The evolution of cerebral revascularization surgery

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Among the relatively few surgeons to be awarded the Nobel Prize was Alexis Carrel, a French surgeon and pioneer in revascularization surgery at the turn of the 20th century. The authors trace the humble beginnings of cerebral revascularization surgery through to the major developments that helped shape the modern practice of cerebral bypass surgery. They discuss the cornerstone studies in the development of this technique, including the Extracranial/Intracranial Bypass Study initiated in 1977. Recent innovations, including modern techniques to monitor cerebral blood flow, microanastomosis techniques, and ongoing trials that play an important role in the evolution of this field are also evaluated. (DOI: 10.3171/2009.3.FOCUS0931)

KEY WORDS • cerebral revascularization • extracranial-intracranial bypass •
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THE story of how cerebral revascularization surgery came into common practice, fell from favor, and reemerged as an effective treatment for specific diseases has developed over the last century and a half. Here we explore the exciting history, current applications, and future developments of cerebral revascularization surgery, with a specific focus on STA-MCA bypass. Through this comprehensive review of the literature, we describe the most prominent trends of the last 50 years, incorporating recent insight and innovation.

It is a sobering thought that just over 50 years ago, most strokes were thought to be due to vasospasm, and it was Fisher¹⁹ who widely promoted the concept that stroke was associated with CA disease. Even now, symptomatic CA occlusion carries an overall risk of subsequent stroke of 2–5% per year.^{25,27,37}

The development of microneurosurgical techniques facilitated the refinement of cerebral revascularization. While EC-IC bypass can be applied with excellent technical results in terms of graft patency (> 95%), review

of the Extracranial/Intracranial Bypass Study Group of 1985 illustrated the importance of defining which disease processes and hemodynamic states are the most amenable to the procedure.¹ With limited medical treatments, surgical intervention may be of great benefit to the properly identified patient population.

History

The Development of Cerebral Microvascular Anastomoses

The first vascular anastomosis was detailed by Eck in 1877 with his operation on dogs to create a side-to-side anastomosis of the hepatic vein to the inferior caval vein (later known as the Eck fistula). Of the 8 dogs undergoing this procedure, 7 died in 1 week and 1 lived briefly before running away.¹⁰ French physician Alexis Carrel published an account in 1902 of the first arterial end-to-end anastomosis utilizing fine suture material and triangulation.¹² For this work and his pioneering the field of vascular surgery and organ transplantation, he was awarded the Nobel Prize for Physiology and Medicine in 1912.

German and Taffel²⁴ began to experiment with cerebral revascularization in 1939 with the transposition of a vascular muscle flap onto the cortex in dogs and primates, the first documented encephalomyosynangiosis. Kredel⁴⁰ attempted this in humans in 1942 but later abandoned the procedure due to a high incidence of postoperative seizures. Soon after, in 1949 Beck and colleagues⁹

Abbreviations used in this paper: CA = carotid artery; CBF = cerebral blood flow; COSS = Carotid Occlusion Surgery Study; EC-IC = extracranial-intracranial; ELANA = Excimer Laser Assisted Nonocclusive Anastomosis; ICA = internal carotid artery; JAM = Japan Adult Moyamoya; JET = Japanese Extracranial-Intracranial Bypass Trial; MCA = middle cerebral artery; OEF = oxygen extraction fraction; RECON = Randomized Evaluation of Carotid Occlusion and Neurocognition; STA = superficial temporal artery.

described their revascularization technique of a carotid-jugular fistula.

The development of vascular bypass techniques and surgical magnification progressed on separate paths until the 1960s, when the merging of these 2 innovations led to the rapid growth of cerebral microvascular surgery. In 1876, Saemisch introduced the first binocular magnifying device to surgery.²⁸ In 1912 surgical microscopes and teloupes began to be used for experiments.⁵² Despite the prior development of microsurgical techniques and equipment in other surgical subspecialties (for example, otology and ophthalmology), neurosurgeons did not embrace the movement until much later. In 1957, Theodore Kurze⁴² of the University of Southern California was the first to use an operating microscope for neurosurgery.⁴¹ Following the suggestion of Julius Jacobson (a general vascular surgeon) to use an operating microscope, in 1962 Jacobson with Donaghy reported the first human microsurgical procedure in neurosurgery: an MCA endarterectomy.^{30,31,42} While the first attempt had failed, in the end 2 of the 9 original MCA embolectomies or endarterectomies remained patent.²⁰

The convergence of microneurosurgical techniques and more refined understanding of the pathophysiology of cerebral ischemic disease set the stage for the EC-IC bypass. Fisher²¹ had quite astutely stated in 1951, “it is even conceivable that some day vascular surgery will find a way to bypass the occluded portion of the artery.” In 1961, Pool and Potts³⁴ first attempted cerebral revascularization with a synthetic graft by using a plastic tube to create a STA to anterior cerebral artery shunt. Arteriography performed < 2 weeks after the operation showed a clotted tube. However, the patient apparently recovered well and was able to return to full-time work.⁵⁵ In 1963, Woringer and Kunlin⁷⁵ performed the first EC-IC bypass of the common CA–intracranial ICA using a saphenous vein graft. While overall the patient did not survive, the graft was patent on autopsy.

The Refinement of the EC-IC Bypass

The actions of the aforementioned pioneers, combined with timely advances in angiography, bipolar, and surgical microscopes, brought cerebral revascularization into the modern era. At this point, Yaşargil, a Turkish native, brought microsurgical techniques into the neurosurgical spotlight. Yaşargil trained in Switzerland under Krayenbühl, and together they published a book in 1965.³⁹ That same year, Yaşargil moved to Vermont to join the Donaghy’s laboratory. Donaghy had worked closely with Littman to develop microsurgical instruments and needles, eventually founding the *Journal of Microsurgery*. It was in Donaghy’s laboratory in 1961 that Jacobson and Suarez³¹ had previously described the technique of vascular anastomosis using the operating microscope. By the time Yaşargil arrived in Vermont, Donaghy’s laboratory was already achieving a 66% patency rate in experimental microvascular anastomotic techniques.⁷⁴

With perseverance, Yaşargil managed to significantly improve on the original techniques of Suarez and Jacobson.^{64,74} He incorporated the bipolar technology of Malis

to carefully dissect the fragile blood vessels of the brain. While at the University of Vermont, Yaşargil performed the first EC-IC bypass from the STA to a branch of the MCA in a dog.²⁰ In 1967, once while in Zürich and then again in Vermont, Yaşargil performed the first EC-IC bypasses in a patient with the purpose of bypassing an occluded ICA.^{20,77} In all, Yaşargil would advance cerebrovascular neurosurgery through significant contributions to the development of the counterbalanced “floating” microscope, novel microsurgical instruments, and aneurysm clips and applicators.⁷⁰

Yaşargil performed the first STA-MCA bypass for moyamoya disease in 1972. The patient was a 4-year-old boy with right hemiplegia and anarthria. He received an end-to-end STA to left insular MCA anastomosis. Two years later, angiography showed improved vascularization and the child’s symptoms had improved.³⁸ Karasawa and colleagues³⁴ achieved good clinical results repeating this procedure in 23 patients with moyamoya syndrome.

Alternatives to the STA-MCA bypass were quick to be developed, and many played a pivotal role in pioneering various intracranial bypass techniques.⁶³ Loughheed performed the first EC-IC bypass using a saphenous vein graft in 1971, and Ausman⁶ used a radial artery graft in 1978.⁶⁸ In the 1970s Sundt and colleagues⁶⁸ and others⁶ introduced posterior circulation revascularization. This was used to treat occlusive disease, vertebrobasilar insufficiency, and unclippable aneurysms.^{13,45} This prolific period in the history of cerebral revascularization was accompanied by a determination to increase patient safety during the procedure with improvements in anesthesia, intraoperative monitoring, the use of barbiturates, and hypothermia.

Testing Cerebral Revascularization: The EC/IC Bypass Study Group

As microneurosurgery progressed, indications for revascularization broadened to include multi infarct dementia, acute stroke, MCA stenosis or dissection, and ischemic retinopathy. To formalize the indications and outcomes of EC-IC bypass, the International Cooperative Study of Extracranial/Intracranial Arterial Anastomosis (EC/IC bypass study) was conducted from 1977 to 1985.² This was an international, multicenter, prospective, randomized study that was to test the concept of STA-MCA bypass surgery as a stroke prevention treatment. Specifically, the study evaluated the value of EC-IC bypass as a means to decrease the subsequent stroke rate for the treatment of “symptomatic atherosclerotic lesions of the internal and/or middle cerebral arteries.”

Eligible patients needed to have either stenosis/occlusion of the MCA trunk or ICA above C-2, or a recent (within 3 months) transient ischemic attack or stroke within the MCA/ICA distribution. A total of 1377 patients met these criteria and were randomized to receive either medical treatment (aspirin and hypertension control) or medical treatment in addition to STA-MCA bypass. The surgeries were carried out by cerebrovascular experts, with > 96% of the bypass grafts patent on follow-up.² The patients had very close follow-up and thorough examinations.

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By the study's close in 1985, the average follow-up was 55.8 months with a minimum of 33 months. While 118 patients were eventually excluded who had initially been randomized, no patient participating in the study was lost to follow-up. The patients with strokes prior to randomization were included in an intent-to-treat analysis.^{1,2}

Ultimately, the data of the study suggested EC-IC anastomosis was not better at preventing stroke in patients with atherosclerotic arterial disease of the CA and MCA compared with best medical therapy.² In fact, timing and incidence of both nonfatal and fatal stroke increased in patients receiving both surgery and medical therapy.¹ Secondary survival analyses were equally discouraging. The study identified 2 important subgroups that appeared to do particularly poorly: patients with severe MCA stenosis and those with persistence of ischemic symptoms in known ICA occlusion.¹

Reaction to the EC/IC Bypass Study Group

Following the publication of the EC/IC Bypass Study group's conclusion in 1985, the number of EC-IC cases performed fell precipitously. In North America, insurance companies began to deny coverage for the procedure, and the use of STA-MCA bypass for symptomatic CA or MCA occlusion was nearly abandoned. A similar pattern of decline also occurred in Europe and Asia. It appeared the technical progress could not be supported by the surgical outcomes.⁸ A decade later it was reported that for 42% of patients undergoing EC-IC bypass, their particular surgeon had performed no bypass procedure during that year.³ A rapid decline in residents training in microsurgery followed. As surgeons performed fewer cases overall, mortality rates increased from 2.8% (1992–1996) to 5.7% (1997–2001).³

The initial main criticisms of the trial included the presence of bias, lack of generalizability, and the inability to section out particular groups with hemodynamic compromise who could potentially benefit from surgical revascularization. Critics focused on observational, allocation, and “randomization-to-treatment” bias.^{4,7} In 1987, 3 committee reports on the EC/IC Bypass Study appeared in the *New England Journal of Medicine*, concluding perhaps that the EC/IC Bypass Study population may not have been representative for the population at risk.⁶⁶

Subgroups consequently identified to potentially benefit from surgical revascularization are those in whom hemodynamic factors play a primary role in the precipitation of stroke. Recent technological advances, not available at the time of the EC/IC Bypass Study, have since made it possible to better identify these potential patients.^{16,36,51,67} One such parameter, the OEF as determined by PET identifies patients with hemodynamic susceptibility, who may then benefit from a bypass procedure.^{18,25,37,76}

Present Practices

Currently, EC-IC bypass is either performed for CBF augmentation or replacement. Examples of the former would be symptomatic patients with CA occlusion and documented hemodynamic compromise or moy-

amoya disease. Bypass surgery for CBF replacement is most frequently performed in complex aneurysm surgery, such as when an aneurysm is trapped, or in skull base tumor surgery associated with vessel sacrifice or injury.^{5,7,23,34,35,43,46,47,51,72} Multiple mechanisms of creating artificial CBF conduits are available in addition to the already discussed pedicled arterial graft of the STA-MCA anastomosis. An STA-MCA bypass has a patency rate of > 95%.^{55,59} Other common cerebral revascularization techniques include interposition vein grafts, such as the greater saphenous vein, free arterial grafts including the radial artery, and artificial grafts such as polytetrafluoroethylene tubes.^{45,69}

The saphenous vein bypass graft has been used for giant intracranial aneurysms, skull based tumors requiring ICA sacrifice or involving the ICA, VA, or CA occlusive disease.^{15,22,49,61,62,65} Internal CA bypasses include cervical-supraclinoid ICA, petrous-supraclinoid ICA, and cervical-petrous ICA.⁴⁴ The radial artery bypass graft has been shown to have long-term patency when used for treatment of giant aneurysms of the cavernous supraclinoid ICA.^{29,60}

Intracranial-intracranial bypasses are occasionally necessary. A short interposition graft such as the patient's own saphenous vein is used. Donor vessels in IC-IC bypasses tend to be from the ICA, M₁ or A₁ vessels, and the recipients as varied as EC-IC procedures, including the ICA, M₁₋₃, A₁₋₂, P₁₋₂, basilar artery, and superior cerebellar artery.

Important developments in monitoring intraoperative flow have also been made. The use of micro-Doppler, transit time flowmetry, such as the Charbel microflow probes (Transonic), and surgical microscope-based indocyanine green video angiography have all had a positive impact on cerebral revascularization surgery by confirming graft patency and flow.

Measuring Cerebral Hemodynamic Insufficiency: the Oxygen Extraction Fraction

One of the major criticisms of the EC/IC bypass trial was the assertion that patients with verifiable cerebral hemodynamic insufficiency from carotid occlusion would potentially benefit from revascularization. Only recently have modern technological advancements allowed us to define this subgroup with hemodynamic failure.²⁵ The OEF, as measured using PET, helps to determine the hemodynamic susceptibility. It has been shown that patients with increased OEF (Stage II hemodynamic failure) are at increased risk for stroke development.^{18,25,37,76} The OEF can be returned to normal in patients with CA occlusion who are undergoing EC-IC bypass.

In addition to OEF, other methods exist to assess cerebral hemodynamics and, therefore, define appropriate surgical candidates. These techniques include Xe-CT, SPECT, CT and MR angiography, perfusion CT and MR imaging studies, and digital subtraction angiography. Focus has also shifted to defining the cerebrovascular reserve by a physiological challenge, such as the use of intravenous acetazolamide. Near-infrared spectroscopy has been used to confirm the increase in cerebral blood oxygenation following EC-IC bypass procedure.⁵⁰ Vali-

TABLE 1: Important past studies on revascularization surgery*

Authors & Year	Study	Hypothesis	Outcome
Anonymous, 1985	EC/IC Bypass Study	EC-IC bypass decreases strokes & improves outcomes	op & medical management fared worse than medical management alone; nonfatal & fatal stroke occurred more frequently & earlier in patients undergoing ops; 30-day op mortality
Grubb et al., 1998	Saint Louis Carotid Occlusion Study	OEF relates to stroke incidence	ipsilat stroke rate at 2 yrs in patients w/ normal OEF is 5.3% compared w/ 26.5% for patients w/ increased OEF (p = 0.004)
Derdeyn et al., 2002	Cost-Effectiveness Analysis of Therapy for Symptomatic Carotid Occlusion	PET screening before selective EC-IC vs medical treatment	PET screening of the cohort followed by EC-IC bypass yielded 23.2 additional QALYs at \$20,000 per QALY compared w/ medical treatment alone
JET Study Group, 2006	JET-1	Stage II hemodynamic compromise improves w/ op bypass	EC-IC bypass surgery reduces the incidence of major stroke or death in the 2-yr period after op
	JET-1 subanalysis	EC-IC bypass changes brain volume & hemodynamics	op increased the affected/unaffected % regional CBF ratio (p < 0.03)

* QALY = quality-adjusted life year.

dated outcomes metrics evaluate functional neurological status and neurocognitive status.⁷³

Saint Louis Carotid Occlusion Study

The St. Louis Carotid Occlusion Study,²⁵ a prospective cohort analysis, evaluated the prognostic abilities of hemodynamic factors (as determined by OEF) for patients with CA occlusion. Factors other than OEF that could have contributed to stroke, including smoking, hypertension, and hypercholesterolemia were controlled. It was found that asymptomatic patients, similar to their symptomatic colleagues in baseline risk factors, had a lower frequency of hemodynamic abnormalities, as determined by significantly elevated OEF.¹⁹ In comparison with symptomatic patients, the never-symptomatic patients were found to have a lower incidence of elevated OEF, which also correlated to a lower incidence of stroke.^{56,71}

Already, PET scans have become commonplace for preprocedure determination of hemodynamic insufficiency. Various smaller studies stratifying patients depending on PET OEF ratios have begun to find improvements in clinical outcome following bypass surgery. For example, a recent study found symptomatic patients with increased OEF indicative of hemodynamic cerebral ischemia had improvements in cognition following bypass (Table 1).⁵⁸

Recent, Ongoing, and Future Studies

The JET-1 Study

Like the Carotid Occlusion Surgery Study, the JET is a multicenter, randomized, prospective study of patients with hemodynamic brain ischemia due to cerebral artery occlusive disease.³² The JET focuses on patients with

Stage II compromise (misery perfusion), as measured by PET OEF, looking to elucidate the idea of collateral circulation and cerebrovascular reserve.⁷³ The study looked at outcomes of CBF and the progression of neurophysiological function. The analysis revealed a significantly lower incidence of stroke recurrence for patients with Stage II ischemia undergoing bypass surgery than those treated with strict medical therapy.^{32,53}

The COSS

With the role of OEF (as defined by PET) in hemodynamic insufficiency and stroke better defined, the next question is how surgical intervention can change this outcome. The COSS²⁶ is a randomized, controlled study looking at the ability of combined STA-MCA bypass and medical therapy to reduce subsequent ipsilateral ischemic stroke. To participate in the study, patients must have atherosclerotic ICA occlusion with resulting hemispheric symptoms and ipsilateral increased OEF as measured by PET. Examples of excluded patients were those with other causes of cerebral ischemia (for example, moyamoya, vasculitis, and cardiac insufficiency), with anticoagulant medical treatment or planned cerebrovascular surgery. The patients must have a PET OEF that corresponded to their symptoms and imaging. Specifically, the ipsilateral/contralateral OEF ratio in the MCA territory must be > 1.130. The COSS trial is currently expected to run until 2013.

The RECON Trial

The RECON trial¹⁴ is an ancillary study to COSS aimed at assessing the relationship between cerebral hemodynamics and cognitive function in patients undergoing treatment for unilateral CA occlusion with EC/IC

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TABLE 2: Current studies on revascularization surgery

Authors & Year	Study Title	Hypothesis
Grubb et al., 2003	COSS	STA-MCA bypass & medical therapy decreases incidence of subsequent ipsilateral ischemic stroke
Chmayssani et al., 2007	RECON	bypass surgery improves cerebral hemodynamics & cognitive function
Miyamoto, 2004	JAM	op revascularization is effective for patients w/ moyamoya presenting w/ intracranial bleeding
JET Study Group, 2002	JET-2	stroke recurrence rate for patients w/ Stage I ischemia is decreased after bypass surgery

bypass in the COSS trial. Cognitive impairment in association with chronic cerebral hemodynamic insufficiency has often been overlooked. This study will help elucidate whether EC-IC bypass can improve cognitive function or prevent against further cognitive decline.

The JET-2 Study

The JET-2 study examines the stroke recurrence rate on medical treatment for patients with Stage I ischemia, as determined by cerebrovascular reserve capacity and rest CBF value. This is determined via paired blood flow studies after a cerebral vasodilatory stimulus. The aim is to be able to determine which patients with Stage I ischemia would have fewer strokes after bypass surgery.⁷³ Additional follow-up studies to the JET study includes the evaluation of JET-1 subgroups.³³

The JAM Trial

The JAM trial is a multicenter randomized trial looking at the efficacy of bypass revascularization for patients with moyamoya disease who present with intracranial bleeding. The aim of the trial is to determine if EC-IC bypass in combination with conservative management can improve prognosis (Table 2).⁴⁸

Novel Bypass Techniques

The ELANA technique allows for anastomosis of vessels without prior occlusion of the recipient vessel. This is a particularly attractive technique for CBF augmentation as it avoids the temporary cessation of CBF in a situation in which there is already a vulnerable blood supply. Essentially, the donor vessel is sutured to the recipient vessel together with a platinum ring. An arteriotomy is then performed using an excimer laser and the resultant flap is removed by a suction device.⁵⁷ The current disadvantages of this technique include the relatively high cost, longer procedure time, and the inability of this technique to work on vessel sizes < 2.6 mm.

A recently developed sutureless ELANA technique has the potential to be easier, with shorter procedure times and equivalent patency rates. A recently published laboratory evaluation in rabbits, comparing the ELANA and sutureless ELANA technique, showed that the sutureless ELANA bypass was faster (20 vs 90 minutes), rarely required occlusion (97%), and had an 89% patency rate.¹¹ These methods can be used for EC-IC and IC-IC bypass.

There is no doubt that revascularization surgery re-

mains an important technique in neurosurgery when CBF augmentation or replacement is required. Just as novel suture materials and the microscope ushered in the modern foundations of revascularization surgery, so will other technologies influence the future direction of this art. Developments in imaging techniques, especially of dynamic blood flow, will better guide surgeons to select patients that would benefit from surgery. Improvements in anastomotic techniques, especially obviating the need for temporary occlusion, will make this form of surgery safer and perhaps easier to impart onto future generations of surgeons. Less invasive techniques, such as endovascular surgery will also contribute as an important part of the cerebrovascular surgeon's armamentarium against ischemic damage to the brain.

Conclusions

Cerebral revascularization has developed from the culmination of several technologies, from the early beginnings of vascular surgical techniques in animals, to the development of the microscope, the bipolar coagulation, and suitable suture material. Its history has been marked by the successful interdisciplinary collaboration of key personalities, some of whom have been mentioned here. Major questions concerning the indications and benefits of cerebral revascularization are being addressed and interest in further advancing this field to make it safer for patients remains strong. Important research into perioperative blood flow assessment will play an important role in determining the success of cerebral revascularization. It is hoped that with better understanding of the pathophysiology of cerebral ischemia and better patient selection, cerebral revascularization will remain an important tool in contemporary neurosurgery.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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