is there a benefit for clipping or coiling. A recent meta-analysis of three randomized clinical trials including ISAT did not show a significant difference in outcomes between patients treated with these two options.[11]

Despite limitations of ISAT, this is a well-executed trial that highlights the necessity of long-term follow-up in aneurysmal SAH patients. The increased rate of rebleeding in untreated and de novo aneurysms underscores that clipping or coiling does not eliminate the underlying pathogenesis of cerebral aneurysms and that aggressive management of secondary risk factors is essential.

Robert M. Starke, MD, MSc
University of Virginia School of Medicine
Charlottesville, Virginia
Ricardo J. Komotar, MD
University of Miami School of Medicine
Miami, Florida
E. Sander Connolly, MD
Columbia University College of Physicians and Surgeons
New York, New York

REFERENCES

1. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet*. 2002;360(9342):1267-1274.
2. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. 2005;366(9488):809-817.
3. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial. *Lancet*. 2014. In press.
4. NECOD. Managing the flow? Available at: http://wwwncepodorguk/2013sahhtm. Accessed November 5, 2014.
5. Bekelis K, Goodney PR, Dzebisashvili N, Goodman DC, Bronner KK. *Variation in the Care of Surgical Conditions: Cerebral Aneurysms*. Dartmouth Atlas of Health Care: 2014. Available at: http://www.dartmouthatlas.org/downloads/reports/Cerebral_aneurysm_report_09_30_14.pdf. Accessed November 5, 2014.
6. Komotar RJ, Schmidt JM, Starke RM, et al. Resuscitation and critical care of poor-grade subarachnoid hemorrhage. *Neurosurgery*. 2009;64(3):397-410.
7. Davies JM, Lawton MT. Advances in open microsurgery for cerebral aneurysms. *Neurosurgery*. 2014;74(suppl 1):S7-S16.
8. Naggara ON, Lecler A, Oppenheim C, Meder JF, Raymond J. Endovascular treatment of intracranial unruptured aneurysms: a systematic review of the literature on safety with emphasis on subgroup analyses. *Radiology*. 2012;263(3):828-835.
9. Molyneux AJ, Clarke A, Sneade M, et al. Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either cerecyte or bare platinum coils. *Stroke*. 2012;43(10):2544-2550.
10. White PM, Lewis SC, Gholkar A, et al. Hydrogel--coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. *Lancet*. 2011;377(9778):1655-1662.
11. Lanzino G, Murad MH, d'Urso PI, Rabinstein AA. Coil embolization versus clipping for ruptured intracranial aneurysms: a meta-analysis of prospective controlled published studies. *AJNR Am J Neuroradiol*. 2013;34(9):1764-1768.

Mammalian Target of Rapamycin (mTOR) Activity Promotes Neuronal Survival in Stroke With or Without Ischemic Postconditioning

Ischemic postconditioning (IPC), a concept derived from myocardial ischemic models, confers neuroprotection in various models of experimental stroke.[1] Following a series of occlusion and reperfusion periods after the initial ischemic insult, IPC improves glucose uptake, reduces free radical generation, inhibits inflammation, and promotes protein activity in the phosphatidylinositol 3-kinase/Akt pathway.[2,3] Although the exact relationship between mammalian target of rapamycin (mTOR), a member of the phosphatidyl 3-kinase–related kinase family, and IPC is still unclear, it is known that modulation of mTOR through IPC promotes cell metabolism, growth, differentiation, development, and cell survival.[4]

Xie et al[5] created an in vivo stroke model incorporating IPC by generating focal cerebral ischemia through bilateral common carotid artery occlusions and permanent distal middle cerebral artery occlusion in male Sprague-Dawley rats. IPC was performed immediately after bilateral common carotid artery occlusions with 30 seconds of reperfusion followed by 10 seconds of temporary reocclusion. This sequence was repeated 3 times. Because Xie and colleagues were unable to clone the mTOR gene in a plasmid backbone, they constructed a lentiviral vector expressing S6K1, a downstream protein of mTOR and indicator of mTOR activity. To inhibit mTOR activity, the authors used rapamycin and a lentiviral vector containing mTOR short hairpin RNA (shRNA) to reduce mTOR expression. Rapamycin (5 μL, 1 mmol/L) was infused into the ventricular space ipsilateral to the ischemic side 1 hour before occlusion with a microsyringe pump. Lentiviruses were injected into the left cortex 5 days before occlusion, and infarct size was measured 2 days after ischemia.

The authors went on to subject mixed neuronal cultures derived from rat fetal brains to oxygen-glucose deprivation (OGD). Nine to 11 days after preparation, 6 hours of OGD was induced in a hypoxic chamber, followed by in vitro hypoxic postconditioning (HPC). HPC was achieved through 3 cycles of 15-minute restoration of glucose and oxygen and 15 minutes of OGD. Lactate dehydrogenase levels were used to quantify cell death 18 hours after OGD.

Initial experiments demonstrated that IPC promotes the phosphorylation and activation of mTOR and other mTOR-related proteins (S6K1, S6, and 4EBPI). The authors showed reduced levels of protein phosphorylation in stroke models without IPC. In the penumbra, phosphorylation of such proteins was elevated in IPC models and reduced in non-IPC models. Furthermore, rapamycin, a known mTOR inhibitor, was found to exacerbate infarct volumes and to lower phosphorylated proteins in common carotid artery occlusion models with or without IPC. Likewise, transfection of shRNA worsened ischemic injury and reversed the protective effects of IPC, whereas gene transfer of S6K, a downstream protein of mTOR, inhibited neuronal death. In vitro, rapamycin worsened cell death induced by OGD and abolished the protective effects of HPC (Figure).

Postischemic neuronal injury occurs through multiple mechanisms, including the disruption of cell growth, a decrease in protein activity, and the creation of a proinflammatory state. Since the discovery of the protective benefits of IPC after myocardial ischemia, neuroscientists have tried to obtain equally positive results and to understand which proteins are affected by IPC in the setting of cerebral ischemia. The ability to successfully promote mTOR phosphorylation and to accelerate its downstream protein production may ultimately represent a novel therapeutic strategy for patients with stroke.

Gregory M. Weiner, MD
Andrew F. Ducruet, MD
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

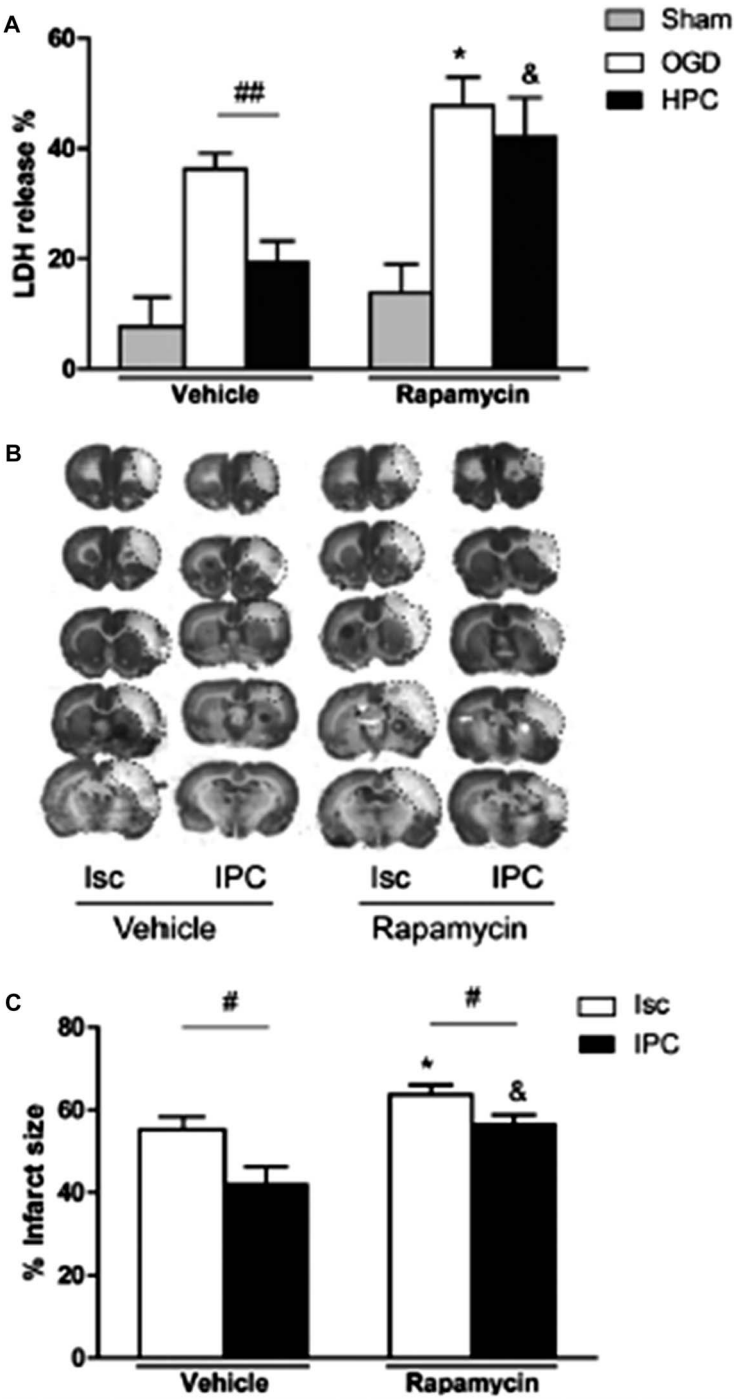

Figure. Rapamycin blocked the neuroprotective effects of hypoxic postconditioning (HPC) and ischemic postconditioning (IPC) both in vitro and in vivo. **A**, *effects of rapamycin and HPC on neuronal death as measured by lactate dehydrogenase (LDH) release in vitro. LDH release was measured 18 hours after oxygen-glucose deprivation (OGD). All data from cultures with OGD were normalized to the values of control, non-OGD samples treated with vehicle that did not contain rapamycin (n = 16 per group).* **B**, *representative coronal sections of ischemic brain stained by the cresyl violet method. Infarct regions are traced.* **C**, *average infarct sizes measured from 5 coronal sections (n = 8 per group). *P <.05 vs the vehicle of the indicated group; #P < .05, ##P < .01 between the 2 indicated groups.* Reprinted with permission from Xie et al.[5]

REFERENCES

1. Zhao H. Ischemic postconditioning as a novel avenue to protect against brain injury after stroke. *J Cereb Blood Flow Metab.* 2009;29(5):873-885.
2. Zhao H, Sapolsky RM, Steinberg GK. Interrupting reperfusion as a stroke therapy: ischemic postconditioning reduces infarct size after focal ischemia in rats. *J Cereb Blood Flow Metab.* 2006;26(9):1114-1131.
3. Pignataro G, Meller R, Inoue K, et al. In vivo and in vitro characterization of a novel neuroprotective strategy for stroke: ischemic postconditioning. *J Cereb Blood Flow Metab.* 2008;28(2):232-241.
4. Jewell JL, Guan XL. Nutrient signaling to mTOR and cell growth. *Trends Biochem Sci.* 2013;28(5):233-242.
5. Xie R, Wang P, Cheng M, Sapolsky R, Ji X, Zhao H. Mammalian target of rapamycin cell signaling pathway contributes to the protective effects of ischemic postconditioning against stroke. *Stroke.* 2014;45(9):2769-2776.

A Previously Unidentified Mechanism of Immune Evasion in Glioblastoma

Despite gradual advancements in surgical technique, chemotherapy, and radiotherapy, current treatments for glioblastoma multiforme (GBM) still have only limited efficacy.[1] One evolving strategy is the development of immunotherapies that upregulate or activate host immune function to target and destroy GBM cells.[2] There is evidence, however, that patients with GBM have suppressed immune function, which may limit the success of immunotherapy.[3]

Natural killer (NK) cells, an important component of the innate immune system, typically express NKG2D receptors on their cell surface. These receptors bind specific ligands (eg, MICB, ULBP-1) on target cells of interest, and binding triggers the release of cytotoxic granules and inflammatory cytokines, ultimately causing target cell death. Interestingly, it has been observed that NK cells have downregulated the expression of NKG2D in patients with GBM.[4]

Myeloid-derived cells, including circulating monocytes and tumor-infiltrating macrophages, are believed to be an important driver of tumor-mediated immune invasion.[5] Crane et al[6] recently studied myeloid-lineage cells from patients with GBM and found that these cells overexpressed the NKG2D ligands MICB and ULBP-1 on their cell surfaces compared with myeloid cells from control subjects without GBM.

Next, the investigators studied several GBM cell lines (U87, SF767, U251) and determined that both lactate dehydrogenase 5 (LDH5), a tetrameric metabolic enzyme produced by