

Access this article online

Quick Response Code:



Website:

<http://www.braincirculation.org>

DOI:

10.4103/bc.bc\_56\_21

# Mini-review (Part II): A clinical consideration on exercise and ischemic conditioning in stroke rehabilitation

Melissa Wills, Yuchuan Ding

## Abstract:

Exercise therapy is commonly recommended and is often considered to be the gold standard of rehabilitation in patients with ischemic stroke. However, implementation and standardization of exercise therapy are challenging as patients vary in their abilities, disabilities, and willingness to participate in exercise rehabilitation after a cerebrovascular event. Remote ischemic conditioning (RIC) is a more passive and accessible therapy that, although remains in its infancy, has the potential to confer similar neuroprotective effects as exercise. In the previously published Part I of this Mini Review, we examined the biochemical evidence for exercise and RIC and noted that the *in vitro* results may be misleading outside of the context of clinical application. In the present review, we investigate the various clinical parameters by which exercise and RIC therapy may be most beneficial to ischemic stroke victims. We also extend our discussion to consider the therapeutic combination of RIC and exercise therapy to maximize functional outcomes after stroke.

## Keywords:

Ischemic stroke, neurorehabilitation, remote ischemic conditioning

## Introduction

Stroke is one of the leading causes of death and the leading cause of disability worldwide.<sup>[1]</sup> Certain valuable efforts to minimize long-term damage from stroke have focused on therapies that enhance endogenous reperfusion mechanisms. For instance, exercise therapy is a well-accepted rehabilitative method in poststroke conditioning that has been shown to promote various neuroprotective mechanisms, such as neurogenesis, neuronal apoptosis inhibition, cerebral inflammation reduction, and blood-brain barrier maintenance.<sup>[2]</sup> These processes are not only vital for recovery from cerebral infarction but are also endogenous physiological responses to physical exercise, thus making exercise an attractive

rehabilitative option after stroke. Ischemic conditioning (IC) is another therapeutic approach for poststroke rehabilitation. In this technique, endogenous responses to sub-lethal ischemia, induced by cycles of limb occlusion, exert neuroprotection to the infarcted brain—much in the same fashion as the response to exercise. IC was initially devised in the context of cardioprotection and requires expanded attention in the field of stroke, particularly with *in-vivo* and clinical studies.<sup>[3]</sup>

In Part I of this Mini Review series, we discussed the mechanisms by which both exercise therapy and IC enhance neurogenesis, angiogenesis, and synaptogenesis after an ischemic stroke, thus facilitating rehabilitation and minimizing lasting disability.<sup>[4]</sup> There, we noted that the passive nature of IC lends itself to be particularly accessible to stroke survivors, who are often less amenable to

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Wills M, Ding Y. Mini-review (Part II): A clinical consideration on exercise and ischemic conditioning in stroke rehabilitation. *Brain Circ* 2021;7:225-9.

Department of  
Neurosurgery, Wayne  
State University School  
of Medicine, Detroit,  
Michigan, USA

### Address for correspondence:

Dr. Yuchuan Ding,  
Department of  
Neurosurgery, Wayne  
State University School of  
Medicine, 4160 John R.  
Street, Suite 930, Detroit,  
Michigan, USA.  
E-mail: yding@  
med.wayne.edu

Submission: 13-07-2021

Revised: 08-09-2021

Accepted: 17-09-2021

Published: 21-12-2021

exercise therapy, particularly during the time shortly after their cerebrovascular accident due to unstable medical status, new disabilities, or lack of motivation. Since exercise and IC have similar neurorehabilitative outcomes and overlapping mechanisms, the more accessible nature of IC beseeches greater investigation and full exploration of its therapeutic potential. Evidently, both therapies merit greater research into their clinical applications to maximize their clinical potential and ultimately standardize effective treatment for patients. The purpose of the present Part 2 of our Mini-Review is to examine recent evidence and recommendations in the clinical application of exercise and IC in ischemic stroke rehabilitation.

## Exercise and Neurorehabilitation

Exercise is widely recommended for the rehabilitation of stroke patients. In Part I of this Mini Review, we examined studies that illustrated the biochemical evidence by which exercise therapy is successful *in-vitro*. We now turn to investigate the ways in which these concepts are reflected in the clinical setting and the potential extent to which the benefits of exercise therapy depend on the parameters of its application. Indeed, there are various types, intensities, and regimens of exercise that must be evaluated and optimized in order for exercise therapy to be a reliable means to maximize poststroke rehabilitation. An important consideration for exercise therapy is that it is performed safely. Stroke survivors differ in their strength level and injury after stroke and therefore should be examined on an individual basis by a licensed medical professional to determine whether they can perform the various forms of exercise.

### Intensity of exercise

Low-intensity treadmill exercise has been shown to improve spatial, nonspatial, and negative reinforcement memory performance in rodents after brain ischemia to a greater extent than high-intensity treadmill exercise. These conclusions have been corroborated by concurrent findings that low-intensity exercise, but not high-intensity exercise, significantly reduced infarct volumes, increased hippocampal neuron density, and increased levels of BDNF, synapsin-I, and PSD-95, as well as LAP2 immunoreactivity, which are proteins known to be involved in synaptogenesis after stroke.<sup>[5,6]</sup> Together, these studies suggest that lower intensity exercise is more conducive to improvements in memory function after a stroke, possibly due to the alterations in infarct volume, neuron density, and proteins of neurogenesis within the hippocampus. The low-intensity exercise was also shown to improve mobility, quality of life, and muscle power in stroke patients to a greater extent than high-intensity exercise.<sup>[7]</sup> These conclusions could be beneficial to the community of stroke survivors, who may be more amenable to lower intensity exercise.

However, these findings are not unanimous. In patients with sub-acute stroke with mild cognitive impairments, those who underwent high-intensity exercise achieved significant improvements in processing speed and divided attention.<sup>[8]</sup> High-intensity treadmill training also led to greater improvements in gait ability, step length, and walking symmetry, enhanced  $\text{VO}_2$  peak, and reduced the cost of walking when compared to low-intensity treadmill training.<sup>[9]</sup> Other studies indicated that neither high intensity nor low intensity improved cognitive functions, and some did not detect differences when the parameter of intensity was adjusted.<sup>[10,11]</sup>

It is possible that high and low-intensity exercise have their respective strengths in terms of recovery after stroke and that both may be combined to create the optimal rehabilitative regimen. Additionally, the body of literature that has evaluated exercise intensity in stroke is broad and its various studies have examined this parameter with study subjects differing in the types of strokes, comorbidities, and disabilities. Substantial conclusions that are generalizable to the entire stroke community are therefore difficult to draw and further research is needed to evaluate exercise intensity as it pertains to these groups.

### Type of exercise

The type of exercise is another parameter that merits examination. Aerobic exercise is often employed in the context of cardioprotection but has also been vastly applied in the sphere of neuroprotection in stroke rehabilitation. Aerobic exercise was shown to improve global cognition, memory, and attention as assessed by the Addenbrooke's Cognitive Examination-Revised, Functional Independence Measure, event-related potentials (P300), Mini-Mental State Examination, and Montreal Cognitive Assessment (MoCA) in the poststroke patient.<sup>[12-14]</sup> Conversely, Kim and Yim investigated the effect of a multidisciplinary exercise regimen, which combined hand-grip training, a power web exerciser, Digi-Flex, and treadmill-based weight loading using a sandbag on cognitive outcomes in patients with chronic stroke. They found that the exercise group had significantly higher scores in the Korean version of the MoCA, Stroop test, Trail Making-B, Timed Up and Go, and 10-Meter Walk tests.<sup>[15]</sup> Furthermore, a study by Ordahan *et al.* examined the use of a balance trainer on balance, level of independence, and ambulation parameters in stroke patients and found that it could safely be used to positively impact balance and postural control.<sup>[16]</sup> These studies indicate that various forms of exercise are capable of enhancing poststroke cognition. This evidence, which supports the notion that several types of exercise can improve cognition in stroke patients, could allow stroke survivors to gain more autonomy and to have a tailored rehabilitation plan.

### Timing of exercise

Timing of therapy is another variable that has been examined as it relates to poststroke rehabilitation and there is rich literature surrounding the application of exercise therapy at the hyperacute, acute, and chronic stages of stroke.<sup>[17]</sup> A Very Early Rehabilitation Trial demonstrated that initiation of exercise training within 24 h of the stroke event— that is, during the hyperacute stage— exacerbated damages from stroke.<sup>[18]</sup> Another study using middle cerebral artery occlusion models of rats indicated that exclusive use of the affected forelimb immediately after focal ischemia was detrimental to sensorimotor function and that its early use led to greater comorbidities.<sup>[19]</sup> Taken together, these findings provide substantial evidence that exercise conducted too early may inhibit the initial physiologic response to stroke and therefore prevent the maximum regeneration of prestroke capacities. Conversely, a study conducted in rat models demonstrated that training reduced infarct size to the greatest extent when performed between 1 and 5 days of stroke onset, which provides insight into the earliest point at which exercise therapy can be safely initiated after stroke.<sup>[20]</sup> Moreover, exercise therapy in chronic stroke patients (>6 months after stroke) is reported to have a broad range of benefits, as it has been shown to improve balance, gait, and cognitive functioning.<sup>[15,21,22]</sup> The findings presented here indicate that exercise therapy introduced at least 24 h after stroke and into the chronic stage of rehabilitation is safe and effective.

### Ischemic Conditioning and Remote Ischemic Conditioning

IC has several strengths that lend it to be a valuable adjunct, and perhaps even worthy challenger, to exercise training. It is noninvasive, easy to use, and well-tolerated by patients. It can be applied to the patient passively, and, therefore, unlike exercise, its success is less contingent on the patient's mobility, disability, and level of motivation. There are very few situations in which IC is unsafe or otherwise not recommended— these include instances such as injury or severe peripheral vascular disease (PVD). In comparison to exercise IC also has fewer modifiable parameters for its application, the most pertinent of which is the timing of the therapy.

### Timing and safety

One study evaluated the effect of nearly immediate poststroke intervention with IC by employing remote ischemic therapy for patients with acute ischemic stroke as early as the prehospital setting. This practice was deemed to yield no adverse events and tissue diffusion analysis results after 3 months demonstrated a lower risk of infarction as well as overall neuroprotection.<sup>[23]</sup> Similarly, England *et al.* initiated

4 cycles of remote ischemic conditioning (RIC) within 24 h of ischemia in patients with acute ischemic stroke and indicated that RIC may improve neurological outcome and reduce ischemic event rate as evidenced by a significant improvement in NIHSS score and a trend to fewer vascular events by 90 days after stroke.<sup>[24]</sup>

The timeframe for effective IC can also predate the cerebrovascular event, as ischemic preconditioning has been shown to be effective. Ischemic preconditioning 24, 48, or 72 h before stroke reduced infarct volumes and led to better neurological outcomes.<sup>[25,26]</sup> Interestingly, the benefits of preconditioning are also observed in patients with PVD, and thus those who have chronic remote hypoperfusion of the distal limbs akin to remote IC. Indeed, these poststroke patients were found to have significantly more favorable outcomes at discharge, lower NIHSS scores, and lower mortality rates.<sup>[27,28]</sup> This finding is significant to stroke patients, who often have comorbidities like atherosclerosis, PVD, and hypertension.

Finally, very delayed IC has also been demonstrated to have considerable effects. IC administered 7 days after stroke significantly reduced long-term brain injury in rodents.<sup>[29]</sup> Similarly, a study found that daily RIC for 300 days in stroke patients was more effective in increasing the modified Rankin Scale score and improving the rate of recovery than the control group, indicating a potentially additive long-term effect of repeated therapy.<sup>[30]</sup>

The above findings suggest that IC has a broad temporal range for its application, as the study provides evidence of safe and effective rehabilitation before, in the hours following, and long after the cerebral ischemic event. Other studies have corroborated the findings that repeated RIC effectively and safely reduces the risk of recurrent stroke and support the hypothesis that the brain demonstrates remodeling that may protect against continued ischemia.<sup>[31-33]</sup>

### Rehabilitative benefits

Since the literature surrounding the clinical uses for IC in the context of stroke rehabilitation is still relatively sparse, it may also be apropos to discuss the scope of the benefits of IC that have been observed. Patients who underwent remote limb IC for either 6 months or 1 year had significantly higher total MoCA scores, and therefore fewer cognitive impairments, than their control counterparts.<sup>[32,34]</sup> Additionally, patients who underwent remote limb IC for 6 months were better able to accomplish their activities of daily living, which is a vital component of poststroke rehabilitation and a major indicator of the quality of life.<sup>[34]</sup> They also scored higher in various assessments of cognition, including

shorter P300 latencies, lower scores in poststroke cognitive impairment.<sup>[34]</sup> RCT performed shortly after ischemic stroke was also shown to significantly reduce 90-day NIHSS scores.<sup>[24,35]</sup> Evidently, the benefits of RIC in the stroke patient are broad and the evidence suggests that it can improve quality of life and reduce disability scores.

### Combining Both Therapies

The discussion of the strengths and weaknesses of exercise and RIC provokes the notion that they could be combined to produce an optimized combination therapy for poststroke patients. We previously examined the novel therapy of RIC with Exercise (RICE), in which RIC is initiated very soon after ischemic stroke and exercise at a later time, thus using appropriate temporal adjustments to maximize the therapeutic potential of both therapies.<sup>[36,37]</sup> Our research and original findings suggest that RICE may have additional benefits in contrast with RIC or exercise monotherapy in stimulating neuroplasticity, synaptogenesis, and angiogenesis after ischemic stroke. Furthermore, from a clinical perspective, the data suggests that RICE may be more successful in causing long-term functional improvements in sensorimotor, learning, and memory domains. Clearly, RICE may be a valid method to marry the strengths of exercise and remote ischemic therapy. However, this data is preliminary and more research into this therapy is needed to make definitive conclusions.

### Conclusion

Exercise is commonly accepted as a primary means of poststroke rehabilitation and its benefits are broad. We report here that various types and intensities of exercise conditioning can improve cognition and memory. However, the clinical application of exercise therapy is complicated by its dependence on patient activity and motivation level, which are often compromised after stroke. The use of exercise therapy also has temporal constraints that can render its application deleterious to clinical progress. IC has emerged in the sphere of ischemic stroke rehabilitation as a more passive option that is less physically taxing for the patient. The evidence surfaced in the present review suggests that IC has similar clinical benefits to exercise but that these can be achieved within a broader temporal window, including in the hours immediately following stroke. This is a valuable conclusion for the stroke community and suggests that a dual regimen using both therapies within their optimal time frame could be combined to maximize therapeutic potential, which we have previously named RICE. Our future studies will continue to examine the safety and clinical efficacy of combining IC and exercise therapy.

### Financial support and sponsorship

This work was partially supported by Merit Review Award (I01RX-001964-01) from the US Department of Veterans Affairs Rehabilitation R&D Service.

### Conflicts of interest

Dr. Yuchuan Ding is an Associate Editor of *Brain Circulation*. The article was subject to the journal's standard procedures, with peer review handled independently of this Editor and their research groups.

### References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al*. Heart disease and stroke statistics-2020 update: A report from the American heart association. *Circulation* 2020;141:e139-596.
2. Pianta S, Lee JY, Tuazon JP, Castelli V, Mantohac LM, Tajiri N, *et al*. A short bout of exercise prior to stroke improves functional outcomes by enhancing angiogenesis. *Neuromolecular Med* 2019;21:517-28.
3. Zhao W, Zhang J, Sadowsky MG, Meng R, Ding Y, Ji X. Remote ischaemic conditioning for preventing and treating ischaemic stroke. *Cochrane Database Syst Rev* 2018;7:CD012503.
4. Wang Q, Wills M, Han Z, Geng X, Ding Y. Mini review (Part I): An experimental concept on exercise and ischemic conditioning in stroke rehabilitation. *Brain Circ* 2020;6:242-7.
5. Shimada H, Hamakawa M, Ishida A, Tamakoshi K, Nakashima H, Ishida K. Low-speed treadmill running exercise improves memory function after transient middle cerebral artery occlusion in rats. *Behav Brain Res* 2013;243:21-7.
6. Shih PC, Yang YR, Wang RY. Effects of exercise intensity on spatial memory performance and hippocampal synaptic plasticity in transient brain ischemic rats. *PLoS One* 2013;8:e78163.
7. Lamberti N, Straudi S, Malagoni AM, Argirò M, Felisatti M, Nardini E, *et al*. Effects of low-intensity endurance and resistance training on mobility in chronic stroke survivors: A pilot randomized controlled study. *Eur J Phys Rehabil Med* 2017;53:228-39.
8. Pallesen H, Bjerck M, Pedersen AR, Nielsen JF, Evald L. The effects of high-intensity aerobic exercise on cognitive performance after stroke: A pilot randomised controlled trial. *J Cent Nerv Syst Dis* 2019;11:1179573519843493.
9. Munari D, Pedrinolla A, Smania N, Picelli A, Gandolfi M, Saltuari L, *et al*. High-intensity treadmill training improves gait ability, VO<sub>2</sub>peak and cost of walking in stroke survivors: Preliminary results of a pilot randomized controlled trial. *Eur J Phys Rehabil Med* 2018;54:408-18.
10. Tang A, Eng JJ, Krassioukov AV, Tsang TS, Liu-Ambrose T. High-and low-intensity exercise do not improve cognitive function after stroke: A randomized controlled trial. *J Rehabil Med* 2016;48:841-6.
11. Hogg S, Holzgraefe M, Drüge C, Hauschild F, Herrmann C, Obermann M, *et al*. High-intensity arm resistance training does not lead to better outcomes than low-intensity resistance training in patients after subacute stroke: A randomized controlled trial. *J Rehabil Med* 2020;52:jrm00067.
12. Nilsson L, Carlsson J, Danielsson A, Fugl-Meyer A, Hellström K, Kristensen L, *et al*. Walking training of patients with hemiparesis at an early stage after stroke: A comparison of walking training on a treadmill with body weight support and walking training on the ground. *Clin Rehabil* 2001;15:515-27.
13. Wang W, Sawada M, Noriyama Y, Arita K, Ota T, Sadamatsu M, *et al*. Tai Chi exercise versus rehabilitation for the elderly with cerebral vascular disorder: A single-blinded randomized controlled trial. *Psychogeriatrics* 2010;10:160-6.



14. El-Tamawy MS, Abd-Allah F, Ahmed SM, Darwish MH, Khalifa HA. Aerobic exercises enhance cognitive functions and brain derived neurotrophic factor in ischemic stroke patients. *NeuroRehabilitation* 2014;34:209-13.
15. Kim J, Yim J. Effects of an exercise protocol for improving handgrip strength and walking speed on cognitive function in patients with chronic stroke. *Med Sci Monit* 2017;23:5402-9.
16. Ordahan B, Karahan AY, Basaran A, Turkoglu G, Kucuksarac S, Cubukcu M, *et al.* Impact of exercises administered to stroke patients with balance trainer on rehabilitation results: A randomized controlled study. *Hippokratia* 2015;19:125-30.
17. Bernardo-Castro S, Sousa JA, Brás A, Cecília C, Rodrigues B, Almendra L, *et al.* Pathophysiology of blood-brain barrier permeability throughout the different stages of ischemic stroke and its implication on hemorrhagic transformation and recovery. *Front Neurol* 2020;11:594672.
18. AVERT Trial Collaboration Group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): A randomised controlled trial. *Lancet* 2015;386:46-55.
19. Bland ST, Schallert T, Strong R, Aronowski J, Grotta JC, Feeney DM. Early exclusive use of the affected forelimb after moderate transient focal ischemia in rats: Functional and anatomic outcome. *Stroke* 2000;31:1144-52.
20. Schmidt A, Wellmann J, Schilling M, Strecker JK, Sommer C, Schäbitz WR, *et al.* Meta-analysis of the efficacy of different training strategies in animal models of ischemic stroke. *Stroke* 2014;45:239-47.
21. van Duijnhoven HJ, Heeren A, Peters MA, Veerbeek JM, Kwakkel G, Geurts AC, *et al.* Effects of exercise therapy on balance capacity in chronic stroke: Systematic review and meta-analysis. *Stroke* 2016;47:2603-10.
22. Liu-Ambrose T, Eng JJ. Exercise training and recreational activities to promote executive functions in chronic stroke: A proof-of-concept study. *J Stroke Cerebrovasc Dis* 2015;24:130-7.
23. Hougaard KD, Hjort N, Zeidler D, Sørensen L, Nørgaard A, Hansen TM, *et al.* Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: A randomized trial. *Stroke* 2014;45:159-67.
24. England TJ, Hedstrom A, O'Sullivan S, Donnelly R, Barrett DA, Sarmad S, *et al.* RECAST (Remote ischemic conditioning after stroke trial): A pilot randomized placebo controlled phase II trial in acute ischemic stroke. *Stroke* 2017;48:1412-5.
25. Ren C, Gao X, Steinberg GK, Zhao H. Limb remote-preconditioning protects against focal ischemia in rats and contradicts the dogma of therapeutic time windows for preconditioning. *Neuroscience* 2008;151:1099-103.
26. Malhotra S, Naggar I, Stewart M, Rosenbaum DM. Neurogenic pathway mediated remote preconditioning protects the brain from transient focal ischemic injury. *Brain Res* 2011;1386:184-90.
27. Wills MA, Fortey RA. The shape of life: How much is written in stone? *Bioessays* 2000;22:1142-52.
28. Pirson FA, Hinsenveld WH, Staals J, de Ridder IR, van Zwam WH, Schreuder TH, *et al.* Peripheral artery disease in acute ischemic stroke patients treated with endovascular thrombectomy; results from the MR CLEAN registry. *Front Neurol* 2020;11:560300.
29. Doeppner TR, Zechmeister B, Kaltwasser B, Jin F, Zheng X, Majid A, *et al.* Very delayed remote ischemic post-conditioning induces sustained neurological recovery by mechanisms involving enhanced angioneurogenesis and peripheral immunosuppression reversal. *Front Cell Neurosci* 2018;12:383.
30. Meng R, Asmaro K, Meng L, Liu Y, Ma C, Xi C, *et al.* Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology* 2012;79:1853-61.
31. Landman TR, Schoon Y, Warlé MC, de Leeuw FE, Thijssen DH. Remote ischemic conditioning as an additional treatment for acute ischemic stroke. *Stroke* 2019;50:1934-9.
32. Wang Y, Meng R, Song H, Liu G, Hua Y, Cui D, *et al.* Remote ischemic conditioning may improve outcomes of patients with cerebral small-vessel disease. *Stroke* 2017;48:3064-72.
33. Meng R, Ding Y, Asmaro K, Brogan D, Meng L, Sui M, *et al.* Ischemic conditioning is safe and effective for octo-and nonagenarians in stroke prevention and treatment. *Neurotherapeutics* 2015;12:667-77.
34. Feng X, Huang L, Wang Z, Wang L, Du X, Wang Q, *et al.* Efficacy of remote limb ischemic conditioning on poststroke cognitive impairment. *J Integr Neurosci* 2019;18:377-85.
35. Zhao W, Li S, Ren C, Meng R, Jin K, Ji X. Remote ischemic conditioning for stroke: Clinical data, challenges, and future directions. *Ann Clin Transl Neurol* 2018;6:186-96.
36. Han Z, Zhao W, Lee H, Wills M, Tong Y, Cheng Z, *et al.* Rehabilitative strategy of remote ischemic conditioning with exercise (RICE) in patients with acute ischemic stroke: A randomized controlled study. *Front Neurol* 2021;12:654669.
37. Wang Q, Wills M, Li F, Geng X, Ding Y. Remote ischemic conditioning with exercise (RICE) promotes functional rehabilitation following ischemic stroke. *Neurol Res* 2021; Online Ahead of Print:1-10..