Ischemic Preconditioning: The Long-Awaited Savior of Neuroprotection. Has It Arrived?

Magdy Selim¹ · Michael Wang^{2,3}

Published online: 16 June 2015

© The American Society for Experimental NeuroTherapeutics, Inc. 2015

Keywords Ischemic preconditioning · stroke · intracranial stenosis

Despite decades of research, a countless number of “neuroprotective” drugs that proved effective in animal models of stroke have failed in translational clinical trials for multiple reasons [1]. Yet, the search for the seemingly elusive neuroprotective strategy continued. Ischemic stroke is a leading cause of adult disability, and there is an unmet need to find effective neuroprotective strategies. One such strategy that has been gaining attention is ischemic tolerance and ischemic preconditioning.

The phenomenon of ischemic tolerance, where brief periods of cerebral ischemia confer tolerance to subsequent ischemic challenges in the brain, has been confirmed in various animal models of cerebral ischemia. However, induction of direct brain ischemia as an effort to protect the brain presents significant challenges in the clinical setting. Thus, significant

recent focus has turned to a specific form of tolerance: remote ischemic preconditioning (rIPC).

In rIPC, repeated cycles of temporary ischemia in a remote organ can activate protective pathways in other organs, including the brain. This strategy presents numerous advantages over direct ischemic preconditioning, as it can be accomplished through noninvasive means without specialized equipment—typically via repeated brief periods of arm or leg ischemia using a blood pressure cuff. The cellular signaling pathways that are activated following ischemic preconditioning include: 1) adenosine release and activation of adenosine A1 receptors; 2) inhibition of glutamate release and enhancement of gamma-aminobutyric acid release thus making neurons more resistant to the excitotoxic insult; 3) amelioration of oxidative damage following cerebral ischemia through increased antioxidant production and DNA repair capacity; 4) suppression of inflammation through stimulation of Toll-like receptors, which activate many proinflammatory pathways; and 5) prevention of mitochondria-dependent cell death pathways [2, 3].

Spurred by the relatively straightforward protocols for rIPC, efforts to translate this accumulating body of knowledge and evidence supporting rIPC as a neuroprotective strategy into the clinical setting are slowly rising. Small clinical studies are ongoing to test the role of rIPC in protecting the brain against delayed ischemic injury after subarachnoid hemorrhage [4]. Recently, the value of rIPC as an adjunct therapy to thrombolysis in patients with ischemic stroke was investigated in an open-label, blinded-outcome, proof-of-concept study. The paramedics administered rIPC in the prehospital setting to 443 Danish patients with suspected acute stroke. Transient ischemic attack was more frequent, and National Institutes of Health Stroke Scale score on admission was lower in the rIPC group compared with controls. The risk of tissue infarction as assessed by diffusion–perfusion magnetic

✉ Magdy Selim
mselim@bidmc.harvard.edu

¹ Department of Neurology – Stroke Division, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Palmer 127, Boston, MA 02215, USA

² Departments of Neurology and Physiology, University of Michigan, 7725 Med Sci II SPC5622, 1137 Catherine Street, Ann Arbor, MI 48109, USA

³ VA Ann Arbor Healthcare System, 2215 Fuller Road, Ann Arbor, MI 48105, USA

resonance imaging was also reduced in the rIPC group [5]. Another proof-of-concept study by Meng et al. [6] evaluated the protective effects of rIPC in 88 Chinese patients younger than 80 years of age with symptomatic intracranial atherosclerosis. Cerebral perfusion status, measured by single-photon emission computed tomography and transcranial Doppler, improved remarkably in patients with rIPC than in controls. In addition, the incidence of recurrent stroke at 300 days was lower and the average time to recovery (defined as modified Rankin Scale Score < 1) was shorter in the rIPC group than in controls.

In this issue, Meng et al. [7] expand on their earlier study by investigating the safety and potential effectiveness of rIPC in 59 octo- and nonagenarian patients with symptomatic intracranial atherosclerosis. They conclude that rIPC safely ameliorates plasma biomarkers of inflammation and reduces stroke recurrence in these patients. Although this study is largely limited by its small sample size, it does suggest that rIPC is feasible and likely safe in older stroke patients.

The studies of Meng et al. and others [5–7] indicate that rIPC holds promise as a simple and easy neuroprotective strategy for a large number of stroke patients. It is suited for 1) primary and secondary stroke prevention in multiple settings, including symptomatic and asymptomatic intra- and perhaps extracranial arterial occlusive lesions; 2) as an adjunctive strategy with or without reperfusion therapy for acute ischemic stroke; and 3) as a prophylactic strategy against delayed ischemic injury in subarachnoid hemorrhage.

However, rIPC is yet to be ready for prime time. More study is needed. Although the overall findings of Meng et al. [7] and others are consistent with data from animal models and are promising, the translation into a possible clinical

benefit remains to be shown in large phase III trials. In addition, the optimal timing, frequency, and duration of rIPC need to be better defined.

While preclinical and early clinical studies of rIPC are promising, the potential utility of rIPC as a successful neuroprotective strategy should be viewed with cautious optimism. Have we not learned our lessons from the failure of an endless number of stroke neuroprotection studies in the past?

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Muir KW, Teal PA. Why have neuro-protectants failed?: lessons learned from stroke trials. *J Neurol* 2005;252:1011-1020.
2. Narayanan S, Dave K, Perez-Pinzon M. Ischemic preconditioning and clinical scenarios. *Curr Opin Neurol* 2013;26:1-7.
3. Stenzel-Poore M, Stevens S, Xiong Z, et al. Effect of ischaemic preconditioning on genomic response to cerebral ischaemia: similarity to neuroprotective strategies in hibernation and hypoxia-tolerant states. *Lancet* 2003;362:1028-1037.
4. Koch S, Katsnelson M, Dong C, Perez-Pinzon M. Remote ischemic limb preconditioning after subarachnoid hemorrhage: a phase Ib study of safety and feasibility. *Stroke* 2011;42:1387-1391.
5. Hougaard KD, Hjort N, Zeidler D, et al. Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke* 2014;45:159-167.
6. Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology* 2012;79:1853-1861.
7. Meng R, Ding Y, Asmaro K, et al. Ischemic conditioning is safe and effective for octo- and nonagenarians in stroke prevention and treatment. *Neurotherapeutics* 2015 May 9.