Superficial temporal artery to middle cerebral artery bypass: past, present, and future

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Object. The aim of this study was to review the historical developments and current status of superficial temporal artery (STA) to middle cerebral artery (MCA) bypass.

Method. A literature review was performed to review the origins and current uses of the STA bypass procedure in neurosurgery.

Results. The idea of providing additional blood supply to the brain to prevent stroke and maintain neurological function has been present in the mind of neurosurgeons for many decades. In 1967 the first STA–MCA bypass was done by M. G. Yaşargil, and an enormous step was made into the field of microneurosurgery and cerebral revascularization. During the decades that followed, this technique was used as an adjuvant or a definitive surgical treatment for occlusive disease of the extracranial and intracranial cerebral vessels, skull base tumors, aneurysms, carotid–cavernous fistulas, cerebral vasospasm, acute cerebral ischemia, and moyamoya disease. With the results of the first randomized extracranial–intracranial (EC–IC) bypass trial and the development of endovascular techniques such as angioplasty for intracranial atherosclerotic disease and cerebral vasospasm, the indications for STA–MCA bypass became limited. Neurosurgeons continued to perform EC–IC bypasses as an adjuvant to clipping of aneurysms and in the treatment of skull base tumors and moyamoya disease; the procedure is less commonly used for atherosclerotic carotid artery occlusion (CAO) with definite evidence of hemodynamic insufficiency. The evidence that patients with symptomatic CAO and “misery perfusion” have an increased stroke risk has prompted a second trial for evaluating EC–IC bypass for stroke prevention. The Carotid Occlusion Surgery Study is a new trial designed to determine whether STA–MCA bypass can reduce the incidence of stroke in these patients. New trials will also reveal the role of the STA–MCA bypass in the prevention of hemorrhages in moyamoya disease.

Conclusions. The role of STA–MCA bypass in the management of cerebrovascular disease continues to be refined and evaluated using advanced imaging techniques and by performing randomized trials for specific purposes, including symptomatic CAO. (DOI: 10.3171/FOC/2008/24/2/E2)

KEY WORDS • bypass surgery • neurosurgical history • superficial temporal artery–middle cerebral artery bypass

THE introduction of microvascular surgery to neurosurgery was made possible by the combined efforts and ideas of a few surgeons during the 1960–1970 decade. Some of the first pioneers were surgeons in Burlington, Vermont. Jacobson and Suarez,26 who were using the microscope to repair vessels in small animals according to the principles and techniques introduced by Alexis Carrel, were successful in achieving a 100% patency rate after reconstructing the carotid arteries of 20 dogs and 6 rabbits by using 7-0 atraumatic silk.

In the Division of Neurosurgery at the University of Vermont, R. M. P. Donaghy was very interested in the field of microvascular surgery as well.57,135 He had established a microsurgical laboratory in which he pursued intensive studies on arterial vasospasm and small-vessel reconstruction in small animals. Using meticulous techniques, micro-instruments, and the surgical microscope, he was successful in reconstructing vessels < 1 mm in diameter.135

Working with Dr. Krayenbuhl in the Department of Neurosurgery in Zurich, M. G. Yaşargil also became very interested in the neurosurgical applications of microvascular surgery. His interest was further stimulated when he was asked to perform an embolectomy of a cortical artery, a technique he had not yet mastered.133 Dr. Senning, a cardiovascular surgeon, encouraged him to pursue a technique that would enable such a procedure to be performed. His enthusiasm to learn techniques of cerebral revascularization increased after the report of an EC–IC bypass in a patient who had an occluded ICA at the neck.132 Professor

Abbreviations used in this paper: CAO = carotid artery occlusion; CT = computed tomography; EC–IC = extracranial–intracranial; ICA = internal carotid artery; MCA = middle cerebral artery; OEF = oxygen extraction fraction; PET = positron emission tomography; rCBF = regional cerebral blood flow; SAH = subarachnoid hemorrhage; STA = superficial temporal artery.
Yasargil then began looking for a position in which he could train in microvascular techniques, and during the International Congress of Neuroradiologists meeting in 1964, Drs. William Sweet and Theodore Rasmussen advised him to contact Professor Donaghy. Professor Yasargil eventually visited Professor Donaghy’s laboratory in Burlington, Vermont, and began his training in microvascular techniques in 1965 (Fig. 1). His initial training involved the use of the operating microscope, microinstruments, and microvascular techniques while experimenting on the femoral and carotid arteries of small animals.

In 1966, the purchase of a bipolar coagulator—designed by Dr. L. Malis—together with the availability of 9-0 sutures allowed a major advance in the development of microsurgical revascularization, enabling the dissection of intracranial structures in a clean field and meticulous repair of intracranial vessels. Initial attempts by Yasargil included a technique to interpose a femoral vascular graft from the common carotid artery to the MCA, as a form of EC–IC bypass, in small animals. Unfortunately, the graft would progress to thrombosis early after the procedure. The idea of performing a bypass from the STA to the MCA was then born. By the end of 1966, 30 such operations in dogs had been performed, and the technique was later described in detail in a paper.

Professor Yasargil returned to Zurich and performed the first STA–MCA bypass on October 30, 1967, in a patient with Marfan syndrome and complete occlusion of the MCA. He later published a paper describing the first 9 cases in which an STA–MCA bypass had been performed, 7 for occlusion of the ICA or MCA and 2 as an adjuvant to the surgical treatment of complex intracranial aneurysms. The feasibility of creating an EC–IC shunt was then demonstrated, and a major step was made into the field of reconstructive intracranial vascular microneurosurgery (Fig. 2).

The Past

Acute Stroke and Emergent Cerebral Revascularization

The idea of performing an emergent cerebral revascularization procedure for acute ischemic stroke was very rational when based on the knowledge of ischemic thresholds for infarction and the concept of ischemic penumbra. Providing additional blood flow to areas of the brain in which the rCBF was low enough to decrease cellular function but not low enough to induce an infarction was very attractive. Encouraging results were reported by some, but others considered the event of acute cerebral ischemia a relative contraindication for an emergent bypass, given the poor results and high rate of complications.

Crowell, working with Jafar, conducted a literature analysis and found 67 cases in which an emergency STA–MCA bypass had been performed in the setting of acute cerebral ischemia. The condition in 27 patients was improved after the procedure and unchanged in 26; 11 patients died. Crowell and Jafar pointed out that more data were needed for firm indications, and only those patients with crescendo transient ischemic attacks or mild to moderate deficits < 6 hours’ duration with no infarction on imaging studies should be considered for an EC–IC bypass.

Subsequently, with the advent of interventional neuroradiology and thrombolytic therapies using tissue plasminogen activator and urokinase, the indications for performing an emergent EC–IC bypass for acute ischemic stroke decreased.

Cerebral Vasospasm and SAH

For decades cerebral vasospasm has been the leading cause of delayed ischemic neurological deficit and a significant factor contributing to poor outcome following aneurysmal SAH. The STA–MCA bypass has been performed to augment blood flow to ischemic areas of the
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brain affected by vasospasm in an attempt to prevent stroke and improve neurological outcome. Batjer and Samson\(^8\) reported on 11 patients who had undergone an STA–MCA bypass in the setting of symptomatic vasospasm. Six patients improved in the first 24 hours after surgery and 2 others had stabilized deficits. Benzel and Kesterson\(^9\) also reported encouraging results and a reversal of neurological deficits in a patient with medically refractory symptomatic vasospasm treated with an STA–MCA bypass. This indication for the procedure did not gain wide acceptance, however. The introduction and development of endovascular techniques by interventional radiologists, such as balloon angioplasty with or without papaverine combined with hypertension, hypervolemia, hemodilution therapy, assumed a pivotal role in the management of symptomatic severe vasospasm.\(^{10,11}\)

**Occlusive Cerebrovascular Disease Not Amenable to Carotid Endarterectomy**

The first STA–MCA bypass in a patient with occlusive cerebrovascular disease was performed by Yaşargil. Subsequently, his results in the first 7 patients who had undergone an STA–MCA bypass for occlusive cerebrovascular disease of the ICA or MCA were published in detail.\(^{12,13}\)

Several neurosurgery leaders around the world soon mastered this elegant technique, and within a few years hundreds of procedures already had been performed. The procedure was still considered experimental though, given absent proof of efficacy in preventing future stroke and its uncertain indications.\(^{14}\) Nevertheless, good to excellent results were obtained in the early cases, promising possible benefits in the prevention of stroke, with a high bypass patency rate and low morbidity and death.\(^{15,16,17,18}\) Subsequently, large studies also demonstrated the feasibility of the STA–MCA bypass and possible neurological improvement in patients with atherosclerotic occlusive cerebrovascular disease, including bilateral disease.\(^{19,20,21,22}\)

By the end of a decade after the introduction of the STA–MCA bypass to the neurosurgical community, the selection of patients and the indications for surgery remained controversial despite attempts to refine the surgical indications based on the concept of hemodynamic insufficiency.\(^{23,24,25}\) Our knowledge of the natural history of occlusive cerebrovascular disease was rather uncertain, and methods for the identification of hemodynamic cerebrovascular insufficiency were still evolving. Moreover, postoperative results had always been compared with the preoperative status in the same patients and not to the natural course of the disease in a randomized control group.\(^{26}\)

In 1977 the North American EC–IC Bypass Study was begun by Dr. Henry Barnett and colleagues to compare the best medical therapy with the STA–MCA bypass plus medical therapy in patients with symptomatic occluded or high-grade stenotic atherosclerotic lesions of the MCA or ICA not amenable to endarterectomy.\(^{27}\) The objective of the study was to determine whether an STA–MCA anastomosis would decrease the incidence of stroke and stroke-related death in those patients. There were 714 patients randomized to the best medical treatment and 663 patients to an STA–MCA bypass plus the best medical therapy. The 30-day surgical mortality and major stroke morbidity rates were 0.6 and 2.5%, respectively. In the surgical group, fatal and nonfatal stroke occurred earlier and more frequently. The investigators concluded that the STA–MCA bypass was ineffective in preventing cerebral ischemia in patients with atherosclerotic disease of the MCA and ICA not amenable to endarterectomy.\(^{28}\) A temporary functional deterioration in several routine daily tasks was also observed during the 1st month of posttreatment in the surgical group, but the difference was not significant at the 6-month follow-up.\(^{29}\) Even though the study was considered exemplary because of its impeccable methods and follow-up,\(^{30}\) several members of the neurosurgical community criticized the results on the following points: 1) Only half of the patients were receiving antiplatelet agents at the time of entry into the study and the other half were not receiving any medical therapy.\(^{31}\) 2) Patients were not evaluated preoperatively in terms of their cerebrovascular hemodynamic status. Patients with symptoms due to hemodynamic insufficiency, the group that would most benefit from a bypass augmentation procedure, were therefore not differentiated from those with symptoms caused by thromboembolic mechanisms.\(^{32,33}\) 3) Both the patient and the therapist were not blinded and, therefore, the potential for underreporting or overreporting was possible.\(^{34}\) 4) Randomization-to-treatment bias could have occurred, in which a large number of patients randomized to surgery had major morbidity events that happened before the operation.\(^{35,36}\) 5) There were no angiographic determinants for entry. The severity of stenosis was not measured, and vertebral artery angiography was not performed in all patients.\(^{37}\) 6) A large percentage of patients had no symptoms between the angiographic demonstration of ICA occlusion and randomization.\(^{38,39}\) 7) A large number of patients underwent surgery outside the study.\(^{40}\) 8) A high percentage of patients had tandem lesions demonstrated on angiography, which may be a condition not very suitable for a bypass.\(^{41,42}\)

Further conclusions from the EC–IC bypass study were later published in a paper addressing those criticisms and once more provided evidence to support the results of the trial.\(^{43}\) Subsequently, a committee appointed by the American Association of Neurological Surgeons was then encouraged to examine the study with an emphasis on 2 aspects: the randomized trial proper and patients who underwent surgery outside of the trial.\(^{44}\) Within the randomized trial proper, none of the issues was believed by the committee and study investigators to be relevant to the point that it would compromise either the design of the trial or any conclusions of the study. Regarding the number of patients who underwent surgery outside of the trial, research done by Sundt\(^{45}\) indicated that at least 2500 patients had a bypass done outside the study in participating centers.\(^{45}\) Some of these patients were eligible for the trial and some were not. This issue raised the concern of whether the EC–IC bypass trial conclusions could or could not be generalizable to the entire population at risk for stroke.\(^{46}\) Due to a lack of sufficient data this question could not be answered correctly. The study investigators also pointed out that randomized trials involve only a small fraction of the population at risk and that this factor does not prevent a study from being valid.\(^{47}\)

Following the publication of the EC–IC bypass trial conclusions, there was a marked decrease in the number of STA–MCA bypasses performed for cerebrovascular occlusive disease.\(^{48}\) Cerebral revascularization continued to be
performed mainly for the treatment of moyamoya disease and as an adjuvant for major parent vessel occlusion during surgical treatment of complex intracranial aneurysms and skull base tumors.91

The Present

Aneurysms and Tumors

The treatment of cerebral aneurysms has been evolving since the 19th century, when occlusion of the ICA in the neck was used to promote obliteration of the sac by a decrease in flow and eventual thrombosis. Carotid artery ligation remained the mainstay for the treatment of some intracranial aneurysms of the anterior circulation.84,95 The results of the Cooperative Study of Intracranial Aneurysms and SAH with regard to the treatment of intracranial aneurysms by occlusion of the carotid artery in the neck were subsequently published.86 The overall incidence of ischemic neurological deficits was 33% in patients with ruptured aneurysms and 12% in those with unruptured lesions. The ischemic deficit rate was also higher in patients with occlusion of the ICA as opposed to the common carotid artery (abrupt occlusion: 59 vs 32%, respectively; gradual occlusion: 41 vs 24%, respectively), irrespective of the presence or absence of an SAH.

Following Yasargil’s description of an STA–MCA bypass in 2 patients who harbored giant intracranial aneurysms of the supraclinoid ICA,18 the option of an EC–IC bypass became a component in the neurosurgeon’s armamentarium for the treatment of complex intracranial aneurysms.

The importance of the STA–MCA bypass in preventing ischemic neurological deficits during major parent vessel occlusion for the treatment of intracranial aneurysms has been well established.21,29,37,40,45,50,58,66,69,91,112,121,141 The utility of revascularization with an STA–MCA bypass has also been shown during the repair of mycotic or traumatic aneurysms of distal cortical vessels, trauma to the cervical ICA, surgical repair of carotid–cavernous fistulas, or removal of skull base tumors.11,15,23,30,41,58,90,113,128 The presence of a patent STA–MCA bypass may not offer complete protection from ischemia, however, when a major intracranial or extracranial vessel has been occluded.20,29,37,40,45,50,58,90,117,119,141 Possible mechanisms of ischemia include embolic phenomena, failure to provide enough blood supply to the entire MCA territory, and retrograde thrombosis of the M₁ segment when the MCA is clipped just proximal to its bifurcation.20,37,40,45,50,58,90,94,116

Based on an analysis of the known risks of the balloon occlusion test,92 de novo aneurysm formation,98 possible contralateral aneurysm enlargement, and the fact that some patients who pass a CAO test will still suffer an ischemic event,74,77,92,118,129 some neurosurgeons have adopted the approach of performing an EC–IC bypass in all cases that require sacrifice of a major cerebral vessel.74,77,101 Others will perform a bypass based on the analysis of clinical, angiographic, and balloon occlusion test results.5,42,83,124 Nevertheless, the use of an EC–IC bypass as part of the treatment of complex aneurysms has been adopted by most cerebrovascular surgeons.

Moyamoya Disease

The first case of moyamoya disease treated with a direct STA–MCA bypass was performed in 1972 by Yasargil in a 4-year-old child, who had remarkable improvement following the procedure.94 Postoperative angiograms showed patency of the anastomosis and evidence of collateral vessels from the verteobasilar system and other extracranial sources. In 1980 an indirect STA–MCA bypass for bilateral occlusion of the supraclinoid ICA was performed in a patient with recurrent symptoms of hemiparesis and aphasia.114 A direct STA–MCA bypass was planned, but at surgery no suitable recipient cortical vessel was found, and the STA and surrounding tissue were basically laid over the cerebral hemisphere and sutured to the arachnoid. The patient had a remarkable clinical recovery, and postoperative angiograms showed extensive collateral vessel formation, establishing the effectiveness of an indirect STA–MCA bypass as a form of cerebral revascularization.

In children, the benefits of improving symptoms, reversing neurological deficits, enabling the development of normal intelligence, preventing further ischemic episodes, decreasing seizure activity, and even the disappearance of involuntary movements have been observed.3,33,48,52,54,59,60,75,89,102,123 Several studies addressing the efficacy of the direct and indirect bypass techniques have been done in pediatric patients, and better clinical and angiographic results are usually seen when a direct bypass is performed.52,54,75,123 Various studies have also demonstrated the benefits of an STA–MCA bypass in ischemic moyamoya disease in adults, preventing further ischemic episodes and improving clinical symptoms and cerebral hemodynamics.28,44,50,51,59,61,68,79,80 On the other hand, the effectiveness of revascularization in preventing hemorrhage remains a controversy.50,53,61,88

A large retrospective study including 57 neurosurgical institutions has been done in Japan, and data were available for 290 patients with the hemorrhagic form of moyamoya disease.27 Conservative treatment was administered to 138 patients, and 152 patients underwent surgical revascularization. In the nonsurgical group, 28.3% of the patients had a recurrent hemorrhage during follow-up, compared with 19.1% in the surgical group. The authors concluded that prospective studies are needed to clarify the efficacy of the STA–MCA bypass in the prevention of hemorrhage in this disease. A large prospective trial is now underway in Japan to evaluate the effectiveness of STA–MCA bypass for the prevention of cerebral hemorrhage in moyamoya disease.52,78,140

Occlusive Cerebrovascular Disease

After the EC–IC bypass trial results appeared, a few centers continued to perform this bypass surgery for the treatment of symptomatic occlusion of the ICA in selected patients, with good outcomes. Indications for the procedure were based on evidence of perfusion abnormalities on imaging studies or the presence of symptoms despite maximal medical management.2,25,29,37,40,45,50,58,90,117,119,125 With advances in neuroimaging and a better understanding of cerebral metabolism, more investigations were performed in an effort to determine the natural history of occlusive atherosclerotic carotid artery disease, the risk of stroke in subpopulations with different states of hemodynamic insufficiency, and whether any of these subpopulations could benefit from a revascularization procedure.58,47,62,97

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The occurrence of ischemic symptoms and stroke in occlusive cerebrovascular disease can usually be attributed to either thromboembolic phenomena or a decrease in cerebral perfusion pressure. Only recently the overall risk of subsequent stroke in patients with CAO has been clarified. A major prospective study by Powers et al. revealed a stroke risk of 0% at 2 years and 4.4% at 3 years in the group of patients who never had any symptoms in contrast to a risk of 7.7% at 1 year, 19% at 2 years, and 21% at 3 years after symptom onset in symptomatic patients with CAO. Additionally, several authors using different imaging modalities, such as xenon-CT, xenon–single-photon emission CT, or PET scanning, have provided evidence that the presence of hemodynamic impairment of the cerebral blood flow/perfusion is significantly linked to an increased risk of stroke.

The St. Louis Carotid Occlusion Study was a prospective blinded study in which the authors evaluated the relationship between the state of “misery perfusion” (increased OEF on PET scanning) and stroke risk in patients with symptomatic CAO. There were 81 patients who were divided in 2 groups: patients with increased OEF (39 patients) and those with a normal OEF (42 patients). In all patients with an increased OEF, the hemodynamic abnormality was ipsilateral to the occluded carotid artery. At the end of the follow-up, in the group with an increased OEF, there were 12 total and 11 ipsilateral strokes, compared with 3 total and 2 ipsilateral strokes in the group with a normal OEF (p = 0.005 and 0.004, respectively). The risk of ipsilateral stroke in the group with an increased OEF was 10.6 and 26.5% at 1 and 2 years after symptom onset, respectively. On the other hand, the group with a normal OEF had a 2.4 and 5.3% risk of stroke at 1 and 2 years after symptom onset, respectively. The authors concluded that the state of misery perfusion is a significant independent predictor of the subsequent risk of stroke in medically treated patients with CAO. This study also led to the conclusion that patients with retinal symptoms only had a low risk of subsequent stroke, a result also found in other studies.

Several investigators have described the effects of an STA–MCA bypass on rCBF, regional cerebral metabolic rate of oxygen, cerebral blood volume, and OEF in patients with occlusive cerebrovascular disease. More importantly, there was a demonstrable reversal of misery perfusion and marked improvements in rCBF and cerebral metabolism in the subpopulation of patients with hemodynamic impairment who had undergone a revascularization procedure.

Recent anecdotal case reports on emergent surgical revascularization for acute stroke have demonstrated restoration of normal flow to regions of ischemic penumbra and improvement in perfusion-weighted MR imaging/diffusion-weighted MR imaging mismatch. Even though the area of mismatch does not accurately correspond to the penumbral zone, with further developments in imaging modalities and better definitions of ischemic but viable tissue (increased OEF) thresholds, there will likely be more thoughts on emergent surgical revascularization procedures for acute stroke in cases in which intraarterial thrombolysis is contraindicated.

Aneurysms and Tumors

The STA–MCA bypass as an adjuvant for aneurysm treatment will likely remain an option in the future. The procedure has been used successfully as an adjuvant to aneurysm or parent vessel occlusion by surgical and endovascular means. The threshold of lowered rCBF indicating that the collateral circulation will be adequate to prevent ischemia after permanent major vessel occlusion is still to be determined. Advanced brain imaging perfusion technologies may improve the accuracy of the balloon occlusion test. Newer imaging modalities may also allow a more accurate prediction of whether certain aneurysms can be clipped safely or whether wall thickness and the presence of calcification mandates parent vessel occlusion/reconstruction combined with an EC–IC bypass as an adjuvant. New STA–MCA bypass techniques may be useful in certain circumstances when a 2-limb end-to-end bypass with good blood flow and a short anastomotic time are needed.

Moyamoya Disease

The role of the STA–MCA bypass in moyamoya disease awaits the results of large randomized trials. As mentioned, previous studies have indicated improved metabolic and hemodynamic outcomes in patients with this disease. More detailed outcome studies on the prevention of ischemic stroke and hemorrhagic events in adult patients are also expected. The Japan Adult Moyamoya Trial will be conducted to determine whether EC–IC bypass plus risk factor modifications are effective in reducing the incidence of hemorrhagic phenomena and improve outcome in patients with this disease. The efficacy of the STA–MCA bypass in children will also be better defined when the results of large long-term outcome studies become available.

Occlusive Cerebrovascular Disease

The evidence that patients with CAO and Stage 2 hemodynamic insufficiency have an increased risk of stroke and the substantiation that an EC–IC bypass may reverse this stage of misery perfusion reveals the need for a new prospective randomized trial. The Carotid Occlusion Surgery Study is a new trial in which investigators will prospectively evaluate the efficacy of the STA–MCA bypass in the prevention of stroke in patients with symptomatic CAO and evidence of misery perfusion on PET scans. It will be a multicenter randomized trial, and the EC–IC bypass will have a primary objective of augmenting blood flow to the cerebral hemisphere that is hemodynamically impaired by an ipsilateral occlusion of the ICA. The trial will enroll only those patients...
who have symptoms of the cerebral hemisphere referable to the occluded ICA, and all patients will receive the best medical therapy. Patients with retinal symptoms will not be enrolled unless they have hemispheric symptoms as well. The primary outcome event of the study is the occurrence of ipsilateral ischemic hemispheric stroke from the time of randomization to the end of the follow-up at 24 months or any stroke or death within 40 days of entry into the trial. Secondary end points include any fatal or nonfatal stroke, ipsilateral disabling stroke, death, quality of life, and function. Other outcome events include transient ischemic attack, surgical complications other than stroke, perioperative myocardial infarction, and bleeding complications.

Conclusions

The STA–MCA bypass is an elegant procedure developed by M. G. Yasargil and was first applied in the treatment of occlusive cerebrovascular disease in 1967. It was soon added to the surgical management of other complex vascular lesions of the nervous system. It has proved to be feasible with a low complication rate but has been shown to be ineffective in preventing stroke in nonelected populations harboring occlusive carotid artery or MCA disease. The finding that a subpopulation of patients with symptomatic CAO and increased OEF has an increased risk of stroke, together with the evidence that an STA–MCA bypass procedure can reverse the state of misery perfusion brings us to a new trial. The Carotid Occlusion Surgery Study will be performed to determine whether the STA–MCA bypass can decrease the incidence of stroke in these patients with evidence of misery perfusion. An international multicenter trial will probably further define the role of the STA–MCA bypass in the setting of hemorrhagic moyamoya disease. This elegant surgical technique will likely remain an important tool in the neurosurgeon’s armamentarium for the management of occlusive atherosclerotic and traumatic cerebrovascular disease, intracranial aneurysms, skull base tumors, moyamoya disease, and possibly acute stroke.

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