Beyond reperfusion: Enhancing endogenous restorative functions after an ischemic stroke

In a mere instant, an ischemic stroke can cause devastating and permanent consequences. The medical community is rife with efforts to prevent stroke, to recognize its ominous signs, and to intervene swiftly. However, endeavors to restore function and to prevent the sequelae of infarction beyond the scope of initial reperfusion are equally vital to a patient's recovery and prognosis. Exercise therapy and ischemic conditioning (IC) are two treatments that lead the vanguard of the long-term rehabilitative strategies.

In "Exercise and Ischemic Conditioning in Stroke Rehabilitation: Part I of a Mini Review on Experimental Concept," we considered the ways in which exercise therapy stimulates the endogenous processes necessary for recovery from ischemic insults. *In vitro*, exercise has been shown to promote the expression of proteins involved in angiogenesis, synaptogenesis, and neurogenesis.[1,2] Unsurprisingly therefore, exercise is recommended for patients in order to both restore various cognitive functions and to minimize the breadth of ischemic damage from stroke. However, many clinical parameters of exercise therapy, such as timing, type of exercise, and feasibility, are yet to be entirely optimized to achieve maximum therapeutic efficacy. By the way of illustration, while early poststroke mobilization is beneficial, doing so within 24 h of infarction has been shown to exacerbate ischemic brain damage through hyperglycolytic and pro-apoptotic mechanisms,[3-5] and the therapeutic window for safe exercise intervention may only begin 48 h after infarction.[6]

IC, a novel therapy by which patients receive cycles of subcritical ischemia, has been shown to reduce infarct volumes and help patients regain various cognitive and motor skills via similar physiologic mechanisms as exercise.[7,8] In contrast to exercise therapy, IC's passive nature enables benefit to a potentially broader clinical spectrum of patients, as it is essentially accessible to patients with any level of disability. Its practicality and straightforwardness also invite less uncertainty and more opportunity for standardization in its clinical application. Like its exercise counterpart, the timing of IC is under scrutiny. However, there is no evidence yet to suggest that very early intervention with IC is detrimental or unsafe for the stroke patient – it has even been employed as early as the acute prehospital setting to effectively enhance neuroprotection.[9] Based on the current body of evidence, we find it reasonable to suggest that IC could be used to bridge the temporal gap between the ischemic event and the initiation of exercise therapy, as a dynamic counterpart to exercise therapy, or even as prophylaxis to patients at risk of stroke.

Exercise therapy and IC have been established as catalysts of the body's inherent neuroplastic mechanisms in minimizing the consequences of ischemic stroke. However, supplementary research is needed to refine and standardize these therapeutic regimens, as well as to identify the ways in which their clinical application must be varied to accommodate differences in patient disability, motivation, and stroke subtype. In Part II of this Mini Review, we will explore the clinical outcomes of these highly accessible and affordable therapies and how each one can be optimized.

Melissa Wills, Yuchuan Ding

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

Address for correspondence:
Dr. Melissa Wills,
Wayne State University School of Medicine, Detroit, Michigan.
E-mail: melissa.wills2@med.wayne.edu

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Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_72_20

How to cite this article: Wills M, Ding Y. Beyond reperfusion: Enhancing endogenous restorative functions after an ischemic stroke. Brain Circ 2020;6:223-4.

Submission: 12-12-2020, Accepted: 14-12-2020, Published: 29-12-2020