Timing is everything: Exercise therapy and remote ischemic conditioning for acute ischemic stroke patients

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Abstract:
Physical exercise is a promising rehabilitative strategy for acute ischemic stroke. Preclinical trials suggest that exercise restores cerebral blood circulation and re-establishes the blood–brain barrier’s integrity with neurological function and motor skill improvement. Clinical trials demonstrated that exercise improves prognosis and decreases complications after ischemic events. Due to these encouraging findings, early exercise rehabilitation has been quickly adopted into stroke rehabilitation guidelines. Unfortunately, preclinical trials have failed to warn us of an adverse effect. Trials with very early exercise rehabilitation (within 24 h of ischemic attack) found an inferior prognosis at 3 months. It was not immediately clear as to why exercise was detrimental when performed very early while it was ameliorative just a few short days later. This review aimed to explore the potential mechanisms of harm seen in very early exercise administered to acute ischemic stroke patients. To begin, the mechanisms of exercise’s benefit were transposed onto the current understanding of acute ischemic stroke’s pathogenesis, specifically during the acute and subacute phases. Then, exercise rehabilitation’s mechanisms were compared to that of remote ischemic conditioning (RIC). This comparison may reveal how RIC may be providing clinical benefit during the acute phase of ischemic stroke when exercise proved to be harmful.

Keywords:
Acute stroke, autoregulation, dysautoregulation, neuroprotection, stroke rehabilitation, subacute stroke

Introduction

Stroke is a leading cause of mortality and morbidity worldwide.¹² As life expectancy around the world increases, the global lifetime risk of stroke has also increased.³ Of the various categories of strokes that plague the elderly, acute ischemic stroke comprises the largest portion.⁴ And yet, treatment of acute ischemic stroke is currently limited to thrombolysis and, for a limited few, clot retrieval.⁵ Despite improvements in recanalization rates and broadening of treatment eligibility criteria,⁶ the rate of disability among survivors remains at a staggering rate of 50%.⁷ Development of new treatment modalities with broad indications is necessary to relieve the tremendous disease burden of acute ischemic stroke.

Physical exercise is a promising rehabilitative strategy for acute ischemic stroke patients. Preclinical trials suggest that exercise rehabilitation can help to restore cerebral blood circulation⁸⁹ and re-establish the blood–brain barrier’s integrity¹⁰ with improvements of neurological functions¹¹¹² and motor skills.¹³ Clinical trials have demonstrated that exercise improves prognosis, decreases complications after ischemic events¹⁴ and improves motor function.¹⁵ Due to these encouraging findings, early exercise rehabilitation has been quickly adopted into stroke rehabilitation guidelines¹⁶. Unfortunately, preclinical trials have failed to warn us of an adverse effect. Trials that started very early exercise rehabilitation (i.e. within
It is currently being used for ischemia resulting from alteration of blood flow. Ischemia resulting in the acute phase of stroke is precipitated primarily by time frames of hours to days, and weeks to months, respectively. The pathogenesis of acute ischemic stroke has been described extensively by Kurisu and Yenari. They divide the pathogenesis of acute ischemic stroke into three phases: acute, subacute, and chronic. The time frames for these phases are minutes to hours, hours to days, and weeks to months, respectively. The acute phase of stroke is precipitated primarily due to alteration of blood flow. Ischemia resulting from an embolus, thrombus, or severe hypotension initiates a cascade of metabolic disequilibrium. Energy storing capacity quickly becomes impaired, leaving the neuron to depend on anaerobic respiration, a considerably inefficient method of ATP generation compared to oxidative phosphorylation. Anaerobic respiration generates lactic acid and inevitably acidosis. Inadequate ATP stores lead to cellular ion pump failure and loss of ion gradients across the membrane; these result in receptor activation from significant calcium influx and membrane insufficiency from hyperemia. The combination of cellular excitotoxicity from receptor activation and mitochondrial failure from membrane insufficiency ultimately ends with neuronal death.

The subacute phase relies on slower molecular signaling pathways for its tale of neuronal apoptosis to unfold. Its fate is determined by an interplay between proapoptotic and antiapoptotic molecules. Apoptosis can be divided into intrinsic and extrinsic pathways. The intrinsic pathway involves proapoptotic molecules of BCL-2-associated X (BAX), protein kinase Cδ, and cytochrome C, which are antagonized by antiapoptotic molecules, such as BCL-2 and PKCe. The extrinsic pathway involves the proapoptotic signaling pathway initiated by FAS-ligand-induced FAS activation. Both pathways ultimately end with caspase activation and subsequent apoptosis.

In summary, as depicted by Figure 1, the acute phase of stroke is progressed by the immediate consequences of interruptions to circulation within minutes to hours of the onset. The subacute phase of stroke counts on molecular cascades and marker expressions that are induced within hours to days. Exercise therapy should have underlying physiological mechanisms affected by time frames of acute and subacute phases of stroke. Understanding the mechanisms could help elucidate how the intended clinical amelioration occurs and how in other times they cause unintended harm instead.
Therapies and Subacute Phase of Stroke

Exercise and remote ischemic conditioning
As mentioned in the introduction, exercise rehabilitation has demonstrated its ameliorative effects in stroke patients by improving neurological function and outcomes, granted that it is not prescribed within 24 h of the ischemic event. Exercise helps to maintain the blood–brain barrier and prevent neuronal death, which supports the associated observations of mitigated neurological impairment and memory loss.

RIC is a lesser-known method of postischemic stroke conditioning. RIC is based on an intrinsic process, named ischemic preconditioning, in which ischemia of short duration protects internal organs against subsequent ischemia. Ischemic preconditioning can be experimentally induced with a blood pressure cuff that creates a transient blood flow blockage at a distal limb. This procedure instigates endogenously protective effects on important internal organs from lethal ischemic damage. RIC has also been induced through hypobaric and normobaric chambers. This treatment method has been used for protection after myocardial infarction, during carotid artery stent placements, prophylactically for SIAS, global cerebral ischemia, and subcortical ischemic vascular dementia. RIC has been reported to improve outcomes in chronic stroke as well.

Exercise has been found to have very similar neuroprotective effects of RIC as it pertains to the subacute phase of acute ischemic stroke. It supports neuroprotection and regeneration by enhancing angiogenesis, cerebral perfusion, cerebral collateral formation, and cerebral ischemia tolerance. Further neuroprotection is established by reducing nerve injury, promoting nerve remodeling, and restoring function of paralyzed limbs.

Therapies and mechanism of amelioration in the subacute phase
Hunted by their similar neuroprotective effects, it has been found that exercise and RIC have many overlaps in their ameliorative mechanism of action during the subacute phase of acute ischemic stroke. Exercise and RIC protect brain tissue against injury by preventing apoptosis, modulating neuroplasticity regulation, and securing resources through angiogenesis.

Apoptosis, as described above, is regulated through a fine balance between the pro and antiapoptotic pathways. Apoptosis is prevented through Bcl-2 interacting-domain death agonist inhibition by RIC and exercise. Increases in the Bcl-2/Bax ratio are favorable for neuron survival and are upregulated by RIC and exercise. ROS causes apoptosis through oxidative stress. Exercise decreases oxidative stress by increasing catalase and glutathione peroxidase. RIC also increases antioxidant activity through glutathione, catalase, and SOD. NO scavenges ROS to prevent apoptosis, exercise, and RIC increase NO production.

Neuroplasticity can be assessed with many molecular markers. Synaptogenesis plays a critical role in neuroplasticity and can be measured with synaptophysin (SYN), a marker of synaptic plasticity in cerebral ischemia and damage. Interestingly, SYN is increased by ischemic preconditioning and exercise. In addition, neuroplasticity is regulated by CAM response element-binding protein (CREB), brain-derived neurotrophic factor (BDNF), and tropomyosin receptor kinase B (TrkB), which act in coordination. Ischemic preconditioning and exercise increase CREB as well as BDNF.

CREB supports neurogenesis by encouraging functional recovery and increases circuit plasticity after stroke. It also activates antioxidants and antiapoptotic proteins to augment cell survival. The presence of BDNF indicates neuronal survival and synaptic plasticity; BDNF works with TrkB to trigger an intracellular signaling cascade to mediate neuronal survival and differentiation, angiogenesis, and neuroplasticity.

HIF-1α is a marker that is upregulated in hypoxic conditions and helps to mediate hypoxia by inducing vascular endothelial growth factor (VEGF), erythropoietin (EPO), and the respective receptors. Through downstream effects of VEGF and EPO induction, HIF-1α ensures O2 supplies to the brain. VEGF accelerates cognitive rehabilitation.

Figure 2: Subacute phase of stroke and the mechanism of exercise rehabilitation and remote ischemic conditioning
Cerebral autoregulation in the acute phase of ischemic stroke

Tissue death and injury in the acute phase of ischemic stroke are precipitated by inadequate blood supply due to a thrombus, emboli, or severe hypotension. In a healthy individual, perfusion of the cerebrum is supplemented by cerebral autoregulation through myogenic, neurogenic, metabolic, and endothelial mechanisms. However, cerebral blood perfusion can still be insufficient following reperfusion. Various injuries to the head, such as traumatic brain injury, hemorrhagic stroke, and ischemic stroke, can lead to autoregulation impairment, known as cerebral dys-autoregulation. Inability to control blood flow to the brain may lead to both hypo and hyperperfusion. Cerebral dys-autoregulation results in hemorrhagic transformation and cerebral edema, which are often associated with a poor prognosis. The mechanism of these complications is hyperreperfusion, in which dys-autoregulation permits low vascular resistance and high blood flow velocity to the brain. Studies have stressed the importance of maintaining cerebral autoregulation, which is associated with less atrophy and better neurological function in chronic ischemic infarctions. At times, dys-autoregulation has been found to spread to the contralateral side of the injury as well, which was unsurprisingly associated with poor outcomes.

Clinical studies have found that vascular recanalization helps to preserve the function of autoregulation, but the extent of its preservation is not well understood and requires more investigation. Interestingly, animal studies have found rt-PA to cause dys-autoregulation. Ma et al. discuss in their clinical trial that the superior autoregulation in the recanalized population may be because the patients with milder ischemia were eligible for the recanalization treatment, acting as a confounding variable. Furthermore, cerebral dys-autoregulation has been observed from as early as 22 h to as late as 6 months following an ischemic event, making it relevant to our discussion.

Exercise and dys-autoregulation

Exercise induces changes to the hemodynamics of blood flow in the body. For instance, as skeletal muscles demand greater blood flow, other organs compete to maintain their critical perfusion levels to avoid ischemic damage. To supply both sides of the competition, heart rate and stroke volume increase to boost the overall cardiac output. Normal cardiac output is around 5 L/min for a resting adult human. With exercise, it can go up to 20 L/min for an average adult or to 40 L/min for athletes. Organs that are not directly involved in exercise, such as the kidneys and liver, have their blood flow redirected to skeletal and cardiac muscle tissue, decreasing their perfusion to ~25% of the flow at rest. The exception to this compensatory mechanism is the brain in a healthy individual, which maintains the same blood flow of 0.75 L/min both at rest and exercise. In addition to the changes to the blood flow during exercise, the chemical composition of blood changes due to the increased metabolism in muscle tissues. Cerebral autoregulation must take these chemical changes into account in addition to the changes of the cardiac output to ensure consistent blood flow to the brain – the mechanism of which has been reviewed by Smith and Ainslie.

Patients in the acute phase of ischemic stroke are unable to regulate cerebral blood flow during exercise because of cerebral dys-autoregulation. Brain tissues of patients with acute stroke can be overstressed by the changes of the cerebral blood flow’s hemodynamics, intracranial pressure, and intra- and extracellular chemistry while undergoing exercise rehabilitation. The brain can be hyperperfused or hypoperfused, depending on the specific regimen of the exercise and posture of the patient. Exercise during the acute phase of ischemic stroke may worsen prognosis by tempering blood supply to the brain during its vulnerable moments of dys-autoregulation [Figure 3].

Remote ischemic conditioning in the acute phase of ischemic stroke

Those who are unfamiliar with RIC may express concerns for potential damage to the ischemic site and consequent cardiopulmonary response, which may potentially worsen cerebral perfusion. It has been reported that up
to 3 h of remote ischemia will not cause muscle damage to the ischemic site, \(^{[95]}\) and concern for reperfusion damage is only necessary from 1 h of ischemia onward. \(^{[96]}\) Because RIC protocols in ischemic tissue amelioration typically induce ischemia for only minutes at a time, ischemic tissue damage is not significant.

RIC has been demonstrated to be safe in a variety of contexts. As a preconditioning method, it has proven its safety and efficacy in pulmonary dysfunction \(^{[97]}\) without damage to remote organs. \(^{[98]}\) As a postconditioning method, its usage has been proven for spinal cord ischemia \(^{[99]}\) and vascular endothelial dysfunction. \(^{[100]}\) Finally, RIC is safe in acute ischemic stroke \(^{[101]}\) as well as other cranial injuries, such as intracranial atherosclerosis, \(^{[102]}\) carotid stenting, endarterectomy, \(^{[24]}\) cerebral small vessel disease, \(^{[103]}\) and aneurysm subarachnoid hemorrhage. \(^{[24]}\)

As further reassurance, RIC in acute ischemic stroke has shown its efficacy with stable blood pressure, heart rate, intracranial pressure, cranial perfusion pressure, and peak velocity of middle cerebral artery. \(^{[103]}\) Despite the brain’s inability to autoregulate in the context of acute ischemic stroke, the cerebral perfusion remains intact as RIC does not disturb the body’s circulatory dynamics. Stable cerebral perfusion is an important advantage of RIC because it does not occur with exercise rehabilitation. If the deleterious effects of exercise in the acute phase of stroke are primarily due to the instability of cerebral blood flow, RIC can be an excellent adjunct therapy. Exercise may not be able to induce clinical amelioration and prevent acute stroke damage within the first 24 h but RIC could [Figure 4].

**Additional considerations for exercise therapy**

Although this review has focused on dys‑autoregulation as a possible source of exercise’s detriment in the very early stages of acute ischemic stroke, the reality is likely more complex. Calcium overload \(^{[104]}\) and ATP depletion \(^{[105]}\) after exercise are clearly counterproductive to acute ischemic stroke therapy. Glutamate excitotoxicity is also a detrimental consequence of exercise to stroke patients; \(^{[106,107]}\) however, these were observed only in intense exercise; \(^{[108,109]}\) while mild exercise proved to decrease glutamate levels. \(^{[110‑112]}\) ROS production with exercise contributes to oxidative damage, \(^{[113,114]}\) but counterintuitively the same oxidative stress is seen to benefit patients with neurodegenerative diseases. \(^{[115]}\)

Moderate exercise decreases pro‑inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6 (IL-6), IL-1 beta (IL-1 \( \beta \)), and C-reactive protein, while intense exercise increased them. \(^{[116]}\) On a similar note, muscle damage increases both inflammation and white blood cell recruitment, \(^{[117]}\) which was believed to be only detrimental. However, recent evidence points to microglia/macrophage polarization, in which some populations contribute to the tissue damage, while others assist in clearing cellular debris and facilitate neuronal restoration. \(^{[118]}\)

As more research is conducted to better understand exercise’s role in acute ischemic stroke therapy, improved models of its interaction with the damaged and recovering brain are beneficial for discovering alternative treatment modalities and understanding stroke pathophysiology.

**Conclusion**

Although exercise has proven to be therapeutic for patients with acute ischemic stroke, it is harmful when implemented within 24 h of the ischemic event. RIC is another stroke therapy that is not used as widely. Exercise and RIC both induce ameliorative effects through similar mechanisms during the subacute phase of stroke, primarily through promoting neuroprotection, angiogenesis, and apoptosis inhibition. During the acute phase, tissue death and injury are caused by the ischemic event initiating a series of events consequent to lack of perfusion and ATP depletion. Injury during the acute phase may be aggravated by cerebral dys‑autoregulation, a phenomenon observable in many types of injuries to the cranium. Exercise perturbs the cardiovascular physiology, causing hyper or hypoperfusion of the brain during cerebral dys‑autoregulation. This combination may explain the reason for exercise’s deleterious effect during the first 24 h following the ischemic event. Meanwhile, RIC does not cause significant changes to the brain’s circulation during its dys‑autoregulation. Because RIC is therapeutic through the same mechanisms as exercise without causing harm, RIC may be the suitable candidate for stroke therapy during the first 24 h following an ischemic event, followed by exercise therapy several days afterward. Together, RIC and exercise therapy may induce additive, if not synergistic, amelioration for acute ischemic stroke patients.

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