Mini Review (Part I): An Experimental Concept on Exercise and Ischemic Conditioning in Stroke Rehabilitation

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Abstract:
Stroke remains a leading cause of adult death and disability. Poststroke rehabilitation is vital for reducing the long-term sequelae of brain ischemia. Recently, physical exercise training has been well established as an effective rehabilitation tool, but its efficacy depends on exercise parameters and the patient’s capacities, which are often altered following a major cerebrovascular event. Thus, ischemic conditioning as a rehabilitation intervention was considered an "exercise equivalent," but the investigation is still in its relative infancy. In this mini-review, we discuss the potential for physical exercise or ischemic conditioning and its relation to angiogenesis, neurogenesis, and plasticity in stroke rehabilitation. This allows the readers to understand the context of the research and the application of ischemic conditioning in poststroke rehabilitation.

Keywords:
Ischemic conditioning, physical exercise, stroke rehabilitation

Introduction
Stroke is a leading cause of adult death and disability worldwide.¹,² Consequently, it is vital to improve the quality of life and functional prognosis of stroke victims. Stroke rehabilitation is the medical specialty that integrates a variety of techniques to maximize patient recovery following a stroke.³,⁴ Recent research indicates that increases in angiogenesis, neurogenesis, and plasticity such as synaptogenesis, dendrite remodeling, and axonal reorganization occur during the recovery phase after a stroke.⁵‑⁷ Modulating and optimizing these processes of the recovery phase can minimize functional loss and enhance rehabilitation in patients who have experienced stroke. Physical exercise is a behavioral intervention that is known to enhance stroke rehabilitation through biochemical mechanisms.⁸⁻¹⁰ However, the benefits of physical exercise are variable and are highly dependent on the patient’s abilities, which can be limited by the early complications of a stroke. Moreover, ischemic conditioning has been proposed as an accessible therapy that could confer the benefits of exercise with minimal dependence on these limitations.⁶ Both of these nonpharmacological techniques for rehabilitation are low cost and noninvasive, and therefore merit to have their benefits explored in great depth. This mini-review intends to discuss the potential for physical exercise or ischemic conditioning and its relation to angiogenesis, neurogenesis, and plasticity in stroke rehabilitation, as well as elucidate the potential for clinical application.

Effect of Physical Exercise on Neurorehabilitation
Neurorehabilitation
Physical exercise can play a major nonpharmacological role in the rehabilitation

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of the poststroke patient, as it can protect against plasticity impairments caused by the stroke as well as stimulate angiogenesis and neurogenesis. Ding lab reported that motor training, particularly motor skill training involving balance and coordination, facilitates a uniquely lateralized synaptogenesis in the thalamus. Analogously, involuntary, voluntary, and forced exercises induced high expressions of postsynaptic density 95 (PSD-95), synapsin I (SYN), microtubule-associated protein 2 (MAP-2), and Tau, thereby reducing the loss of dendrons and neurons in the hippocampus after stroke and improving cognition. In the molecular events, ischemic postconditioning was found to restore voltage-dependent anion channel (VDACs) to protect against mitochondrial damage. In the clinical setting, the efficacy of physical exercise rehabilitation is dependent on other variables, such as temporal measures and the types of training strategies employed. For example, global indices of disability have shown a tendency to improve after cardiorespiratory training, which may be mediated by improved mobility and balance, whereas interventions that employ resistance training have less reliably shown benefits. 

Consequently, the volume, intensity, and exercise session frequency as well as initiation time must be optimized. Our study recently suggested that the beneficial effect of intense exercise was not superior than its milder counterpart, thus mild exercise may be adequate and sufficient to elicit neurorehabilitation poststroke. Our previous study underlined that too early poststroke exercise increased cell stress and expression of pro-inflammatory cytokines, which amplified tissue damage, and suggests that exercise interventions between 24 h and 3 days may optimize rehabilitation benefit. In addition, Yágita et al. suggested that running as a form of exercise may be too intense and cause spikes in endogenous corticosteroid levels that limit poststroke neurogenesis. Moreover, complex and variable poststroke disability could limit patients' participation. The amenability of patients to poststroke physical activity may vary in relation to age, motivation, and other factors, and may be significantly affected by the level of disability conferred from the cerebrovascular accident. These differences within the patient population could limit efforts to standardize and optimize care for these patients. For example, patients with anterior cerebral artery infarcts may lose the ability to ambulate, whereas those with middle cerebral artery infarcts may be unable to move the upper limbs. As such, different exercise protocols must be explored to accommodate patients based on the type and extent of injury. Moreover, recent clinical trials do not show consistent rehabilitative benefits in stroke patients undergoing early physical exercise. Therefore, an alternative intervention known as ischemic conditioning, which confers similar neuroplastic benefits with fewer interuser particularities, is of interest to our group.

Ischemic Conditioning and Neurorehabilitation

Neuroprotection

Recently, ischemic conditioning has emerged as a noninvasive and low-cost therapy for victims of cerebrovascular accidents. By way of controlled and transient periods of subcritical ischemia to nonvital arteries, it works to activate endogenous tissue repair mechanisms to exert neuroprotective effects, cardiovascular protection, and promote neurological recovery. Ji lab reported that repetitive bilateral arm ischemic preconditioning (BAIPC) safely inhibited stroke recurrence and enhanced tolerance of cerebral ischemia, by improving cerebral perfusion and attenuating inflammation and coagulation in patients with symptomatic intracranial arterial stenosis for all ages. In the molecular events, ischemic postconditioning was found to restore voltage-dependent anion channel proteins (VDACs) to protect against mitochondrial damage. Brain ischemic preconditioning was demonstrated to protect blood–brain barrier against ischemic injury by activation of the nuclear
Neuroplasticity

Rehabilitation

Figure 1: Physical exercise and ischemic conditioning favorably decrease brain damage and stimulate synaptogenesis, angiogenesis, and neurogenesis to enhance neuroplasticity, which promotes poststroke rehabilitation. Some underlying mechanisms of exercise and ischemic conditioning have been evidenced to overlap – both therapies demonstrate regulation of the immune and inflammatory system and upregulated the expression of SYN1, PSD95, growth-associated protein 43, and brain-derived neurotrophic factor (erythroid-derived 2)-like 2 (Nrf2) pathway. Esposito et al. have found that ischemic conditioning significantly reduced infarction, improved neurological outcomes, and involved the promotion of neurogenesis and angiogenic remodeling during the recovery phase after focal cerebral ischemia. The combination of early and delayed ischemic postconditioning may activate ERK1/2 and CREB and induce the production of BDNF in neurons and astrocytes lead to long-term potentiation and neurogenesis, which highlights the neuroprotective potential of these therapies. Likewise, Ramagiri indicated that remote ischemic postconditioning (RIPostC) alleviated cerebral ischemic-reperfusion injury and exerted neuroprotective effects through the GSK-3β/CREB/BDNF pathway, which is known to be involved in cell survival and metabolism during stress. RIPostC promoted cognition mediated by endothelial nitric oxide synthase (eNOS)-dependent augmentation of angiogenesis. Furthermore, ischemic conditioning after stroke upregulated the expression of SYN1, PSD95, and GAP43, which are also key players in the context of exercise therapy, and promoted neuroprotection and plasticity. Doeppner et al. found that ischemic conditioning enhanced neurological recovery and neuronal survival in response to neural precursor cell transplantation, which could stimulate brain plasticity. Similarly, astrocytes play an important role in developmental synaptogenesis and blood–brain barrier modulation and RIPostC could regulate its activity and inhibit STAT3 phosphorylation to promote neurological function recovery. Moreover, it was proposed that ischemic conditioning could stimulate arteriogenesis and enhance cerebral blood flow by increasing expressions of Notch1 and Notch intracellular domain (NICD) in the ischemic brain. Arteriogenesis plays a vital role in regulating vascular recovery of neurological function.

Neurorehabilitation and plasticity

Recent studies demonstrate that ischemic conditioning may induce neurorehabilitation through similar mechanisms as physical exercise. In contrast to physical therapy, the passive nature of ischemic conditioning allows less dependence on the patient’s motivation and level of physical activity and is not limited by poststroke disability. In addition, it is less likely to be harmful or present risk to the patient. The investigation of ischemic conditioning as a therapy for stroke recovery is still in its relative infancy, especially when compared to that of its cardioprotective effects. The patients of noncardiac ischemic stroke received RIPostC were demonstrated to improve significantly in cognitive domains, such as visuospatial and executive functioning and attention 6 months poststroke. Pilot studies showed that ischemic conditioning increased the paretic leg strength and muscle activation and improved self-selected walking speed of chronic stroke survivors. Doeppner et al. showed that very delayed RIPostC started on day 5 after stroke induction stimulated angioneurogenesis and reversed immunosuppression occur to induce sustained neurological recovery. Vaibhav et al. found that RIPostC mediated neurological recovery after ICH through AMPK-dependent immune
During the recovery phase, RPostC increased a pro-inflammatory CCR2 + monocyte subset to improve outcomes.\cite{64} Taken together, ischemic conditioning was considered an “exercise equivalent” as a rehabilitation intervention. However, a plethora of questions remains regarding ischemic conditioning in the setting of stroke rehabilitation. Since the clinical research of ischemic therapy is still in its infancy, investigation efforts are not standardized in the precise methods in which they deliver the therapy or monitor results. They vary by the type of vessel occluded and the duration and frequency of therapy. Future directions are essential to optimize these parameters to maximize poststroke cerebral angiogenesis and neurogenesis and should also consider how treatment will vary with the individuality of the patient.

**Conclusion and Prospective**

Based on current research, physical exercise and ischemic conditioning favorably induce neuroprotection to decrease brain damage after stroke, as well as stimulate neuroplasticity, angiogenesis, and neurogenesis, which is conducive to poststroke rehabilitation [Figure 1]. More research is required to investigate the precise benefits and application of poststroke exercise therapy, especially in the context of patient individualities. However, compared to physical exercise, a paucity of data exists regarding the efficacy and underlying cellular mechanism of ischemic conditioning in poststroke rehabilitation. A larger number of well-organized animal and in vitro experiments are needed to further compare the efficacy of physical exercise and ischemic conditioning to discuss if ischemic conditioning could be an adequate substitute for physical exercise in stroke patients. Moreover, it is necessary to establish long-term and large preclinical and clinical trials with sufficient sample sizes and multidisciplinary research to further explore the optimal parameters of physical exercise and ischemic conditioning and to avoid undesirable effects.

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**Conflicts of interest**

There are no conflicts of interest.

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