The Evolution and Future Directions of Endovascular Therapy

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INTRODUCTION

The past two decades have seen tremendous strides in endovascular therapeutics for the treatment of neurovascular disease. They include new management strategies for hemorrhagic disease, as well as ischemic stroke. The development of the Guglielmi detachable coil and its Food and Drug Administration (FDA) approval in 1995 introduced a potential alternative treatment of intracranial aneurysms in certain patient populations. Currently, more than 200,000 patients have been treated worldwide using this technique with endosaccular deposition of platinum coils. Stent-assisted coiling techniques, along with complex coil shape development and bioactive coil technology, have expanded both the efficacy and durability of endovascular aneurysm treatment. Management of intracranial stenosis has evolved from angioplasty and/or stenting with cardiac devices to a new flexible system specifically designed for the cerebral circulation. Laboratory investigation into the underlying molecular and genetic basis of cerebrovascular diseases is rapidly expanding with development of cell-mediated therapies.

HEMORRHAGIC STROKE

The development of the Guglielmi detachable coil in the late 1980s and application in the early 1990s led to a revolution in the management of aneurysmal subarachnoid hemorrhage. With microcatheter technology, the aneurysm could be selectively catheterized, making delivery and withdrawal of platinum microcoils possible. Early studies were clearly complicated by primitive technology and resulted in thrombosis and perforation.[10,11,48] The development of softer coil technology and the use of anticoagulation reduced these complication rates to acceptable levels.[38] Recanalization of the aneurysm, necessitating retreatment either surgically or endovascularly, has continued to be a significant issue, particularly with broad-necked aneurysms.[12,47] Several strategies to treat complex aneurysm shapes and configurations have evolved. The introduction of three-dimensional shaped coils and basket-like framing coils has allowed aneurysms with unfavorable geometry to be successfully treated by embolization.[19,28,31,41] Balloon-assisted coil embolization has been demonstrated to be a successful method of treating wide-necked aneurysms.[3,27,30,37] The next quantum leap in endovascular therapy has been the development of microstent technology. Many of the problems facing the early stents were tractability, as many endovascular therapists started using coronary stents.[22,34] Due to their stiffness, as well as their requiring balloon expansion, these were fraught with significant complication rates. Endoaneurysmal stents were developed, including the TriSpan, which was placed within the aneurysm to form a buttress. However, this has not been widely accepted.[42] The most widely applicable intracranial stent has been the development of the Neuroform stent, which is a nitinol polymer which is self-expanding and has been able to be navigated within the intracranial circulation with marked ease as compared to the coronary devices previously used.[4,13,29] With the advent of such technology, a better knowledge and understanding of anticoagulation including newer antiplatelet therapy, such as 2b3a inhibitors, has markedly reduced complications associated with implantation of these devices and has necessitated expansion of our information base in neurological surgery regarding the use of anticoagulation.[14] *Figure 19.1* demonstrates successful endovascular stent-assisted treatment of a wide neck middle cerebral artery aneurysm in a poor surgical candidate for a craniotomy and clip ligation. Numerous investigators have sought to increase the bioactivity of the coil mass by application of bioactive coatings such as the Matrix coil (Boston Scientific) and Cerecyte coil (Micrus). A different bioactive coil technology, the Hydrogel coil (Microvention), consists of a platinum coil coated with a polymer that ”swells” upon contact with blood increasing coil volume by a 3–9-fold increase. Early data involving the Hydrogel coil and the Matrix coil suggest equivalent or inferior periprocedural outcomes and recanalization rates respectively.[8,15,39]

The ISAT trial is the only Level 1 evidence that has indicated that patients treated with endovascular therapy have reduced morbidity and mortality up to 84 months after em-

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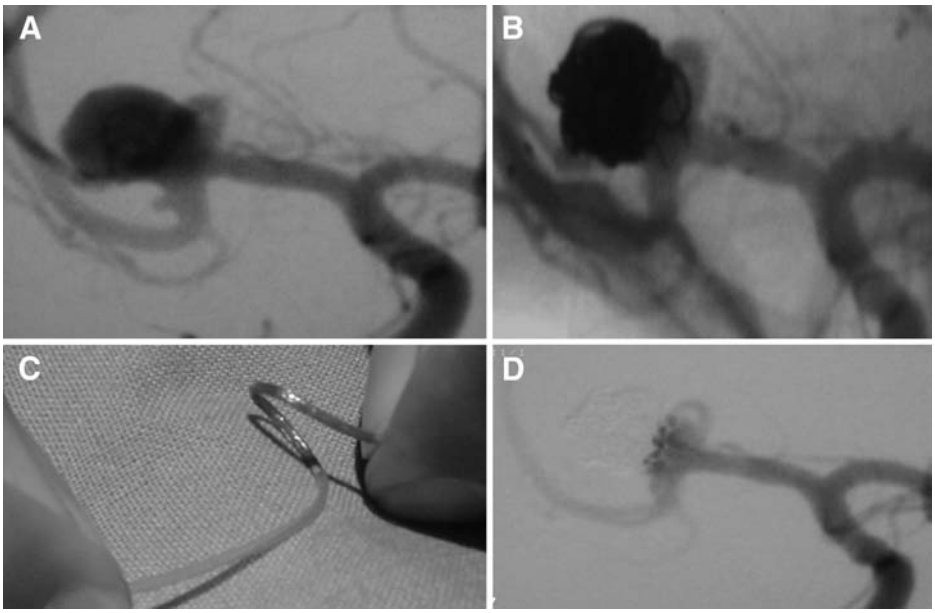

FIGURE 19.1. A, wide-neck middle cerebral artery aneurysm in a 70-year-old woman with a Hunt-Hess grade of 3, subarachnoid hemhorrhage, and acute myocardial infarction. B, subtracted view after placement of a stent into the inferior division and subsequent coil embolization. C, final view with a small neck remnant and patent M2 branches. D, photograph demonstrating the flexibility of the Neuroform stent.

bolization, primarily in patients with a modified Rankin score (mRs) of 3 through 6.[35,36] This study identified 9559 patients with ruptured aneurysms and randomized the 2143 patients deemed to be equally amenable to either endovascular or microsurgical treatments. The primary outcome assessment was a modified Rankin score of 3 to 6 (dependent or dead) at the 1-year clinical follow-up evaluation. The study concluded that the endovascular group had a relative and absolute risk reduction in disability or death of 22.6 and 6.9%, respectively, which was significantly better than the surgical group. The study also found a low cumulative rebleeding rate in both treatment groups, although this was slightly more frequent in the endovascular group. Given the impact of this study, particularly in the United States, critics were quick to question the outcomes of the more than 7000 patients not randomized, the potentially unequal level of experience for open surgical sites involved, the applicability beyond good grade patients (WFNS Grade 1–3, 88%) and certain aneurysm morphology and location (size $<$ 10mm, 93%; anterior circulation, 97%), and the lack of significant outcome difference in all mRs groups other than 3 to 6.[20] The follow-up analysis of this trial did indicate, however, that in aneurysms amendable to both microsurgical and endovascular therapy, the better outcome is maintained up to 84 months, even in the face of increased rebleeding in the endovascular group.[36] This study continues to be of significant controversy, but further long-term follow-up is needed to determine whether or not certain subgroups exist in which microsurgery has lower morbidity and sustained durability.

The exciting future for intracranial aneurysm therapy involves the application of gene therapy to promote endothelial healing. A study published in the *The Journal of Vascular Surgery* described an experiment in which ex vivo gene therapy with adenovirus-mediated transforming growth factor β 1 expression was used to determine whether or not more complete occlusion and durability would occur. Vascular smooth muscle cells were infected with adenovirus vector encoding rTGF- β 1 and delivered via embolization into the aneurysm on sponges seeded with the VSMC-infected material. It was noted that neointimal growth markedly improved with the coded vascular smooth muscle cells, but there was absolutely no difference in long-term occlusion. The authors hypothesized that perhaps additional stromal mesh was needed, although this was extremely promising.[43] Laboratory investigation has identified several molecular mechanisms associated with aneurysm wall remodeling and rupture that may provide more specific targets for pharmacological agents or endovascular devices.[16,17] The future of bioactive endovascular technology will likely involve delivery of growth factors (VEGF, TGF-B, FGF), gene therapies, or cellular substrates within the aneurysm that will regenerate an endothelial wall layer across the aneurysm neck.[2,9,23,33]

ISCHEMIC STROKE

Ischemic stroke continues to be the third leading cause of death, behind cancer and heart disease. However, it is the leading cause of disability in the United States. With the advent of endovascular technology, ischemic stroke was initially treated with thrombolytics, and it is clearly determined that a 3-hour window exists for intravenous dosing and a 6-hour window exists for endovascular intervention as it relates to the use of fibrinolytic agents.[18,24] It is becoming clear that mechanical recanalization is becoming important for cerebral vascularization and may reduce the need for lytic

therapy with its associated hemorrhagic complication rate. Hasegawa et al.[21] described the use of a basket-like retrieval device to successfully open an occluded basilar artery resistant to angioplasty and fibrinolytics. The results of the MERCI trial further support the role of mechanical thrombectomy, as well as suggest that the time to treatment window may be safely expanded to 8 hours.[45]

Intracranial atherosclerotic stenosis accounts for 5 to 10% of all ischemic strokes.[44] The natural history is poor, with annual stroke rates varying between 5 and 30%. There is little data in the literature suggesting that medical therapy is effective in preventing strokes from intracranial atherosclerosis. The recent WASID trial indicates that medical therapy with either aspirin or warfarin is associated with a 22% risk of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke over a mean follow-up period of 1.8 years.[7] Given the poor results of medical therapy alone, endovascular therapies have been developed. The techniques of intracranial angioplasty have greatly evolved since its introduction more than 25 years ago. Marks et al.[32] demonstrated excellent angiographic results and low morbidity/mortality with intracranial angioplasty on a total of 120 symptomatic patients with 124 intracranial lesions. The combined periprocedural stroke and death rate was 5.8% in this series with long-term annual stroke rates of 3.2% in the territory of treatment and a 4.4% annual rate for all strokes. Suh et al.[46] reported outcomes of endovascular treatment in symptomatic intracranial vascular stenosis associated with an acute event. They treated 35 patients with symptomatic intracranial vascular stenosis in whom angioplasty was performed in a horizontal segment of middle cerebral artery, in the basilar artery, intradural vertebral artery, and the cavernous internal carotid system. Stenting was performed in the cavernous and petrous segment or in the intradural vertebral artery in a small number of patients as well. The angiographic success rate was 97%. There were four procedure-related complications (11% including a death and a minor stroke). Quite interestingly, during the mean 20-month follow-up period, the asymptomatic restenosis rate was only 9% and the symptomatic restenosis rate was 6% in the target lesion. They concluded that the high angiographic success rate and accepted periprocedural complication rate now allows routine use of intracranial angioplasty and/or stenting in this high-risk patient population. Lee et al.[26] reported preliminary results of endovascular stent-assisted angioplasty for symptomatic middle cerebral artery stenosis in 17 patients. Despite a 56% incidence of acute in-stent thrombus treated with a 2b3a inhibitor, long-term follow-up demonstrated symptomatic relief in 15 patients and no cases of delayed in-stent stenosis. The introduction of a flexible stent (Wingspan, Boston Scientific) specifically designed for the intracranial circulation will likely expand the role of endovascular management for atherosclerosis (*Fig. 19.2*). The future of intracranial angioplasty and stenting remains bright as drug-eluting stents may provide an even greater benefit by improving long-term vessel patency rates.[1]

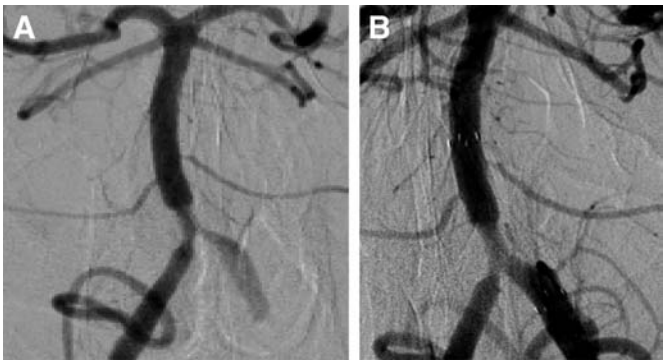

FIGURE 19.2. A, anteroposterior view of severe stenosis at the vertbrobasilar junction in a 55-year-old man with recurrent transient ischemic attacks despite anticoagulation and angioplasty alone. B, post-angioplasty and stenting view demonstrating a 70% increase in the luminal diameter.

CAROTID DISEASE

The treatment of disease at the carotid bifurcation associated with an acute stroke continues to be problematic and controversial. Older literature indicated that emergency carotid endarterectomy is fraught with significant complications associated with hemorrhage at both the surgical site, as well as intracranially, and this was primarily related to the remaining intracranial embolic lesion, which was not dealt with at the time of carotid endarterectomy. Zaidat et al.[49] reported on early carotid artery stenting and angioplasty in patients with acute ischemic stroke. They reported on 38 patients with 39 procedures in which the carotid artery showed severe to high-grade stenosis in 28 of the patients. Dissection was present in six, and the remainder had an acute occlusion treated with thrombolysis followed by carotid artery stenting. The mean time from stroke onset to angioplasty and stenting was 55 $\pm$ 14 hours. Neurological deterioration occurred in three (7.7%) of the patients, with minor disabling stroke in two and death from intracranial hemorrhage in one. The conclusion of this study was that, if deemed necessary, early carotid artery stenting seems to be safe after acute ischemic stroke if the infarction volume is small and neurological deficit is mild. The role of carotid artery angioplasty and stenting for acute disease at the bifurcation is becoming more widespread and, in an attempt to determine safety and efficacy, examination of the plaque is becoming more important. Biasi et al.[6] reported on how carotid plaque echolucency may influence the risk of stroke during carotid angioplasty and stenting. It is known that cerebral embolization is the most devastating compli-

cation of carotid artery stenting and that the echogenicity of the carotid plaque has been indicated as one of the risk factors involved. Even though distal protection is used, their conclusions are that carotid plaque echolucency as measured by GSM 25 increases the risk of stroke in carotid angioplasty and stenting and that the inclusion of echolucency as measured by ultrasonographic evaluation may become important in the planning of any endovascular procedure involving carotid or vertebral revascularization.

VASCULAR BIOLOGY

One of the most exciting fields brought to neurovascular disease is the understanding of vascular biology and its implications for the neurovascular system. Ohta et al.[40] reported on how the development of vascular biology over the past 10 years has become extremely important, particularly looking at heme oxygenase 1 and cardiovascular hemostasis. It seems that heme oxygenase 1 is extremely important and has interactions associated with hypoxia, hypertension, diabetes, cigarette smoking, transplantation, angioplasty, and the inflammatory process, all of which participate in the development of atheromatous plaque and may lead to an understanding of why plaques form and behave in a malignant versus a benign fashion. The understanding of vascular biology is one of the greatest challenges facing neurological surgery and needs to be brought into core curriculum. In addition, developing techniques of revascularization has become extremely important. The use of the Excimer laser is something being evaluated for peripheral and cardiac interventional procedures and has been shown to be efficacious in femoral popliteal salvage and revascularization.[25] Concerning ischemic stroke, further directions looking at mechanical thrombolysis with photoacoustic recanalization and dissolution of the embolic event may become extremely important.[5]

CONCLUSIONS

Future understandings of anticoagulation, such as the use of bilirubin for percutaneous carotid interventions, will continue to improve outcomes of endovascular therapies by increasing patency rates and reducing hemorrhagic complications. The development of new embolic materials, such as calcium alginate gel for intracranial aneurysms and arteriovenous malformations, may make occlusion of these different pathologies safer, more effective, and more durable. Lastly, local endovascular delivery of gene therapy again is a major challenge for neurological surgery as it relates to neurovascular disease. The future is very bright as the traditional operating room is changing from the use of the operating microscope and microsurgical tools to multimodality capabilities to manage cerbrovascular diseases in a manner that may reduce morbidity and mortality and improve outcomes.

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