

# The Evolution of Future Directions of Neuroendovascular Therapy: From Clips to Coils to ?

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Like many specialties, vascular neurosurgery has evolved over the past several decades, and the nature of the discipline continues to change. This subspecialty of neurological surgery has survived and flourished because of its ability to reinvent itself in the normal process of evolution and scientific advancement. Vascular neurosurgery is a field that should be disease, not procedure, oriented. The environment illustrated in Figure 1 is one that we are familiar and comfortable with, in terms of microsurgical technology, tools, and procedures. Added to our current armamentarium is the utility of intraoperative angiography. However, the scene illustrated in Figure 2 is an extension of the operating room; it is essentially neurosurgical care delivered in a critical care environment in its own right, with dedicated neuroanesthesia and neurophysiologic monitoring, suitable for treatment of complex intracranial revascularization, aneurysm, and arteriovenous malformation therapies.

The question arises, What tools and skills are necessary for a complete neurovascular surgeon? Certainly, they involve the microsurgical skills of the cerebrovascular physician and surgeon such as basic neurosurgical skills and a working knowledge of critical care medicine. Complete knowledge of medical therapy of ischemic and hemorrhagic disease is an absolute necessity if we are to be considered stroke specialists not only in the surgical arena but also in the medical arena. However, vascular neurosurgery at present requires additional tools and skills beyond the traditional ones listed above. Vascular neurosurgery can now be described as extraluminal and endoluminal. The extraluminal approach, or open cranial microsurgical technique, involves the use and knowledge of the aneurysm clip and bipolar cautery. Cortical mapping still has its role in arteriovenous malformation resection and/or cavernous malformation resection. The endoluminal approach requires mastery of the microcatheter, coils, balloon systems, liquid embolic materials, and stent technology. Finally, stereotactic neurosurgery/stereotactic radiosurgery has

become an integral part for the treatment of certain select cerebral arteriovenous malformations.

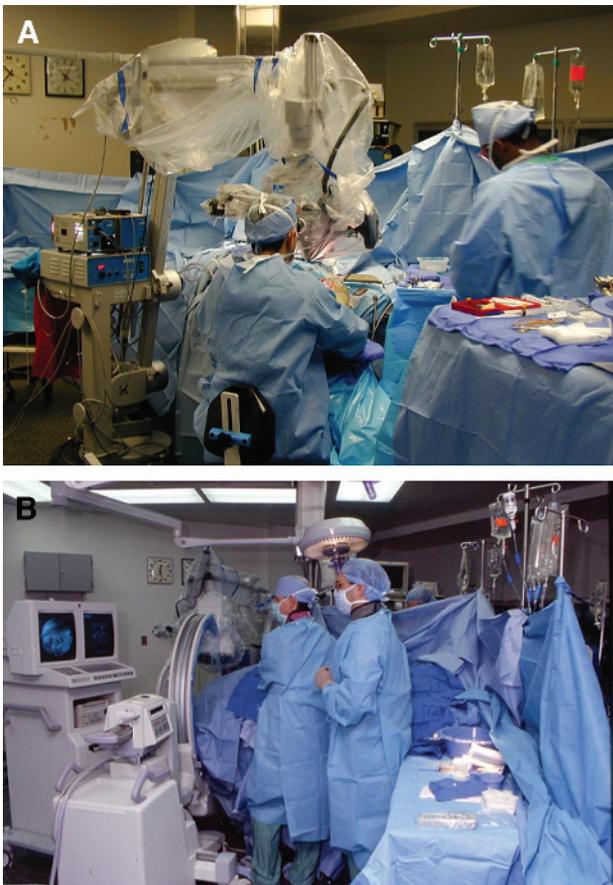
## NEUROENDOVASCULAR SURGERY

The most rapid progress in vascular neurosurgery has been made in the endovascular domain. Figure 3 depicts the endovascular coil/endoaneurysmal coil, originally invented by Guglielmi in the late 1980s, a major albeit controversial milestone in the treatment of aneurysmal disease.<sup>1,2</sup> This was the first time that a device could be placed into an aneurysm, deposited, detached if acceptable anatomically, and most important, retrieved if placement was less than ideal. Advances have been made in coil technology since the introduction of the Guglielmi detachable coil in terms of coil shapes, lengths, and bioactivity. Additionally, significant progress has been made in intracranial stents improving delivery and deployment. The use of stent technology has dramatically improved the application of coil technology to treat aneurysms and may in fact reduce the main problem associated with recurrence.

## THE INTERNATIONAL SUBARACHNOID ANEURYSM TRIAL

### Overview

The International Subarachnoid Aneurysm Trial (ISAT), which was published in 2005, changed the flavor of the treatment of subarachnoid hemorrhage greatly in Europe but also to a lesser extent in North America.<sup>3</sup> This study included 2143 patients with a diagnosis of subarachnoid hemorrhage in 42 centers mainly in England and Europe. Patients were evenly divided between microsurgery and endovascular therapy (1070 microsurgery, 1073 endovascular). The primary outcome in this study was death or dependence at 1 year, defined primarily by a modified Rankin Scale (mRS) score between 3 and 6. The secondary outcome was rebleeding and risk of seizures. The findings indicated that at 1 year, 250 of 1063 patients (23.5%) allocated to the endovascular treatment group were dead or dependent. Of the patients treated with



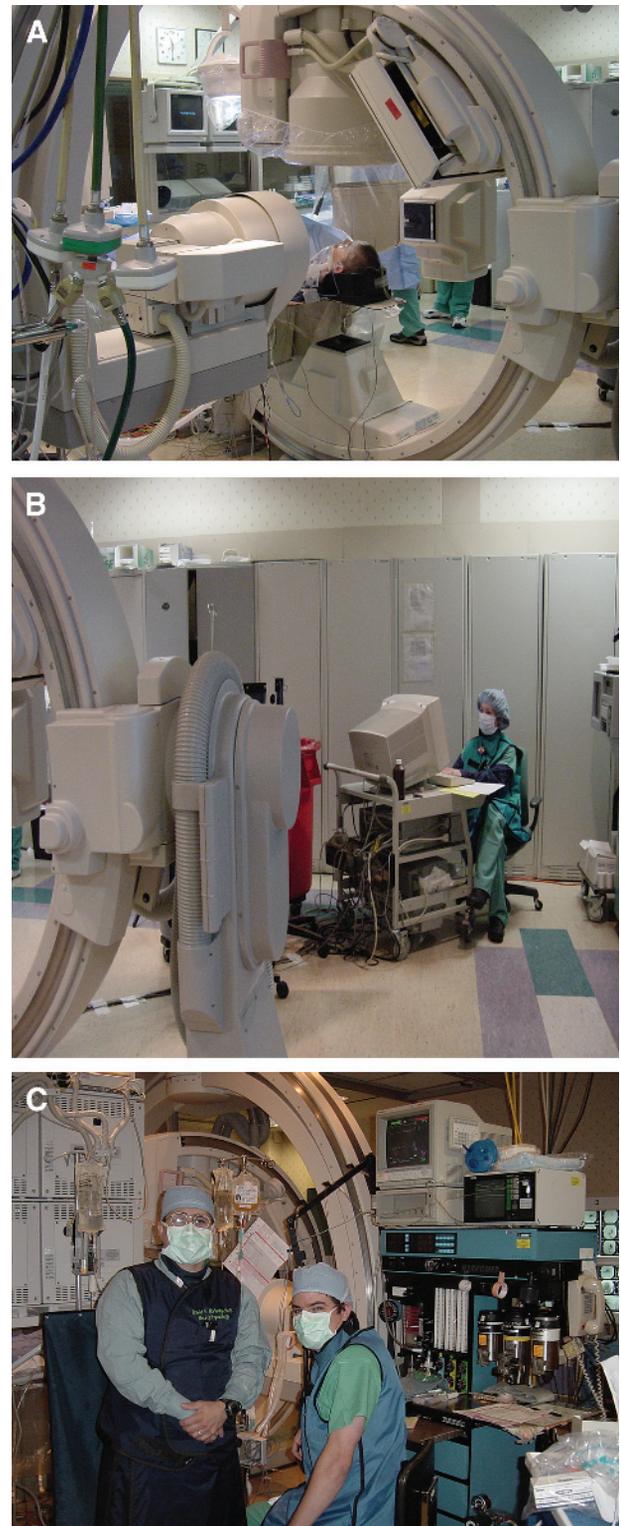
**FIGURE 1.** A, operating room set up for conventional craniotomy for microsurgical aneurysm clipping ligation. B, intraoperative cerebral angiography following aneurysm clipping.

open microsurgical techniques, 326 of 1055 patients (30.9%) treated were dead or dependent at 1 year. These data demonstrated an absolute risk reduction of 7.4% between the endovascular and open microsurgical groups that reached statistical significance ( $P = .001$ ). The results showed that the early survival advantage was maintained for up to 7 years and was significant in patients treated with endovascular techniques ( $P = .03$ ). The risk of epilepsy was substantially lower in patients allocated to the endovascular treatment group, but the risk of late rebleeding was higher.

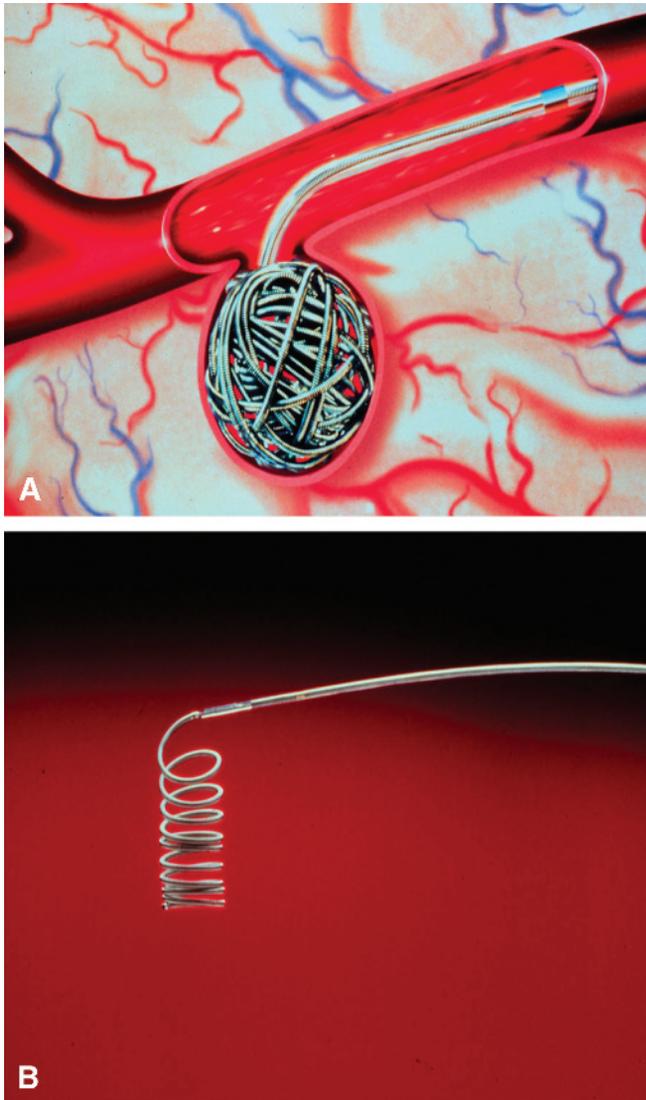
The conclusion was that in patients with ruptured intracranial aneurysms suitable for both types of treatments, endovascular and microsurgery, endovascular therapy is more likely to result in independent survival at 1 year and at 84 months. Despite the fact that rebleeding has a higher incidence with endovascular therapy, the survival benefit continues for 7 years on the basis of data from ISAT II.

**Critical Analysis**

The critical analysis of this trial involves several questions. First, what happened to the 7416 patients treated



**FIGURE 2.** Interventional neuroradiology suite setup depicting: (A) the conventional biplane for cerebral angiograph; (B) continuous neurophysiologic monitoring; and (C) neuro-anesthesia.



**FIGURE 3.** Schematic depicting bare platinum coils: (A) coiled within an aneurysm model; (B) delivered through a micro-catheter as described by Guglielmi.

outside the study, which, according to a purist and statistics, perhaps could be considered cherry picking or preselection bias? Second, this was statistically significant only for an mRS score of 3 to 6, not 0 to 1 or 0 to 3.<sup>3</sup> Third, the 1-year rebleed rate of 2.7% in the endovascular group compared with the 0.9% rate in the surgical group was concerning. Although this was not the experience in North America, the study's argument has been that this was a "real-world experience." The other concern is that there was no adjudication of surgical operators. Some surgeons in this trial had a microsurgical experience of < 10 aneurysms per year, in contrast to the interventionalists in the trial who were some of the most experienced in the world.

Furthermore, this study has been quoted and used extensively as a generalization to all aneurysms. This is

absolutely not the case; one cannot use the results of the ISAT Trial to make generalizations regarding middle cerebral aneurysms, as only 14% in this location were treated by endovascular techniques. Similarly, generalizations cannot be made for basilar aneurysms since fewer than 10% of patients were treated microsurgically in the study. In addition, this trial has no place in the discussion of unruptured aneurysms because it was a trial of subarachnoid hemorrhage only.

## AN INSTITUTIONAL EXPERIENCE

### Overview

In our institutional experience at the Thomas Jefferson University Hospital, the year 2000 was the last year that more patients were treated transcranially than endovascularly (Table). As the years have progressed, more patients have been treated endovascularly primarily because of experience and improvement in neurointerventional technology. The continued referral of patients has maintained our surgical volume, and most important, the patients who are being referred for surgical treatment generally have aneurysms that are more difficult to treat based on our experience. When our group at Thomas Jefferson reviewed a series of 1307 endovascular cases from 1995 to December 2004, we discovered that a total of 1554 cases were attempted to be treated endovascularly.<sup>4</sup> In this group, the technical failure rate was 16%, and 247 patients were referred to surgery. There has been discussion that this failure rate is quite high; however, generally after 60 to 120 minutes, the decision often can be made whether a patient can be successfully treated with an endovascular procedure.<sup>5</sup> Another argument has been that perhaps because the same surgeon performed both the endovascular and open surgeries, he/she was more likely to take the patient to surgery and not aggressively pursue an endovascular success. In that initial group, the intraprocedural rupture rate was 1.4%, and there were 77 delayed thromboembolic events. To date, 7.2% of patients have required

**TABLE.** Data Showing the Thomas Jefferson Neurovascular Experience Between 2000 and 2006, Differentiating Between Endovascular and Open Microsurgical Treatment of Patients With Cerebral Aneurysms

Year	Total Patients Treated, n	Surgical Treatment, n	Endovascular Treatment, n
2000	284	162	122
2001	301	141	160
2002	351	134	217
2003	389	158	231
2004	427	161	266
2005	472	156	316
2006	511	147	364

additional treatment, although that number is increasing annually with longer follow-up.

### Cross-Over Analysis

A case-control analysis was performed in the 247 patients who crossed over from an endovascular to a surgical treatment option. Results were controlled for age, neurologic grade, medical and surgical comorbidities, and aneurysm site. In patients who were  $\leq 60$  years of age with anterior circulation aneurysms (38% of the group), there was no difference in outcome between endovascular and microsurgical interventions. Of the Hunt and Hess grade I and II subarachnoid hemorrhage patients  $< 60$  years of age, 9.9% of patients in the endovascular group compared with 11.1% in the microsurgical group had an mRS score between 3 and 6 (Figure 4). There was no statistical difference in outcome between the endovascular and microsurgical groups in this patient subdivision. However, subarachnoid hemorrhage patients with Hunt and Hess grades III and IV and anterior circulation aneurysms showed clear differences between endovascular and surgical outcomes. Twenty-one percent of patients treated endovascularly had an mRS score of 3 to 6 compared with 33% of patients treated microsurgically. Therefore, the chance of improved outcome was higher in the endovascular group in that subgroup of patients. In our experience, surgically treated patients had a 0% incidence of rebleeding (Figure 4). In the subgroup of patients who were  $\geq 60$  years of age with posterior circulation aneurysms (156 of 247 patients, 62%), endovascular intervention always had a more favorable outcome with respect to open microsurgery (Figure 5).<sup>6</sup> Specifically, low-grade subarachnoid hemorrhage patients (grades I and II) had an mRS between 3 and 6 in 12%

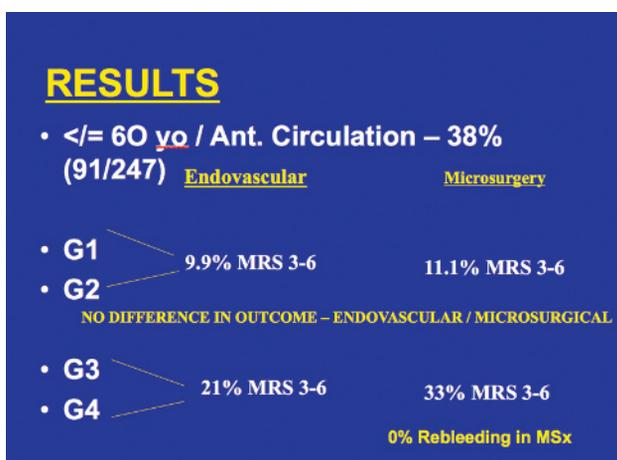
of the endovascular group compared with 29% of the microsurgical group. Similarly, high-grade subarachnoid hemorrhage patients (grades III and IV) had an mRS between 3 and 6 in 22% of the endovascular group as opposed to 37% of the microsurgical group.

### FUTURE DIRECTIONS

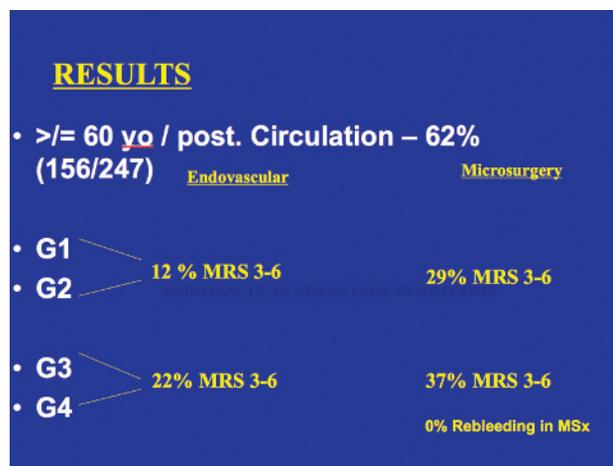
#### Gene Therapy

An extremely important article published in the *Journal of Vascular Surgery* in 2003 investigated ex vivo gene therapy with adenovirus-mediated recombinant transforming growth factor- $\beta 1$  (rTGF $\beta 1$ ) expression for the endovascular treatment of intracranial aneurysms.<sup>7</sup> This particular experiment involved the bilateral carotid aneurysm canine model in which vascular smooth muscle cells were infected with an adenovirus vector encoding rTGF $\beta 1$ . The virus was delivered via embolization into the aneurysm on sponges seeded or not seeded with the vascular smooth muscle cells infected with rTGF $\beta 1$ . The results demonstrated that there was improved neointimal growth with encoded vascular smooth muscle cells but there was no difference in aneurysm occlusion between rTGF $\beta 1$ -infected and noninfected cells. Similar studies have shown that aneurysmal healing is intimately linked to the interaction of endothelial cells with platinum coils.

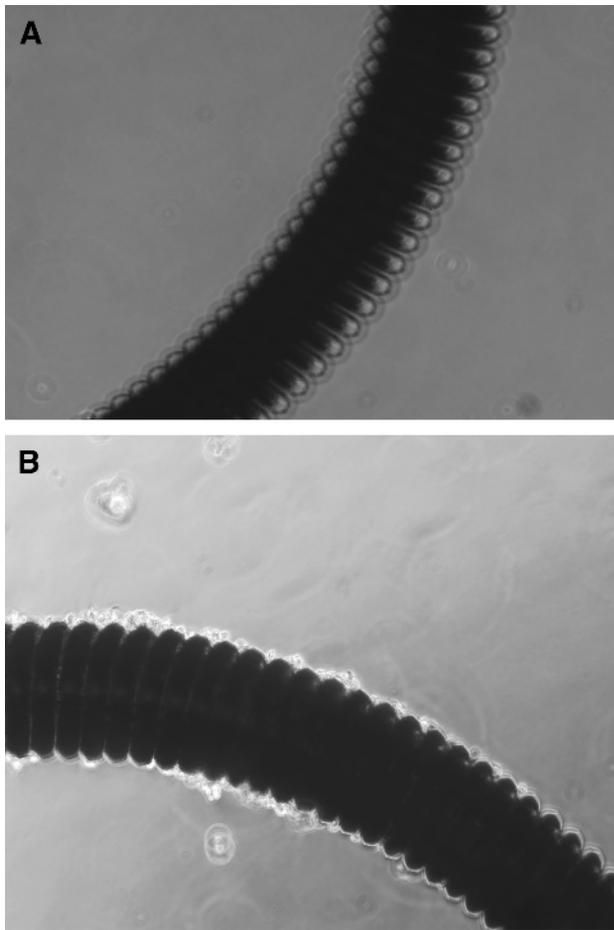
Endovascular research in a canine aneurysm model in our institution and many others has demonstrated that human endothelial cells adhere to platinum and that there is a distinct endothelium-coil interaction (Figures 6 and 7). It has been demonstrated that differential expression of endothelial genes can facilitate vessel intima healing via upregulation and downregulation techniques. With aneurysm recurrence being



**FIGURE 4.** Schematic depiction of combined endovascular and microsurgical experience at Thomas Jefferson University Hospital in the patients  $\leq 60$  years of age with anterior (Ant.) circulation aneurysms based on the Hunt and Hess grading system (G). MRS, modified Rankin Scale.



**FIGURE 5.** Schematic depiction of combined endovascular and microsurgical experience at Thomas Jefferson University Hospital in the patients  $\geq 60$  years of age with posterior (post.) circulation aneurysms based on the Hunt and Hess grading system (G). MRS, modified Rankin Scale.



**FIGURE 6.** Low magnification view of electron microscopy depicting endothelial adherence to Guglielmi detachable bare platinum coils in a canine aneurysm model.

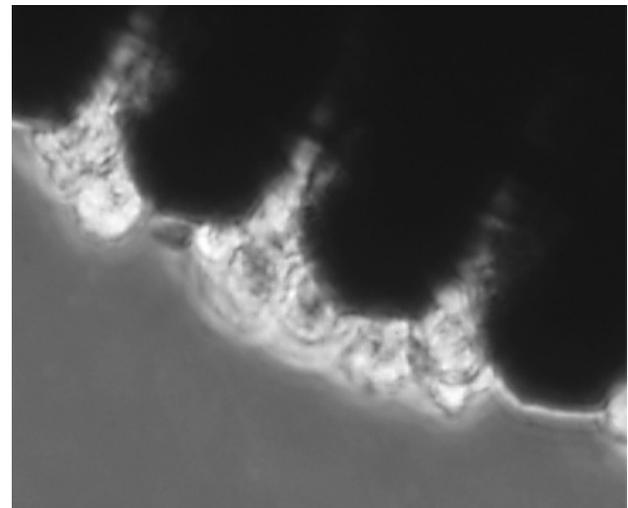
a significant concern, healing of the intima through the use of “bioactive coils” mediated by such genes is still an interesting and attractive hypothesis.

### Liquid Embolic Agents

An innovative direction of aneurysm therapy is the use of liquid embolic materials in endovascular occlusion. The Onyx HD500 material (ev3, Irvine, California), a methylcellulose polymer, has demonstrated excellent efficacy in endovascular aneurysm occlusion with specific indications.<sup>8-11</sup> The disadvantages of this new endovascular technique include the prolongation of brain ischemia from temporary balloon inflation in the parent vessel and the potential of thromboembolic events from the polymer.<sup>12</sup> An area of intense study and investigation involves flow diversion.

### Flow Diversion Techniques

The Pipeline embolization device (ev3) is a new endovascular flow diversion technique in which the metal surface area of aneurysm coverage approaches 30% to 35%, as

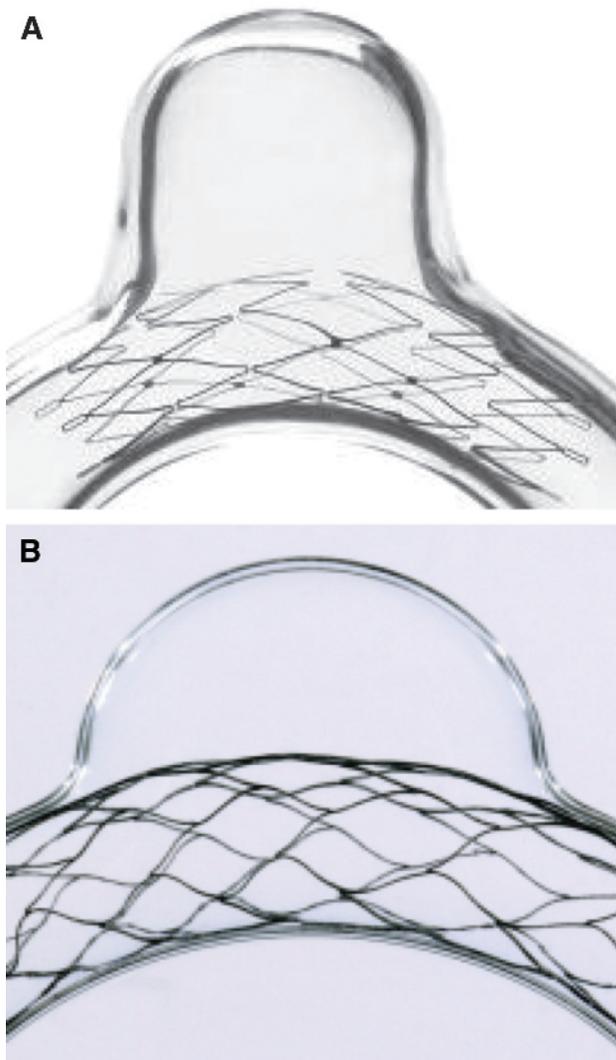


**FIGURE 7.** High magnification view of electron microscopy depicting endothelial adherence to Guglielmi detachable bare platinum coils in a canine aneurysm model.

opposed to traditional stenting such as Neuroform (Boston Scientific, Fremont, California) and Enterprise (Cordis Neurovascular, Miami Lakes, Florida) with 6.5% or 9.5% coverage (Figure 8). An illustrative case is the following: A 58-year-old woman with a right sixth cranial nerve palsy presented with headache and eye pain. Preoperative angiography showed a giant right cavernous aneurysm (Figure 9). The magnetic resonance image in Figure 10A demonstrates the significant mass effect on the optic apparatus. Blood vessel reconstruction with a Pipeline embolization device demonstrated the well-characterized “eclipse sign” shown in Figure 11. Angiographic follow-up in 1- and 6-month intervals showed complete obliteration of the aneurysm with preservation of the parent vessel caliber (Figure 12). Follow-up with magnetic resonance image showed involution of the thrombosed aneurysm and reduction of mass effect (Figure 10B). Obviously, long-term follow-up is necessary to further investigate parent vessel stenosis.

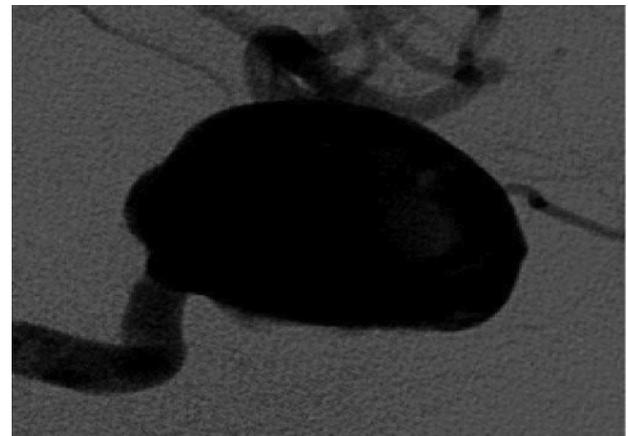
### Endovascular Management of Stroke

An exciting arena for vascular neurosurgery is stroke, which is the third leading cause of death in the United States and leading cause of disability. In 2007, a landmark study, the Interventional Management for Stroke (IMS) Study, was published in *Stroke*.<sup>13,14</sup> The purpose of the study was to investigate the efficacy and safety of stroke revascularization with a combined intravenous and intra-arterial approach. Included were patients between 18 and 80 years of age presenting with acute ischemic stroke and a National Institutes of Health Stroke Scale score >10. All patients received intravenous recombinant tissue-type plasminogen activator (rt-PA) within 3 hours of symptom onset. Among the 81



**FIGURE 8.** Schematic depiction of conventional intracranial stenting vs Pipeline embolization device and metal surface area coverage.

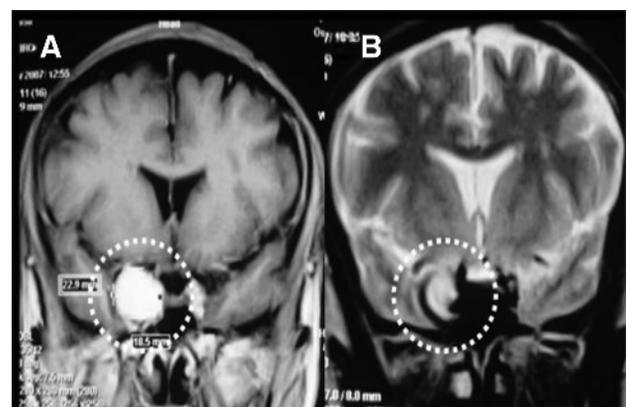
included subjects, if arterial occlusion was confirmed with cerebral angiography, intra-arterial rt-PA was delivered via a microinfusion catheter for 2 hours or until thrombolysis was achieved. This study demonstrated that revascularization interventions in stroke increase favorable patient outcome from 14% to 19% as defined by a normal National Institutes of Health Stroke Scale score 24 hours after the incident. Furthermore, the 3-month mortality rate for the IMS II patients was 16% compared with 24% for placebo and 21% for intravenous rt-PA therapy alone based on the National Institute of Neurological Disorders and Stroke rt-PA Trial (NINDS).<sup>15</sup> Specifically, the 3-month mRS score was 0 to 2 in 46% of the IMS II patients compared with 28% of the placebo and 39% of the intravenous rt-PA patients. Similarly, 27% of



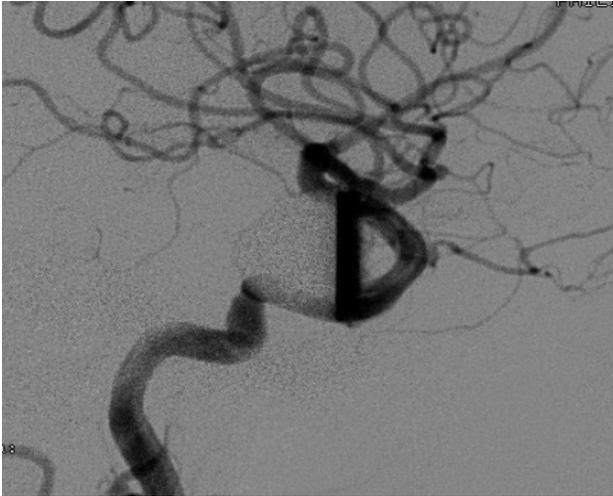
**FIGURE 9.** Preoperative digital subtraction angiography, oblique view under highest magnification, right internal carotid injection showing a giant cavernous aneurysm.

the IMS II, 15% of the placebo, and 25% of the intravenous therapy alone patients had a National Institutes of Health Stroke Scale score < 1. Finally, safety was proven by the similar rates of symptomatic intracerebral hemorrhages in IMS II patients and NINDS rt-PA patients. Clearly, revascularization is critical to maximize neurologic function. Physiologic imaging has been a cornerstone in determining ischemic penumbra from complete infarction, therefore defining patient selection for neuroendovascular intervention.

Several studies and clinical trials have investigated the safety and efficacy of intra-arterial thrombolysis in the setting of acute ischemic stroke. Three major clinical trials are the Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II and the Middle Cerebral Artery Local Fibrinolytic



**FIGURE 10.** A, coronal T1-weighted magnetic resonance image showing a giant right cavernous aneurysm with temporal lobe and optic apparatus compression. B, coronal T2-weighted magnetic resonance image showing postoperative thrombolysis of giant right cavernous aneurysm 6 months after Pipeline embolization device, with improvement of temporal lobe edema and optic apparatus compression.



**FIGURE 11.** Digital subtraction angiography, lateral view, right internal carotid artery injection immediately after Pipeline embolization device deployment with the characteristic "eclipse sign."

Intervention Trial (MELT).<sup>16-18</sup> PROACT I was a phase II clinical trial investigating the safety and efficacy of intra-arterial use of recombinant-pro-urokinase (rpro-UK) in acute ischemic stroke of the middle cerebral artery (MCA). After a negative head computed tomography, arterial occlusion was confirmed by cerebral angiography. Patients were then randomized to intra-arterial delivery of placebo vs 6 mg rpro-UK over 4 hours. The primary end points were rate of recanalization at the end of the infusion period and neurological deterioration from intracranial hemorrhage



**FIGURE 12.** Digital subtraction angiography, lateral view, right internal carotid artery injection 1 month after Pipeline embolization device deployment.

within 24 hours of treatment. Although rpro-UK-treated patients had higher vessel recanalization rates compared with placebo-treated patients (57.7% vs 14.3%), the incidence of intracranial hemorrhage was higher in the rpro-UK group (15.4% vs 7.1%). PROACT II was a subsequent phase III randomized controlled clinical trial that studied the safety and efficacy of rpro-UK in a larger patient population ( $n = 180$ ). Patients with angiographically confirmed acute MCA occlusions were treated intra-arterially with either 9 mg rpro-UK and heparin infusion ( $n = 121$ ) or heparin infusion alone ( $n = 59$ ). Patients who received rpro-UK had significantly lower mRS scores at the 90-day end point compared with patients treated with heparin only. The MCA recanalization rates favored the rpro-UK group as opposed to the control group (66% vs 18%). Although a higher incidence of intracranial hemorrhage was seen in the rpro-UK group (10% as opposed to 2% in the control group), the PROACT II multicenter trial demonstrated that the use of intra-arterial chemical thrombolysis in acute ischemia of the anterior circulation leads to radiographic and clinical improvement.<sup>16,17</sup>

The MELT Japanese study group studied the efficacy of intra-arterial UK use in the setting of acute MCA. The primary end point of the study was a favorable 90-day functional outcome (mRS score, 0-2). Although 49.1% of UK-treated patients vs 38.6% of placebo-treated patients had favorable outcomes, the results did not reach statistical significance. However, the 90-day excellent functional outcome (mRS score, 0-1) data were statistically significant and favored the UK-treated group (42.1% vs 22.8%). Unfortunately, the investigation was aborted prematurely after the approval of intravenous rt-PA in Japan for the management of ischemic stroke.<sup>18</sup>

The Mechanical Embolus Removal in Cerebral Ischemia (MERCİ) and Multi MERCİ clinical trials are major studies that proved the safety and efficacy of a mechanical thrombectomy device. In 80 patients presenting with acute ischemic stroke and internal carotid artery occlusion, 63% were revascularized with the aid of the Mercİ device. The 90-day favorable clinical outcome (mRS) was 39% in the revascularized group vs 3% in the nonrevascularized group of patients. Furthermore, the 90-day mortality rates were 30% in the recanalized group vs 73% in the nonrecanalized group. Overall, the study showed the efficacy of the Mercİ mechanical thrombectomy device in the management of acute ischemic stroke.<sup>19</sup>

The following patient example illustrates the efficacy of endovascular revascularization outside the conventional stroke treatment window. A 67-year-old patient presented in our institution with acute onset of left hemiplegia for approximately 5 hours. Cerebral angiography showed complete occlusion of the right internal carotid artery at the ophthalmic segment (Figure 13). Because of the extensive clot burden, multiple thrombectomy devices were used to manage this

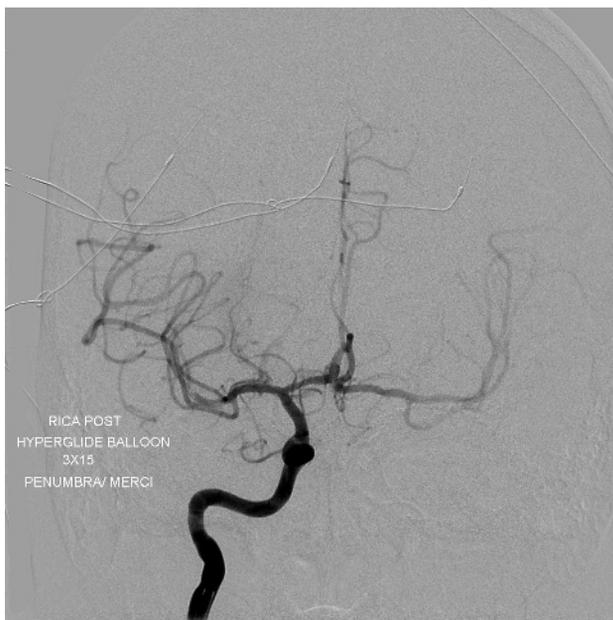


**FIGURE 13.** Digital subtraction angiography, lateral view, right common carotid artery injection (R CCA) showing complete occlusion at the ophthalmic segment.

case. This intracranial pathology was revascularized with the aid of the Penumbra and Merci devices, followed by balloon angioplasty (Figure 14). The patient improved to a normal neurological examination 24 hours after the onset of symptoms.

### CONCLUSION

This is an extremely robust era in neurovascular surgery, and advancements in the field of vascular biology need to be assimilated into the specialty of neurovascular



**FIGURE 14.** Digital subtraction angiography, frontal view, right internal carotid artery (RICA) injection showing revascularization of the intracranial internal carotid artery after Penumbra, Merci, and balloon angioplasty.

surgery. The understanding of the endothelial interaction as an additional organ system needs to be highlighted and further investigated because many of the therapies incite an endothelium-device interaction. It is important that we learn how to manipulate these endothelium-device interactions to maximize occlusion of the aneurysm or arteriovenous malformation and recanalization in atherosclerotic or thromboembolic disease. This is an exciting time, and although the future is unknown, it is extremely bright and promising for our subspecialty.

### Disclosure

Robert H. Rosenwasser, MD, is a consultant to Boston Scientific Corporation. Pascal M. Jabbour is a consultant for Codman, eV3, and Mizuho.

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