period of depressed hippocampal LFP activity. Afterdischarges were less likely to be induced by direct hippocampal stimulation during periods when the hippocampal LFP had already been suppressed with preceding preparatory stimulation. Evoked potentials produced in the hippocampus by thalamic stimulation were also suppressed when preparatory direct hippocampal stimulation was provided.

The authors were also able to demonstrate 2 novel closed-loop control stimulation paradigms whereby the ambient theta band power recorded in the hippocampus was used to trigger deep brain stimulation, leading to suppression of power in this band pass. In the first paradigm, hippocampal theta band power at a specified threshold was used to control the delivery of short 10-second bursts of direct hippocampal stimulation (0.9 V, 300 microseconds, 50 Hz) that successfully produced LFP suppression and maintained this suppression over extended periods of time (Figure). The second closed-loop system demonstrated instead used continuous thalamic stimulation at a frequency of 40 Hz. Changes in recorded hippocampal theta band activity were used to modulate the amplitude of the continuous thalamic stimulation, and by this means, hippocampal activity was suppressed, which was also sustained over a period of time. In summary, Stypulkowski et al have now demonstrated (in awake behaving animals) that both local and remote deep brain stimulation can produce specific effects on hippocampal excitability. Two novel closed-loop control paradigms were demonstrated in which each successfully depressed hippocampal activity within a desired range. This kind of closed-loop deep brain stimulation paradigm is currently actively undergoing investigation with the hope that it can be applied to many different disease states, and because neuromodulation is delivered only when necessary, it is thought that this can be used to minimize possible side effects of stimulation and to increase battery lifetime while also maximizing therapeutic benefit.

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Combined Direct and Indirect Revascularization Is Associated With Low Rates of Recurrent Ischemic and Hemorrhagic Stroke in Adult Moyamoya Disease

Suzuki and Takaku[1] first coined the term moyamoya disease during the late 1960s when studying a peculiar vaso-occlusive disease of the brain. This rare idiopathic syndrome is characterized by luminal stenosis secondary to intimal thickening and smooth muscle cell proliferation of the distal internal carotid arteries and the main branches of the circle of Willis.[2,3] In association with this occlusive phenomenon, there is compensatory neogenesis of an aberrant network of vessels that maintain a collateral circulation to the brain tissue.[3] It is this pathophysiological process that gives moyamoya its characteristic "puff of smoke" feature on angiographic studies.

There is no known medical treatment for moyamoya disease. Treatment involves revascularization, which improves cerebral perfusion with the goal of eliminating or reducing recurrent transient ischemic strokes, strokes, and cognitive deterioration.[4] Surgical options are categorized into direct and indirect techniques. Direct revascularization procedures use extracranial to intracranial bypass to increase perfusion to the brain. Examples include superficial temporal artery and occipital artery to middle cerebral artery bypass. On the other hand, indirect procedures increase revascularization by stimulating neovascularization over time. Some of the described methods include encephalodurogaleosynangiosis, encephalomyosynangiosis, encephaloduroarteriosynangiosis, and burr hole placement.[4-6] Despite several decades of growing experience treating this enigmatic disease, data are lacking on the long-term outcomes, and controversy still remains regarding the best surgical approaches. It remains unclear whether indirect or direct bypass should be preferred. Whether combining the 2 approaches is advantageous also remains an unanswered question.

To address this knowledge deficit, Cho et al[7] conducted a rigorous retrospective case series that highlights the potential added value of using combined direct and indirect revascularization surgery in adults diagnosed with moyamoya disease. They retrospectively evaluated the clinical, angiographic, and hemodynamic outcomes data of 60 patients who had undergone a combined revascularization surgery for moyamoya disease at their center. Their approach consisted of a combined superficial temporal artery to middle cerebral artery anastomosis with encephalodurogaleosynangiosis. The data points were assessed at short-term (5-12 months) and long-term (>5 years) intervals for each of the clinical, angiographic, and hemodynamic variables.

Clinical outcome was assessed based on the Karnofsky Performance Scale and the modified Rankin Scale (Figure). There was an evident improvement on both scales; the Karnofsky performance scores improved from an average of 81.1 to 96.2, and the modified Rankin Scale scores improved from an average of 1.5 to 0.4. This improvement was seen mainly between the procedure and short-term follow-up. The angiographic outcome was assessed on the basis of postoperative revascularization, measured by relative revascularization area [(revascularization area/supratentorial area) × 100], and patency of the direct anastomosis. The data revealed that the relative revascularization area had increased between the short-term and long-term follow-up periods, even though patency of the direct anastomosis had decreased from an average of 94.4% in the short-term to 76.1% in the long-term period. Finally, brain single-photon emission computed tomography was used to evaluate postoperative hemodynamics with respect to preoperative results. After analyzing brain perfusion single-photon emission computed tomography data, the authors found that cerebral blood flow increased significantly until the short-term follow-up but did not increase substantially between the short-term and long-term follow-ups. Impressively, Cho et al reported that the incidences of symptomatic hemorrhage and infarction in the operated hemispheres were 0.4% and 0.2% annually.

The authors hypothesize that both direct and indirect revascularization each play an important role in postsurgical revascularization. In the early phase after surgery, direct bypass plays a dominant role because indirect revascularization can take up to 3 months for neovascularization to mature between the extracranial and intracranial vasculature.[8] However, over the long term, collaterals secondary to indirect processes could play a more dominant role and improve perfusion to areas of the brain that blood flow could not reach via direct bypass.

The limitations of this study are the retrospective design and lack of randomization. The main strength of this study is the rigorous consistency with which the authors treated and followed up their patients and tabulated important data points. The exceedingly low recurrent

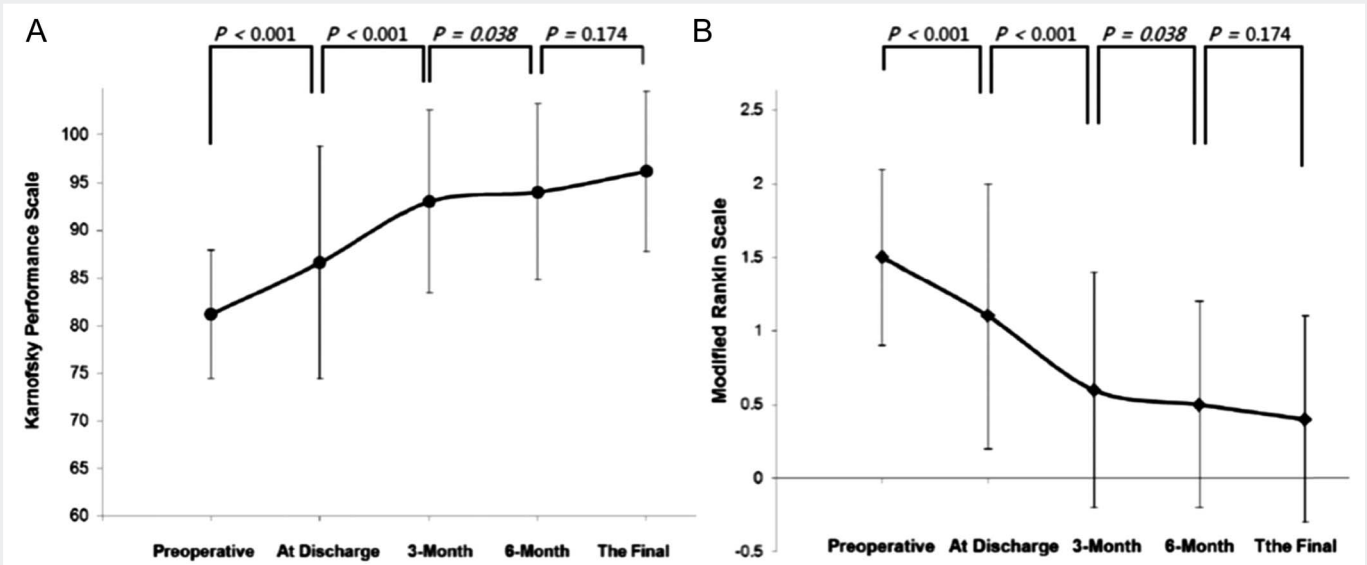

Figure. Clinical status change during each period using the (A) Karnofsky Performance Scale and (B) the modified Rankin Scale. Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Stroke; Cho WS, Kim JE, Kim CH, et al. Long-Term Outcomes After Combined Revascularization Surgery in Adult Moyamoya Disease, (Stroke. 2014;45[10]:3025-31. doi: 10.1161/STROKEAHA.114.005624. Epub 2014 Sep 2.) 2014.

stroke risk and complication rate likely reflects 4 important factors: careful patient selection, excellent surgical technique, meticulous intraoperative and perioperative management, and attentive patient follow-up. Moreover, although this study does not prove that a combined indirect and direct revascularization procedure is superior to other approaches, the low rate of recurrent stroke and hemorrhage is compelling. Moving forward, prospective cohort and randomized trials are needed to further define best evidence-based practice. Future studies should also assess cognitive function and quality of life in greater depth. Adult moyamoya disease is an important cause of stroke and cognitive decline and a critical area for continued research.

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Toxin-Secreting Implantable Therapeutic Stem Cells

Pseudomonas exotoxin (PE) exerts cellular toxicity by inactivating elongation factor-2 and blocking protein synthesis. Conjugation of PE to ligands directed at cancer cell–specific antigens has clinical success in the treatment of some leukemias and lymphomas and limited success in solid tumors. One of the more recent therapeutic targets to gain attention in glioblastoma research has been the interleukin-13 (IL13) receptor α2, a variant overexpressed in glioblastoma cells but not in normal brain. There has been strong preclinical evidence for targeting this receptor to selectively deliver PE to glioblastoma cells. This strategy has yet to yield positive clinical results, as evidenced by the phase III PRECISE trial, which compared convection-enhanced delivery of an IL13-PE conjugate to camustine implants (Gliadel wafers) in patients with first recurrence of glioblastoma.[1] The lack of improved outcomes with the IL13-PE–conjugated drug compared with Gliadel wafers was partly attributed to poor drug delivery from suboptimal catheter positioning in more than half of the subjects.[2] Another highly relevant factor may be the short half-life of the drug and the short administration period of only 4 days.

Conceptually, Gliadel has the advantage of implantation directly at the margins of resection with carmustine diffusion into the surrounding parenchyma over time as the polymer degrades. What if this concept could be used to deliver a highly effective and stable biological agent? Stuckey and colleagues[3] report engineering human neural stem cells to stably express IL13-PE. They first generated PE-resistant human neural stem cells by inducing specific mutations in the elongation factor-2 gene. They then selected and engineered the PE-resistant clones to stably express