Editorial

Remote Ischemic Preconditioning
Making the Brain More Tolerant, Safely and Inexpensively

Michael A. Moskowitz, MD; Christian Waeber, PhD

Circulatory arrest and stroke are among the leading causes of death and disability worldwide, and they are difficult to treat. Only a limited number of therapeutic approaches have reached the bedside (eg, hypothermia and recombinant tissue plasminogen activator)[1] and, unfortunately, relatively few patients are eligible. Virtually all experimental compounds tested so far have failed at some stage of translational development. Preconditioning is an attractive strategy that makes the brain and other visceral organs relatively resistant to tissue injury. It develops when a noxious stimulus, below the damage threshold, leads to reduced tissue injury on subsequent challenge with a stimulus given above injury threshold. It is an appealing strategy to identify novel endogenous protective mechanisms and, as demonstrated by Jensen, Loukogeorgakis, and their colleagues in this issue of *Circulation*,[2] it may prove useful to prevent brain damage in the clinical context when there is a high probability of cerebral ischemia (eg, before high-risk surgery or in patients with subarachnoid hemorrhage).

Article see p 714

Various types of preconditioning stimuli have been used experimentally to protect brain, heart, retina, liver, kidney, and other organs.[3] Some use ischemic preconditioning, in which the blood supply to a target organ is temporarily interrupted before introducing a longer infarct-generating insult that would ordinarily produce infarction; other studies use hypoxic preconditioning, in which animals are exposed to oxygen levels around 8% to 9% for a few hours. But ischemia and hypoxia are just 2 examples in a larger list of strategies that induce tolerance to brain injury: hypoglycemia, hypoxia, kainate-induced seizures, and exposure to volatile anesthetics, to name a few.[4] Preconditioning can protect the brain either rapidly after stimulation (known as early, first window, or classical preconditioning) or after a 24-hour delay to induce protein synthesis-dependent protection lasting up to 96 hours (known as delayed or second window preconditioning).

Because of its longer duration, delayed preconditioning has attracted more preclinical attention, with the hope that pharmacological approaches may mimic the powerful late-phase protection. But clinically, early preconditioning is more appealing because it can be applied, at least in theory, right before procedures that carry a high risk of cardiac or brain complications. Delivering a preconditioning stimulus to the brain itself would be more challenging and less practical than to other organs, and it is therefore likely to be less useful than alternative strategies. The notion that tolerance can be achieved in the brain by inducing ischemia-reperfusion in a distant (remote) nonvital organ is consistent with the idea that transient ischemia in a visceral organ or tissue (eg, heart, kidney, intestine, or skeletal muscle) can protect remote organs against the effects of extended subsequent ischemia-reperfusion injury.

In this issue of *Circulation*, Jensen and colleagues describe their experience with remote ischemic preconditioning (rIPC) in hypothermic circulatory arrest in piglets.[2] Their results in this small but convincing study speak to the potential utility of rIPC during elective or planned procedures that pose a risk to the integrity of vital organs and tissues. They used biochemical, electrophysiological, behavioral, and pathological outcome measures in a randomized group allocation protocol in which the surgeons and postoperative evaluators were blinded to the treatment group assignment. Jensen and colleagues found statistically significant improvement in brain as well as cardiac function after rIPC during the rewarming phase and continuing for at least 7 days after cardiac arrest. They found tissue protection in 2 brain regions exquisitely sensitive to global ischemia, hippocampus, and cortex, as well as electrophysiological and behavioral evidence for better brain function than in the controls. Edema and blood brain barrier disruption were also diminished. The conditioning stimulus used by Jensen and colleagues appears relatively safe, easy, and efficient to administer. Taken together, these results help to solidify remote preconditioning as a potentially useful strategy to improve central nervous system function.

The study by Jensen and colleagues also adds to an emerging literature on rIPC in experimental cerebral ischemia indicating that rIPC may not only preserve brain tissue after global ischemia but after focal ischemic insult as well.[5] The studies are notable for the number of different limb ischemia protocols that were used, including 3 cycles of 10 minutes of bilateral femoral artery occlusion followed by recirculation, 15 or 30 minutes of a single occlusion and 30 minutes with a single occlusion, and 4 cycles of 5 minutes of ischemia followed by 5 minutes of occlusion.[6] The interval between the preconditioning event and global ischemia also varied (immediately after or with an interval of 15 minutes or 48 hours), although a recent study failed to see protection when the interval between remote ischemia reperfusion extended to 48

hours prior to transient global cerebral ischemia in rats.[7] Clearly, more work will be needed to clarify the issues of protocol optimization for brain (eg, ideal timing and magnitude of limb ischemia-reperfusion) and to determine whether remote preconditioning differs sufficiently or mechanistically from prior postconditioning strategies.[4] Clinical trials should be approached cautiously to avoid the myriad of pitfalls that have plagued translational stroke research, a topic that has been debated extensively.[8,9]

More information is available regarding rIPC in organs other than brain, and experimental studies have now begun to translate these findings to the clinic in several randomized trials with exciting, albeit preliminary results. For example, rIPC was associated with reduced incidence of postoperative myocardial infarction and renal impairment in patients undergoing elective abdominal aortic aneurysm repair.[10] Heart protection after rIPC was also reported during coronary stenting[11] and in controlled trials to reduce infarct size after myocardial infarction.[12] rIPC also protected the heart during cardiac surgery using cardiopulmonary bypass in children[13] and improved systemic tolerance to ischemia-reperfusion in a prospective randomized, controlled study of 70 infants undergoing open heart surgery.[14] Encouraging results were also reported in a retrospective secondary analysis assessing the impact of rIPC on acute kidney injury during cardiac surgery. In this study with acknowledged shortcomings, the results show a significant decrease in the risk of acute kidney injury in 78 nondiabetic patients subjected to transient forearm ischemia prior to undergoing elective coronary artery bypass graft surgery.[15] Ultimately, the clinical utility of such a seemingly safe and inexpensive procedure will be determined by larger randomized, controlled trials (eg, *Remote Ischemic Preconditioning in Cardiac Surgery Trial* [Remote IMPACT], ClinicalTrials.gov identifier: NCT01071265; or *Remote Ischemic Preconditioning for Heart Surgery* [RIPHeart-Study] ClinicalTrials.gov identifier: NCT01067703).

The signaling pathways that may be involved in the protection afforded by rIPC are largely undefined, but more than likely pleiotropic, multifactorial, and redundant. Similar to direct ischemic preconditioning, many studies have shown the existence of 2 phases of protection by rIPC, and the delayed phase for both seems to be protein synthesis-dependent.[6] These and other studies suggest that direct and remote ischemic preconditioning are likely to share at least some overlapping signaling pathways. For example, both rIPC and direct ischemic preconditioning promote tolerance in the heart or brain via protein kinase Cε activation leading to the opening of mitochondrial ATP-dependent K^+ channels (K_{ATP}).[16] Mitochondrial K_{ATP} channel opening inhibits the formation of the mitochondrial permeability transition pore, a key step leading to cell death. The mitochondrial permeability transition pore opens during the first minutes of reperfusion and induces cell death by uncoupling oxidative phosphorylation and promoting mitochondrial swelling.[1] Other signaling pathways involved in direct ischemic preconditioning, such as the recently implicated polycomb proteins in brain,[17,18] have been reviewed elsewhere.[3,4]

A unique and intriguing aspect of rIPC is the transfer of the protective stimulus from the remote to the target organ. A role

has been hypothesized for biological factors such as bradykinin, adenosine, nitric oxide/calcitonin gene-related peptide, opioids, or endocannabinoids released by remote tissues. These factors may be carried via circulation to the target organ as rIPC is observed following transient (but not permanent) occlusion of the preconditioning tissue, and following transfer of coronary effluent between isolated hearts.[19] These studies also point to the possibility that putative protective humoral factors might be identified and targeted clinically. There is also evidence that factors released by the preconditioning organ affect the target organ via afferent and efferent neural connections that may involve autonomic and sensory pathways. Whether similar pathways play a role in rIPC within brain, however, is currently unknown.[6]

Finally, rIPC may be part of a systemic protective response associated with the suppression of deleterious inflammatory processes evoked by remote organ ischemia and reperfusion. Neutrophil infiltration, adhesion, and activation play an important role in early and late ischemia/reperfusion injury,[20] and rIPC in humans reduces neutrophil activation through reduced expression of neutrophil CD11b and platelet-neutrophil complexes. rIPC may activate signal pathways in neutrophils modulating the release of proinflammatory cytokines and the expression of adhesion markers. Neural, humoral and antiinflammatory pathways probably interact with each other and are not necessarily mutually exclusive[16]; the relative importance of each pathway may depend on the duration of preconditioning ischemia, the tissue or organ generating the preconditioning stimulus,[19] and the particular species tested.

Based on the best case scenario, remote preconditioning strategies may become applicable to a host of acute neurovascular insults (surgical or otherwise) that negatively impact the integrity of the nervous system. rIPC will gain even wider application if conditioning protects the nervous system even *after* sustaining injury to a vital organ, as appears to be the case for myocardial protection (remote ischemic postconditioning or RIPost).[16] As a final thought, it is tempting to forecast that remote preconditioning might become an established clinical paradigm of notable importance not only in disease but also in health, based on the recent demonstration that rIPC boosted maximal performance in highly trained athletes.[21]

Disclosures

None.

References

1. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. *Neuron.* 2010;67:181–198.
2. Jensen HA, Loukogeorgakis S, Yannopoulos F, Rimpiläinen E, Petzold A, Tuominen H, Lepola P, MacAllister RJ, Deanfield JE, Mäkelä T, Alestalo K, Kiviluoma K, Anttila V, Tsang V, Juvonen T. Remote ischemic preconditioning protects the brain against injury after hypothermic circulatory arrest. *Circulation.* 2011;123:714–721.
3. Sharp FR, Ran R, Lu A, Tang Y, Strauss KI, Glass T, Ardizzone T, Bernaudin M. Hypoxic preconditioning protects against ischemic brain injury. *NeuroRx.* 2004;1:26–35.
4. Dirnagl U, Becker K, Meisel A. Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. *Lancet Neurol.* 2009;8:398–412.

5. 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;151:1099–1103.

6. Kanoria S, Jalan R, Seifalian AM, Williams R, Davidson BR. Protocols and mechanisms for remote ischemic preconditioning: a novel method for reducing ischemia reperfusion injury. *Transplantation.* 2007;84:445–458.

7. Saxena P, Bala A, Campbell K, Meloni B, d'Udekem Y, Konstantinov IE. Does remote ischemic preconditioning prevent delayed hippocampal neuronal death following transient global cerebral ischemia in rats? *Perfusion.* 2009;24:207–211.

8. Moskowitz MA. Brain protection: maybe yes, maybe no. *Stroke.* 2010;41:S85–S86.

9. Tymianski M. Can molecular and cellular neuroprotection be translated into therapies for patients?: yes, but not the way we tried it before. *Stroke.* 41:S87–S90.

10. Ali ZA, Callaghan CJ, Lim E, Ali AA, Nouraei SA, Akthar AM, Boyle JR, Varty K, Kharbanda RK, Dutka DP, Gaunt ME. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation.* 2007;116:I98–I105.

11. Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, Clarke SC, Shapiro LM, Schofield PM, O'Sullivan M, Dutka DP. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. *Circulation.* 2009;119:820–827.

12. Bøtker HE, Kharbanda R, Schmidt MR, Bøttcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sørensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2010;375:727–734.

13. Cheung MM, Kharbanda RK, Konstantinov IE, Shimizu M, Frndova H, Li J, Holtby HM, Cox PN, Smallhorn JF, Van Arsdell GS, Redington AN. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol.* 2006;47:2277–2282.

14. Zhou W, Zeng D, Chen R, Liu J, Yang G, Liu P, Zhou X. Limb ischemic preconditioning reduces heart and lung injury after an open heart operation in infants. *Pediatr Cardiol.* 2010;31:22–29.

15. Venugopal V, Laing CM, Ludman A, Yellon DM, Hausenloy D. Effect of remote ischemic preconditioning on acute kidney injury in nondiabetic patients undergoing coronary artery bypass graft surgery: a secondary analysis of 2 small randomized trials. *Am J Kidney Dis.* 2010;56:1043–1049.

16. Hausenloy DJ, Yellon DM. Preconditioning and postconditioning: underlying mechanisms and clinical application. *Atherosclerosis.* 2009;204:334–341.

17. Zukin RS. Eradicating the mediators of neuronal death with a fine-tooth comb. *Sci Signal.* 2010;3:pe20.

18. Stapels M, Piper C, Yang T, Li M, Stowell C, Xiong ZG, Saugstad J, Simon RP, Geromanos S, Langridge J, Lan JQ, Zhou A. Polycomb group proteins as epigenetic mediators of neuroprotection in ischemic tolerance. *Sci Signal.* 2010;3:ra15.

19. Przyklenk K, Darling CE, Dickson EW, Whittaker P. Cardioprotection 'outside the box'–the evolving paradigm of remote preconditioning. *Basic Res Cardiol.* 2003;98:149–157.

20. Yilmaz G, Granger DN. Cell adhesion molecules and ischemic stroke. *Neurol Res.* 2008;30:783–793.

21. Jean-St-Michel E, Manlhiot C, Li J, Tropak M, Michelsen MM, Schmidt MR, McCrindle BW, Wells GD, Redington AN. Remote preconditioning improves maximal performance in highly-trained athletes. *Med Sci Sports Exerc.* 2010 Dec 1. [Epub ahead of print].

Circulation

American Heart Association

Remote Ischemic Preconditioning: Making the Brain More Tolerant, Safely and Inexpensively
Michael A. Moskowitz and Christian Waeber

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/123/7/709