significant increase for regional blood flow in brain functional areas related to motor-sensory control, including neocerebellar and paleocerebellar cortex, motor-sensory cortex and spinal cord, which might be due to the reason that local dilator which was caused by exercise predominated over the constrictor stimulus which was closely associated with hypocapnia [13]. Five weeks of exercise training improves cognitive function of monkey evidently compared to sedentary control group. Five months of regular exercise training increases the vascular volume fraction of the motor cortex compared to sedentary control group. Although promoted vascular volume does not sustain apparent after three months sedentary period, regular exercise could increase the blood flow to the cerebral cortex in the period of exercise training [14]. The vigorous physical exercise increases metabolic demands by shortening the diffusion distance from vascular molecular layer of the paramedian lobule. Meanwhile, motor skill learning promotes neuropil volume, remarkably increasing mitochondrial volume fraction per Purkinje cell [15].

The effect of exercise on ischemic cerebrovascular diseases via VEGF

Vascular endothelial growth factor (VEGF) plays a key role in the process of angiogenesis with therapeutic potential in ischemic stroke. Intracerebroventricular administration of VEGF decreases infarct size, alleviates neurological deficits, promotes survival of newborn neurons and increases angiogenesis in the striatal ischemic penumbra following MCAO/Reperfusion in rat [16]. Exercise preconditioning can resist ischemia/reperfusion injury by heightening brain microvascular integrity through TNF-alpha

(rather than VEGF), which increases the expression of integrins. This study indicates that exercise enhances neurovascular integrity through the up-regulation of integrins after stroke [17]. Five months of treadmill training increases the vascular volume fraction in the cerebral cortex, but the increased blood flow does not remain after 3 months rest, indicating that the regular training is required if the exerciser intends to keep the effect of exercise on brain [14]. Exercise training increases the mRNA and protein expression level of VEGF in hippocampus of brain, indicating that new transcription seems to be a key exercise-induced regulatory procedure to increase VEGF expression in brain [18]. Exercise preconditioning also could resist ischemia/reperfusion injury by heightening brain microvascular integrity through TNF-alpha (rather than VEGF), which increases the expression of integrins. This study indicates that exercise enhances neurovascular integrity through the up-regulation of integrins after stroke [17].

The effect of exercise on ischemic cerebrovascular diseases via other factors

Meanwhile, CD31 is the specific marker of the neogenetic microvessels. Compared with control group, the amount of CD31 positive cells remarkablely increase in physical exercise group in rats, indicating that physical exercise plays an important role in the induction of angiogenesis [19]. Treadmill training exercise obviously promotes the genes and proteins expression of VEGF and matrix metalloproteinase 2 (MMP2) after cerebral ischemia. Moreover, the regional cerebral blood flow of the striatum following ischemia is remarkably increased in exercise group compared to sedentary group. All of above mentioned effects of exercise on MMP-2, cerebral blood flow and neurobehavioral score are abolished by the VEGF-targeting antibody, indicating that the MMP2-VEGF-dependent mechanisms are crucial pathways underlying the effect of exercise on ischemic stroke [20]. The hypoxia-inducible factor-1 (HIF-1) and HIF-2, which are known to be related to the mediation of VEGF and VEGFR gene expression, are significantly up-regulated in the ischemic border at 72 hours after ischemic stroke, indicating the involvement of VEGF/VEGFR system in the growth of new vessels following ischemic stroke [21]. Three weeks of exercise preconditioning alleviates heat-stroke-induced brain damage via sustaining mean arterial pressure and cerebral blood flow at suitable levels in the rat brain, which might be associated with over-expression of HSP72 [22]. The protective effect of exercise training is entirely abolished in eNOS-deficient mice, indicating that the promoted eNOS activity by exercise training is the key mechanism by which this modality protects against brain injury [23]. Furthermore, promoteded expression of Ang-1 and Tie-2 induced by exercise training improves recovery of brain function in rats following ischemic stroke [24].

The protection of exercise on ischemic cardiovascular diseases

The protective effect of exercise on vascular endothelium: In the past ten years, it is well established that vascular endothelium is a key regulatory organ, participating in sustaining the cardiovascular homeostasis, also involving in the pathogenesis of several cardiovascular disease. The normal endothelium regulates hemostasis, cellular proliferation, and inflammatory factors and immune reactions in the vascular wall via capacity to respond to chemical, physical and humoral environment changes and producing a large number of bioactive substances. Although the important role of vascular endothelium is well established, there is still not widely admitted method to treat endothelial dysfunction [25]. The basic molecular mechanism of blood vessel growth involves in the interactions among endothelial cells, periendothelial cells, matrix molecules and various growth factors and receptors [26].

For human studies, a one-year moderate-to-high training can cause adaptive changes which may be attributed, at least to some extent, to coronary flow improvement in some patients with myocardial infarction [27]. A single exercise bout of cardiopulmonary exercise testing (CPET) improves circulating angiogenic cells (CAC) migration which is related to endothelial dysfunction in patients with chronic heart failure (CHF), restoring CAC to approximately normal level, indicating that the acute exercise training has a potential to improve CAC dysfunction for CHF patients with endothelial dysfunction [28]. According to the result of a clinical survey, even a short program of physical training could increase endothelial progenitor

cells (EPCs) count and angiogenic factors, exerting beneficial effects on chronic heart failure patients [29]. The maximal stress test leads to significant promotion of circulating endothelial progenitor cells (EPCs) as well as plasma concentrations of VEGF in patients with symptomatic coronary artery disease (CAD), and the same intervention had no influence on non-ischemic patients and healthy subjects, indicating that the protective effect of exercise might be related to increase of EPC and VEGF [30]. Strenuous activity resultes in a time-dependent promotion in progenitor cells (PCs), mature endothelial cells (mECs) and endothelial progenitor cells (EPCs), which might be involved in the regulation of VEGF and IL-6, potentially forming the mechanism basis of exercise on angiogenesis pre- and post cardiovascular and cerebrovascular diseases [31].

For animal studies, the altered control of coronary vascular includs changed responses of the coronary circulation to vasoactive substances, alterations in endothelium-mediated vasoregulation, and changes in the cellular-molecular control of intracellular free Ca^{2+} in both endothelial and vascular smooth muscle cells removed from coronary arteries of animals following exercise training [32]. It is reported that exercise training repairs the injury of EPC in hypertension, which could be related to peripheral revascularization, indicating a possible mechanism for therapeutic application of exercise in vascular diseases [33]. Twenty-eight days of moderate exercise training obviously promotes circulating EPCs, increases neoangiogenesis and alleviates EPC apoptosis, partially through a NO-dependent pathway, indicating the beneficial role of exercise on cardiovascular diseases [34].

The protective effect of exercise on vascular vasodilation

Up to six months of exercise training improves peripheral blood flow and increased peak oxygen uptake which is significantly correlated with endothelium-dependent vasodilation in patients with chronic heart failure (CHF) [35]. Exercise training for 4 weeks increases agonist induced endothelium-dependent vasodilatory capacity and average peak flow velocity (APV) of left internal mammary artery (LIMA) in patients with stable CAD, which is associated with endothelial NO synthase (eNOS) and AKT phosphorylation [36]. A cross-sectional study demonstrates that regular aerobic exercise could avert the age-associated loss of endothelium-dependent vasodilation and regain levels similar to young adults, indicating that regular aerobic exercise could decrease the risk of cardiovascular disease for middle aged population [37].

Acute exercise training on a drum exerciser promotes receptor-mediated vasodilation responses, at least partially via regulating the number or affinity of endothelial receptors [38]. Eight weeks of exercise training exerted beneficial effect on both flow-mediated dilation (FMD) and exercise capacity, without relation to oxidative stress, inflammation or endothelial progenitor cells, which might be the underlying mechanism for the protective role of exercise on cardiovascular [39]. The mechanisms underlying vascular remodeling in response to exercise and/or muscle contractions included up-regulation of angiogenic processes, interactions between potent growth factors and with their receptors, and key tissue reorganization processes that were coordinated to affect vascular remodeling [40].

The protective effect of exercise on collateral circulation following ischemic cardiovascular diseases

Therapeutic promotion of collateral vessel development and/or functional improvements in collateral and collateral-dependent arteries to decrease resistance into the ischemic myocardium represent a desirable goal in the treatment of coronary artery disease. Substantial evidence demonstrates the therapeutic effect of exercise training programs on patients with coronary artery disease (and collateralization). The mechanisms of such therapeutic effects are numerous and multifaceted, and at present under investigation in many laboratories worldwide [41]. Three months of endurance exercise training increases coronary collateral supply to unaffected blood vessels, and even to the previously stenotic arteries following percutaneous coronary intervention before participating in the program. Meanwhile, there seems to be a dose dependent relationship between coronary collateral flow promotion and exercise capacity promotion [42].

For animal studies, the evolution from chronic coronary artery stenosis to occlusion advances the formation of the collateral circulation which developed mainly in or surrounding the ischemic zone in myocardial ischemia in pigs, and exercise training promotes the development of the collateral circulation [43]. Sixteen weeks of exercise training promotes the total vascular bedcross-sectional area by 37%. Capillary density promotes at 3 wk and then goes back to control levels at 16 wk while the amount of arterioles (20-30 microgram) promotes at 16 wk. It was speculated that the "extra" capillaries at 3 wk were transforms to new arterioles at 16 wk [44]. Five weeks exercise following gradual LCx coronary artery occlusion in pigs significantly improves systolic wall thickening and increases transmural myocardial blood flow in the LCx region, indicating that long-term exercise could promote myocardial function and improved coronary collateral reserve in pigs after gradual LCx coronary artery occlusion [45].

The involved factors underlying the protective effect of exercise on ischemic cardiovascular diseases

The protective effect of exercise on schemic cardiovascular diseases via VEGF: Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis, and the accomodation of angiogenesis to meet the demand of the tissue relies on the regulation of VEGF production by changing the stability of its mRNA and rate of transcription [46].

For animal studies, exercise may enhance the circulating levels of vascular endothelial growth factor (VEGF), which is very important to angiogenesis [47]. Both exercise training and intramuscular administration of VEGF promotes angiogenesis in rat heart. Moreover, exercise alone also up-regulates angiogenesis obviously [48]. Three days of treadmill exercise enhances the expression level of VEGF and its receptors in mice with MI compared to control group. Furthermore, exercise training prior to myocarial infarction (MI) up-regulates both mRNA and protein levels of VEGF following MI, decreasing infarct size and improving angiogenesis [49].

For human studies, four weeks exercise training (ET) is proved to improve circulating progenitor cell integration into endothelial networks, and ischemic ET promoted expression levels of vascular endothelial growth factor (VEGF), CXC chemokine receptor 4 (CXCR4) and circulating progenitor cells, thus improving regional perfusion in ischemic syndromes [50]. Eight weeks of exercise training increases the peripheral exercise capacity and citrate synthase activity, as well as VEGF at both the protein and mRNA levels in skeletal muscle biopsies, indicating that VEGF might be one probable mediator of exercise-induced angiogenesis and regulate an early and important step in accommodation to enhanced muscle activity of patient with chronic heart failure [51]. Supervised aerobic training (SAT) promotes EPC levels as well as plasma stromal cell-derived factor (SDF)-1 and vascular endothelial growth factor (VEGF) levels, which is beneficial to the patients with heart disease. However, discontinued supervised aerobic training (DSTA) could not maintain the exercise induced VEGF/SDF-1-associated EPC levels and clonogenic potential [52].

The protective effect of exercise on schemic cardiovascular diseases via other factors

The experimental animal studies demonstrates that regular exercise training could defend the heart against the ischemia-reperfusion (IR) injury by exercise preconditioning. Currently, the specific mechanisms of exercise training-induced cardioprotection are still not very clear. The possible factors involved in exercise cardioprotection are numerous, including collateral circulation development, enhanced ER stress proteins, up-regulated COX-2 activity, promoted heat shock protein (HSP-72) levels, strenthened activity of mitoK-ATP and sarcoK-ATP channels, and improved myocardial antioxidative capacity [53].

For human studies, bone marrow derived endothelial progenitor cells (EPC) participates in the growth and repair of blood vessels. A bout of muscular endurance resistance exercise which is composed of three times of six exercises at participants' 15-repetition maximum without resting significantly increases circulating EPC and serum concentrations of matrix metalloproteinases (MMP-1, MMP-2, MMP-3 and MMP-9), granulocyte colony stimulating factor, soluble Tie-2, soluble fms-like tyrosine kinase-1, and vascular endothelial growth factors (VEGF-A, VEGF-C, and VEGF-D), probably play-

ing a key role in vascular adaptation and vasculoprotection [54]. Circulating progenitor cells (CPCs) increases organ perfusion and improves cardiovascular function by strengthening the capacities of neovasculogenesis and endothelial repair. The hypoxic training (HT) could increase the proliferative capacity of these CPCs subsets, and promote concentrations of plasma nitrite/nitrate, vascular endothelial growth factor-A (VEGF-A), matrix metalloproteinase-9 (MMP-9) and stromal cell-derived factor-1 (SDF-1), indicating that HT regimen promotes cardiac and muscular hemodynamic adaptations, possibly via increasing the mobilization/function of CPCs and promoting the production of angiogenic factors [55]. Twelve weeks of supervised running training remarkably promotes the level of circulating EPCs, which is positively related with the change of flow-mediated dilation (FMD) and raise of degradation products of the NO pathway (NOx), indicating that the beneficial effect of exercise on patients with cardiovascular risk factors (CVRF) and coronary artery disease (CAD) is associated with improvement of vascular function and NO synthesis [56]. Eight weeks resistance exercise has positive influences on the concentration of blood myokines and a series of angiogenesis factors, including interleukin (IL)-6, IL-8, IL-15, vascular endothelial growth factor (VEGF) and angiopoietin (Ang) 1 [57]. Four weeks of exercise training improves acetylcholine mediated endothelium-dependent vasodilatation in coronary artery disease (CAD), which might be partially due to the regulation of the endothelial response to VEGF and erythropoietin (EPO) [58].

Conclusion

The investigation on the mechanisms of protective effect induced by physical exercise may initiate the research on new strategies to alleviate brain and heart damage after cardiovascular and cerebrovascular diseases. The knowledge of the explicit mechanisms by which physical exercise training can increase brain and heart tolerance may encourage patients with high risk factors of cardiovascular and cerebrovascular diseases to energetically take part in appropriate exercise programs.

Acknwoledgements

The present study was supported by the National Natural Science Foundation of China (No. 81201512).

Disclosure of conflict of interest

None.

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