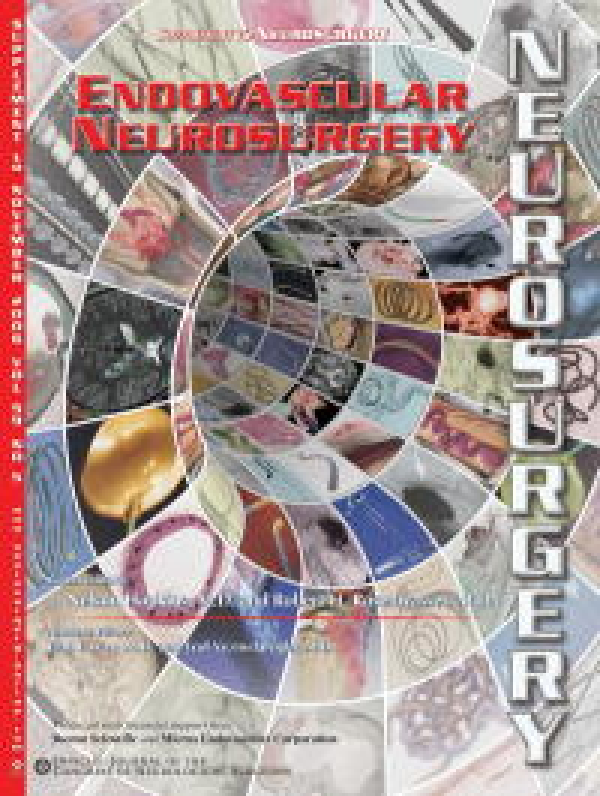
ENDOVASCULAR NEUROSURGERY
NEUROSURGERY

This is the first comprehensive NEUROSURGERY Supplement devoted specifically to Neuro-Endovascular Therapeutics. It has been a particularly exciting project and is the culmination of over two years of planning and preparation, covering 16 topics with a total of 29 articles which provide the most comprehensive and current information on endovascular neurosurgery to date.

The first four articles are on history, with contributions by fathers of the specialty, such as Alejandro Berenstein, Charles Kerber, and Bernd Richling. These are followed by a blending of the historical perspective of microsurgical and endovascular treatment.

The next article addresses current technology and where we are heading in the 21st century. Following these are two articles discussing the endovascular suite as an operating room, dealing with such issues as neuroanesthesia and neurophysiologic monitoring.

These are then followed by five articles about intracranial aneurysms, ruptured and unruptured, and the particular challenge of giant aneurysms from both a surgical and an endovascular perspective. Vasospasm continues to be an issue which is effectively addressed with medical and endovascular management.

Following is an outstanding article on the therapy of brain arteriovenous malformations addressing a multi-modal approach by one of the pioneers in the field, Bernd Richling. Additional articles regarding cerebral AVMs discuss a potential new grading scale for glue embolization of cerebral AVMs.

No discussion of cerebral AVMs is complete without a discussion of malformations with a magnificent contribution by Pierre Lasjaunias, a master in dealing with this type of pathology.

There are four articles addressing spinal arteriovenous malformations which, to this day, remain a difficult challenge from a microsurgical and endovascular standpoint.

Therapy for stroke from a medical, surgical, and endovascular standpoint is finally gaining the attention that it deserves, primarily as a result of increased understanding of the pathology and physiology and, for the first time, having interventions that are efficacious.

There are four articles concerning atherosclerotic disease, including current concepts in the management of intracranial atherosclerotic disease, cervical carotid revascularization, and a tremendous contribution on the vascular biology of intracranial carotid atherosclerotic disease. The emergent area of acute ischemia is addressed in the last article in the subsection.

Endovascular therapy continues to play a role in the management of head and neck tumors, and there is a thoughtful discussion dealing with this topic. In neurological surgery, we are at a crossroads regarding manpower issues. These are addressed in two articles dealing with work-force needs and in the final two articles which address the training of residents and fellows in cerebrovascular disease.

I wish to acknowledge my Co-Editor, L. Nelson Hopkins, for his wisdom and experience in helping to prepare this supplement, with special thanks to Drs. Erol Veznedaroglu and Elad Levy as Associate Editors. We also wish to thank the industry for helping make this publication possible and all the members of the editorial staff of NEUROSURGERY.

We hope you find this supplement a useful reference in addressing new challenges of neurovascular disease.

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The perpetual evolution and transformation of the field of endovascular neurosurgery challenge its practitioners to maintain their depth of knowledge on a wide variety of technical and clinical issues related to this clinical practice.

This endovascular neurosurgery supplement succeeds in presenting a comprehensive, up-to-date review of the most relevant issues that are brought to light when a therapeutic endovascular decision needs to be made to treat a patient with cerebral or spinal cord hemorrhagic or ischemic strokes or vascular tumors.

A camaraderie of internationally recognized experts report their personal experiences in a wide spectrum of historical, technical, and clinical topics related to the genesis, historical developments, and present standards of training and practice in endovascular neurosurgery.

This supplement provides excellent updated information on the modern classification of cerebrovascular diseases, improvements on new techniques, and the addition of new endovascular devices, as well as overall anatomical and clinical outcomes.

Some topics are discussed more than once (i.e., the history of endovascular neurosurgery, giant intracranial aneurysms, arteriovenous malformations [AVMs], etc.) by experts with different training backgrounds and viewpoints. Their articles are more complementary than controversial and demonstrate the value of multidisciplinary therapeutic approaches to complex cerebrovascular diseases.

This supplement includes 29 chapters, starting with historical accounts (Chapters 1–4); and continuing with current endovascular techniques (Chapter 5) and operative techniques (Chapters 6 and 7); intracranial complex and giant aneurysms (Chapters 8–12); the endovascular management of vasospasm (Chapter 13); pediatric and adult, cerebral and spinal cord arteriovenous fistulae and AVMs (Chapters 14–20); current endovascular and surgical approaches to extra- and intracranial atherosclerotic disease (Chapters 21–24); the endovascular approach to head and neck vascular tumors (Chapter 25); and the current status of manpower and standards of training (Chapters 26–29).

A special note should be given to the articles on manpower and standards of training. The authors perform an excellent critical analysis of the impact of new technologies (mostly endovascular) on the present standard of practice for the management of cerebrovascular diseases, as well as a synthesis on future changes on manpower allocation and standards of training.

The information delivered in this supplement will be invaluable to a growing number of young physicians from different specialties, including neurosurgery, radiology, neuroradiology, neurology, and cardiology), who would benefit from reading updated data on neuroendovascular techniques and clinical outcomes delivered by unquestionable experts in these fields.

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Sydney Brenner, a recipient of the 2002 Nobel Prize for discoveries concerning the genetic regulation of organ development and programmed cell death, stated that progress in science depends on new techniques, new discoveries, and new ideas, probably in that order. Although his comments pertained to pure science, they also apply to our discipline. By presenting a comprehensive historical review of the current techniques and concepts of endovascular neurosurgery, this unique supplement invites the reader to look for another path toward the resolution of difficult problems that plague our specialty. With their personal anecdotes and glimpses into the evolution of endovascular neurosurgery, its contributors, themselves pioneers and now leaders in this specialty, illuminate the progressive development of this new modality that has taken it to the current level of sophistication. They applied new techniques, made discoveries, and developed new ideas, and we are well advised to emulate their strategies for the benefit of patients in our care.

Below is a summary, with or without short comments, on each chapter in this supplement.

Berenstein et al. present their personal accounts of the evolution of endovascular neurosurgery. These events occurred at a time when few neurosurgeons were able to imagine the possibilities and future contributions of endovascular intervention as an effective modality in the treatment of cerebrovascular diseases. They provide a well-documented summary of the evolutionary course of interventional neuroradiology and their recounting of events is full of implications for the present and future. They describe not only the history of endovascular surgery, but also tell the story of a young physician endowed with a strong sense of responsibility and his involvement in a newly developing field that opened new vistas of the future. We are struck by the enthusiasm, dedication, and energy he brought to this undertaking.

Kerber describes the relatively short, but highly interesting, history of neuroendovascular therapy, especially as it applies to the embolization of cerebral aneurysms, AVMs and dural AVMs, and angioplasty of stenotic arteries. This senior colleague's efforts and struggles teach much about the development of angioplastic and stenting techniques for the treatment of steno-occlusive diseases.

Richling's summary of the history of endovascular surgery focuses on surgical strategies. In addition, he offers his opinions on both endovascular and direct vascular approaches. Although advances in endovascular techniques have increased the number of patients eligible for endovascular treatment, direct vascular surgery remains an essential therapy and we should not overlook the importance of educating and training the next generation of neurosurgeons in both strategies.

Prestigiacomo presents a review of the evolution of both microsurgical and endovascular treatments for intracranial aneurysms. He documents the high level of enthusiasm and energy brought to this developing field by its pioneers. He cites Dr. Walton's persuasive phrase, "This advance may re-

quire considerable recasting of the commonly accepted views on management," and emphasizes the cyclical and parallel growth of surgical and endovascular techniques applicable to aneurysm therapy. The concept of non-linear development is an important point of his article that cannot but encourage the new generation of readers of *Neurosurgery*. He also reviews articles on the development of neuroendovascular surgery and sketches the technological and technical progress made in this field. His review covers a broad area and includes devices used in relation to specific diseases. As indicated in the title of his offering, "What lies ahead" presents a perspective of not only emerging technologies, but also of the concepts that form the foundation of modern neuroendovascular surgery.

Bell et al. demonstrate the advances achieved in endovascular neurosurgery and recount the evolution of intensive care unit management of patients with neurovascular diseases, such as ruptured aneurysms, vasospasms, intracranial stenosis, and ruptured AVMs. They stress the importance of a framework of incorporation of the endovascular operating room within the intensive care unit.

Armonda et al. show that coordinated anesthesia support is a critical element in the neurointerventional operating room. It includes airway protection, hemodynamic control, anticoagulation management, neuroprotection, and rapid recovery from anesthesia. In addition, several types of neurophysiological monitoring methods are available to the neuroanesthesist as early warning systems of impending danger. They stress that coordination of these multi-faceted support systems is essential for safe neurointervention.

Nelson et al. applied Neuroform-supported coil embolization to treat large cerebral aneurysms characterized by a neck size between 7 and 14 mm. Compared with the endosaccular coil treatment of aneurysms, this embolization method yielded superior results during a medium-term follow-up period. Although it entails possible complications, such as perforator occlusion, and increases the risk for thrombus formation and stenosis within stents, the combined use of improved endoluminal devices may make it possible to address complex cerebral aneurysms effectively and safely with endovascular treatment methods.

Koebbe et al. describe their clinical and angiographic outcomes in 1307 patients undergoing endovascular treatment for intracranial aneurysms and review their procedural protocols and patient selection criteria. Theirs is a single-center experience and their protocols are well organized. Therefore, their report constitutes an excellent reference for other institutes. In addition, their advice on, for example, how to avoid intraprocedural rupture and how to prevent thromboembolism will help readers to improve their techniques.

Parkinson et al. review the literature relevant to the use of endovascular techniques in the treatment of giant intracranial aneurysms. They describe their definition and classification, their natural history, and the endovascular therapeutic indications, options, and results. In addition, they discuss current treatment paradigms and the status of current research on giant intracranial aneurysms. This is a welcome review of the history of endovascular treatment and of the current concepts that underlie this approach to treat patients with giant intracranial aneurysms.

Gonzalez et al. review the literature and offer their personal experiences with the endovascular treatment of giant aneurysms. Besides discussing actual endovascular techniques, these contributors describe the anatomic and hemodynamic peculiarities of giant intracranial aneurysms and comment on the therapeutic objectives and possible complications of their treatment. Although the results of endovascular treatment of giant intracranial aneurysms, among the most challenging of vascular lesions, have improved by combining endovascular and surgical treatment options and the use of various new materials, they are not yet satisfactory and necessitate the development and deployment of better new coils and liquid embolic materials.

Hopkins et al. review the recent literature and their clinical experience with on the endovascular treatment of giant cerebral aneurysms. They also present currently available endovascular techniques and discuss techniques under development to address these lesions. It is clearly stated that the endovascular methods and technical nuances described in this article reflect the opinions and practices of the senior authors and the limitations of their treatment strategies are acknowledged.

Zwienenberg-Lee et al. provide an informative review of the endovascular treatment of cerebral vasospasm. Given that vasospasm is the major contributor to morbidity and mortality in patients with aneurysmal SAH, efforts must be targeted at preventing its occurrence and minimizing its sequelae. These contributors present preliminary results of the National Institutes of Health-funded Balloon Prophylaxis of Aneurysmal Vasospasm Trial. The final results of this trial will help to determine whether or not prophylactic angioplasty represents a reasonable treatment alternative for the prevention of this potentially devastating complication of aneurysmal SAH.

Richling et al., who summarize strategies for the treatment of cerebral AVMs, focus on the differences among direct surgery, radiosurgery, and endovascular surgery. They detail the features of these three modalities and assess their clinical usefulness of the combination of these modalities. They also discuss the limitation of conventional grading systems in clinical trials of AVM treatment.

Amar et al. embolized AVMs and arteriovenous fistulae (AVFs) by delivering 5% dextrose in water transarterially through a guiding catheter. Simultaneously, they injected n-butyl cyanoacrylate (n-BCA) through a microcatheter. This method, the so-called D5W push technique, delivers n-BCA closer to the lesion than conventional methods and may represent a useful option for the embolization of AVMs and AVFs whose feeders are too tortuous for navigation close to the lesion.

Lasjaunias et al. present 317 patients with vein of Galen aneurysmal malformations (VGAM) that they encountered over a period of 20 years. The large number of cases made it possible to study the angioarchitecture, natural history, and

management of VGAM in neonates, infants, and children. Because long-term follow-up was possible in a large number of patients, this contributor was able to use the patients' original evaluation scores to develop a proposal concerning the natural history of VGAM.

Kim et al. used their extensive experience to develop a modified classification system for spinal arteriovenous lesions and they discuss its implications for microsurgical strategies. Their classification method is of value to neurosurgeons and neuroendovascular surgeons because it is comprehensive and has direct implications on the choice of treatment strategies. These contributors also emphasize the importance of close collaboration between microsurgical neurosurgeons and endovascular surgeons engaged in the treatment of patients with neurovascular lesions.

Veznedaroglu et al. classify spinal cord AVMs into four groups and detail the endovascular treatment of cerebral AVMs. They categorize endovascular therapies for AVM into five distinct procedures and succeed in translating these complex concepts into comprehensive scenarios. They also provide a description of embolic agents and offer detailed recommendations for postprocedural care. Their contribution is a step forward in the treatment of AVMs.

Fiorella et al. analyze the problems inherent in the embolization and radiosurgery of AVMs. They conclude that the further development and improvement of bioactive and radioactive materials is necessary and that the acquisition of ideal materials requires the accumulation of more knowledge regarding the vascular biology of AVMs.

Alexander et al. present an analysis of the problems encountered in the embolization and radiosurgery of AVMs. These contributors stress the importance of a clear understanding of the vascular biology of AVMs and the biology of the endothelial wall.

Ecker et al. discuss the clinical developments and evolving concepts related to the endovascular treatment of intracranial atherosclerotic disease. Their review of the literature focuses on the efficacy and limitation of balloon angioplasty and stenting to treat intracranial stenotic lesions. They also present current preliminary indications for the choice of endovascular techniques to treat this disorder.

Virmani et al. present a review of their own data in a comparison of the histopathological and molecular characteristics of carotid plaques and plaques of the coronary artery. They emphasize that the risk of recurrent stroke depends on the histopathological characteristics of the plaques. They also point out that recent advances in MRI may facilitate the less invasive molecular characterization of carotid plaques.

Hanel et al. review the literature to clarify the indication for and limitation of carotid angioplasty with stenting (CAS) and they compare this modality with carotid endarterectomy (CEA). These contributors evaluate the results of clinical trials and examine the risk factors for CEA and they present their endovascular technique for CAS and their treatment outcomes. They conclude that CAS and CEA are complimentary procedures.

Veznedaroglu et al. review the recent outcomes of endovascular surgery for acute cerebral ischemia. They discuss new treatments such as the intra-arterial and/or intravenous injection of tissue plasminogen activator and mechanical or laser spallation of emboli as well as local fibrinolytic intervention. These contributors also explain in detail the technical aspects of revascularization treatment for acute cerebral ischemia.

Gupta et al. review the literature to clarify the clinical significance of endovascular therapies for brain and neck tumors. Their selected treatment strategies are based on the vascularization of the tumor.

Zipfel et al., in their review of recent advances in the neuroendovascular treatment of cerebral aneurysms, AVMs, carotid artery stenosis and occlusion, and ischemic stroke, refer to Collaborative Review of Sterilization and ISAT studies. They calculated that 500 to 600 endovascular surgeons are needed to treat patients with cerebrovascular disease. They pose the question of whether or not neuroendovascular surgery should be regarded as a subspecialty of neurosurgery, endovascular surgery, or strokology, and opine that practitioners require knowledge and experience in neurosurgery to deliver successful neuroendovascular treatment. Therefore, they suggest that neuroendovascular surgery be regarded as a neurosurgical subspeciality.

Ecker et al. claim that technological improvements and lower morbidity rates in patients undergoing endovascular surgery have led to an increased demand for endovascular surgeons with neurosurgical skills and expertise. These contributors stress that it is important for neurosurgeons to embrace endovascular techniques and they warn that, unless neurosurgeons become proficient in endovascular surgery, many patients with cerebrovascular disorders will be treated, possibly suboptimally, by cross-trained neuroradiologists, peripheral interventionists, cardiologists, vascular surgeons, and neurologists. I wish to add my opinion that neurosurgeons with endovascular surgical expertise are ideally suited for providing optimal treatments to these patients.

Harbaugh and Agarwal comment on ideal training programs for neurosurgical residents by reviewing the recommendations for endovascular surgical training of the American Society of Interventional and Therapeutic Neuroradiology and CVS. These organizations recommend that trainees interpret 100 cases by diagnostic angiography before proceeding to the next step. In Japan, the development of endovascular surgical techniques has been undertaken primarily by neurosurgeons because they acquire and read diagnostic angiographs. The skillful handling of catheters is thought to be best learned by the acquisition of diagnostic angiographs. Although Harbaugh and Agarwal do not consider angiographic expertise as highly important, it is indispensable for the training of practitioners expected to perform endovascular procedures.

Sauvageau and Hopkins suggest that in order to provide high quality treatment to patients with cerebrovascular disease, neurosurgeons must acquire knowledge and skills in endovascular therapies. They advocate revolutionizing neuro-

surgical training and that aspiring neurosurgeons be taught endovascular techniques during their residency. These contributors contend that for neurosurgery to retain its leading role in the treatment of cerebrovascular disease, neurosurgical training programs must be adapted to contemporary clinical realities. They propose a curriculum that allows residents to acquire the multifaceted understanding and skill sets necessary for becoming leaders in the management of cerebrovascular diseases.

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This supplement archives the development of endovascular neurosurgery as a specialty providing minimally invasive therapy for disorders of the central nervous system and its vasculature, discusses contemporary techniques and their limitations, and provides a glimpse into the promising future of this specialty. The general readership of *Neurosurgery*, as well as practitioners of endovascular neurosurgery, will benefit from the collective wisdom of the assembled contributors who are leaders in the field.

The first section on the history of endovascular neurosurgery contains many unique perspectives and insights on the journey that this discipline has taken to reach its present level of refinement. The collaborative and productive relationship between endovascular surgeons from different backgrounds repeatedly emanates from these articles. The illustrations nicely highlight some of the pioneering work by individuals ahead of their time. It is still true today that many of our visions are still ahead of our practical ability to apply them, although industry is focusing their resources on trying to keep pace.

The next article provides a thoughtful attempt at forecasting future directions of this specialty. The way in which this burgeoning field will harness advances in gene therapy, nanotechnology, materials science, robotics, imaging, training and other areas remains an exciting prospect. The ultimate vision of providing a durable cure for patients harboring lesions of the central nervous system in a minimally invasive fashion has clearly been established. The journey through which this vision will be fulfilled continues to be a relatively uncharted and exhilarating endeavor that awaits the input of creative and innovative multidisciplinary teams in which neurosurgeons are prominent contributors.

The next section discusses the perioperative care and anesthetic management of patients harboring particular diseases managed with endovascular technology. A point raised in this section that must be further emphasized is that neurosurgeons should remain intimately involved in the intensive care management of neurosurgical patients. We vehemently oppose the concept of a closed intensive care unit in which the responsibilities of the intensive care management of neurosurgical patients are solely relegated to non-neurosurgeons. Rather, we support and personally adopt a collaborative model in which neurointensivists and other clinicians make valuable contributions to patient care in conjunction with neurosurgeons. With respect to anesthesia for endovascular neurosurgery, the anesthetic management of patients undergoing endovascular procedures has undergone significant changes in parallel with the techniques themselves. Although specific details of anesthetic techniques vary between institutions and by personal preference, certain generalizations apply across practices. Although not proven through rigorous scientific investigation, our experience (in accord with the experience of others) has clearly demonstrated that excellent neuroanesthesia can be critically important for the outcomes of patients, particularly when an unfortunate calamity occurs in the endovascular operating room.

The articles discussing the endovascular management of intracranial aneurysms provide an excellent overview of contemporary techniques. Stent-assisted coiling of intracranial aneurysms is increasingly used in the management of challenging aneurysms, although its long-term efficacy and potential consequences (such as in-stent stenosis) remain unclear. A balanced analysis of the ISAT study is provided. As the authors point out, this study examined only aneurysms that were deemed suitable for treatment by either method. As such, only 22% of patients screened were enrolled and almost all patients were enrolled from European centers (with five centers enrolling more than 50% of all patients). Precisely how these results may or may not apply to the general population of patients with ruptured intracranial aneurysms remains unknown. It is clear that the management of intracranial aneurysms has undergone a significant evolution with the introduction and implementation of endovascular techniques and that the management of these patients continues to evolve today.

Giant intracranial aneurysms remain a formidable challenge for all clinicians treating patients harboring these lesions. These three articles, from leading centers across the country, review the management of these challenging lesions with an emphasis on endovascular and multi-modal strategies. They nicely illustrate both deconstructive and reconstructive strategies. Currently, both microsurgical and endovascular techniques have limitations, although the endovascular option is perpetually being refined. With persistent focus, treatment options will continue to evolve to optimize therapeutic efficacy while minimizing potential morbidity. Endovascular therapy should continue to assume an increasingly important role in the treatment of giant intracranial aneurysms; however, skill in microsurgical repair and revascularization will undoubtedly remain important in the armamentarium of the treating team.

The endovascular treatment of cerebral vasospasm after SAH is discussed in the next section. Endovascular therapy has become safer and seemingly more effective with contemporary techniques. It is hoped that better medications will be developed to prevent and treat vasospasm. However, endovascular therapy will remain as an important rescue therapy.

The next three sections on cerebral AVMs, vein of Galen malformations, and spinal AVMs provide a comprehensive

and balanced discussion of these disorders. In terms of cerebral AVMs, it is clear that the management of patients with these lesions has benefited from a multidisciplinary approach with application of microsurgical, endovascular, and radiosurgical techniques. It is likely that minimally invasive techniques will continue to improve and play an increasing role in attaining durable cures for patients harboring these lesions. However, despite the techniques available, the management of patients with certain lesions (such as Spetzler-Martin Grades IV and V AVMs) remains problematic. In these patients, the fundamental question of whether or not the risks of treatment (especially incomplete treatment) outweigh the risks imposed by the natural history of the condition remains unanswered. Additionally, the treatment of certain unruptured and asymptomatic AVMs requires further definition and we await the results of the National Institutes of Health-funded Randomized Trial of Unruptured Brain AVMs trial. The discussion of management of vein of Galen aneurysmal malformations provides an excellent review based on the work of the senior author. The section on spinal AVMs is superbly illustrated and thorough. It is important to emphasize that treatment must be individualized for each patient harboring these lesions. Microsurgical and endovascular strategies remain important options in the treatment of patients harboring spinal AVMs, and preliminary data suggest that spinal radiosurgery may play a future role in the management of certain patients with select lesions.

Atherosclerosis of the vessels supplying the brain and ischemic stroke is addressed in the next four sections. It has become clear that symptomatic intracranial atherosclerotic disease portends a poor prognosis in untreated patients. Balloon angioplasty and stenting (as well as thrombolytics and intravenous antiplatelet agents) have equipped clinicians with important treatment options for patients with ischemic cerebrovascular disease. Indeed, endovascular revascularization for cerebral ischemia is perhaps the most rapidly expanding portion of many endovascular surgeons' practices. At our institution, we use endovascular therapy as a first line therapy in patients with symptomatic, medically refractory intracranial atherosclerotic disease, reserving surgical revascularization for those patients failing endovascular therapy. Endovascular management of intracranial atherosclerotic disease is a welcome addition to the treatment armamentarium for those treating this subset of patients who often have significant and debilitating co-morbidities. The next article provides an excellent outline of the basic vascular biology of atherosclerosis. Atherosclerosis is a complex, systemic, and important disease with regional differences by vascular bed. A greater understanding of atherosclerosis, particularly of its genetic, cellular, and molecular underpinnings, will help us to design and further refine preventative and therapeutic measures to combat this common and formidable problem. The next two articles discussing cervical carotid revascularization and endovascular management of acute ischemic stroke authoritatively review these topics. Stroke continues to be the third leading cause of death and the leading cause of disability in the United States. Outcomes remain suboptimal and new treatment paradigms are critically needed to favorably alter the disturbing natural history of ischemic stroke. Indications and techniques continue to evolve, and we predict that endovascular surgeons will play a key role in pushing the frontier of contemporary management and prevention of ischemic stroke forward.

The next article details endovascular considerations for the treatment of intracranial and head and neck tumors. Preoperative embolization is commonly performed for select tumors and the rationale and techniques are nicely discussed. Future techniques in the endovascular management of neoplasms are also presented.

Projected manpower and workforce needs for endovascular neurosurgery are the subject of the next section. Speculations presented in these two articles are interesting and what projections will prove to be accurate will become clear over the coming years. Two concepts that are particularly important are that the demands for and volumes of endovascular services will continue to increase and that neurosurgeons should be intimately involved in the evolution of this specialty.

The last section discusses training in cerebrovascular disease and endovascular surgery, particularly as applied to neurosurgical resident training. This is a timely and important topic and one that is contentious across some circles. We fundamentally agree that neurosurgeons should be leaders in the development and embracing of this technology and that these skill sets will become essential for those who care for patients with cerebrovascular disease. There is little doubt that the number of diagnostic angiograms being performed is decreasing across the United States as noninvasive studies are being increasingly adopted. Skills in diagnostic angiography will have to be acquired, at least in part, through performance of the diagnostic portions of neurointerventional procedures (the volume of which continues to increase), simulation models, and laboratory research. Exactly how competency and certification will be achieved for endovascular therapists and how governing regulations will be drafted and implemented by this evolving specialty is not clearly discussed. For those individuals treating complex cerebrovascular disease, focused training beyond that which is obtainable in a general neurosurgical residency (unless an in-folded fellowship recognized by governing bodies is utilized) will likely be necessary except in the most unusual circumstances. How all of these aforementioned issues will be dealt with and resolved remains to be seen, nevertheless, neurosurgeons should be involved in the further development and practice of endovascular neurosurgery.

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This endovascular neurosurgery supplement is unique in its scope and content. Not only have the authors provided personal vignettes regarding the formative years of the field, they have also provided a captivating glimpse of the present

and future. This supplement is also distinguished by the wide array of authors, from those who were pioneers in the field to those who continue in its leadership. While addressing a number of attendant issues, such as current technology, operative venues, manpower, and training, this supplement also elaborates on the current endovascular management of cerebrovascular lesions. Such lesions include intracranial aneurysms, giant aneurysms, vasospasm, cerebral AVMs, vein of Galen malformations, spinal AVMs, cranio-cervical atherosclerotic disease, stroke, and neoplasms. By publishing this supplement, *Neurosurgery* continues in its efforts to develop and enhance this burgeoning surgical subspecialty.

Of particular note are the personal vignettes of Drs. Berenstein, Kerber, and Richling. These technical masters have made monumental contributions to this very young subspecialty. Dr. Richling's article is an articulate juxtaposition to those of Berenstein and Kerber. These contributions offer differing perspectives and assessments of those critical events that shaped the field of endovascular neurosurgery. Similarly, the contributions of Dr. Prestigiacomo serve to highlight the current and future surgical and endovascular techniques used in the treatment of cerebral aneurysms. The management of cerebral aneurysms remains one of the most vexing challenges facing microsurgeons and endovascular surgeons alike. Perhaps the most exciting aspect of endovascular neurosurgery is that it is a field of history in the making. What we do today will likely be eclipsed by even greater accomplishments in the next decade. Particularly problematic lesions include complex and giant aneurysms. In the series of articles by Nelson, Koebbe, and Parkinson et al., these challenges are intelligently delineated. In addition, the interventional group from University of California at Los Angeles offers an endovascular assessment of these lesions and reflects on their vast experience.

Articles describing the evolution of the endovascular operating room and anesthesia for endovascular procedures highlight the unique demands of this subspecialty. Although certainly less invasive than open cranial surgery, endovascular techniques are still fraught with potential risks and complications. A suitable operative venue, trained support staff, and experienced anesthesiologists are vital to reducing these pitfalls. AVMs of the brain and spinal cord are troubling lesions that continue to challenge interventionalists and microsurgeons. Richling et al. provide their unique insights into a "multimodality" approach to the management of cerebral AVMs, whereas Amar et al. describe an innovative technique for embolization. Lesions of the vein of Galen and the spinal cord are also addressed by masters of the field who articulately describe their endovascular and microsurgical techniques for managing these complex and thankfully rare pathologic entities.

With stroke being of such monumental concern to the public health, it is essential that endovascular surgeons take the lead in addressing its causes and treatment. The pathology and management of intracranial and cervical atherosclerotic disease are reviewed within a series of pertinent articles. Both extra- and intracranial stenting remain controversial subjects that are currently being evaluated by many centers throughout the country and world. Although these techniques are attractive on a number of fronts, their long-term efficacy has yet to be established. This supplement assesses these techniques from many differing points of view.

Finally, as endovascular techniques continue to evolve, more practitioners of the art will need to be trained. This too is a controversial topic among neurosurgeons, neuroradiologists, and neurologists. Through four insightful articles, these issues of manpower and training standards are critically reviewed. Although the issue of length of training remains hotly contested, what remains clear is a growing need to provide endovascular services. The goals of this supplement are not only to review the current status of endovascular techniques, but also to encourage young practitioners to join in their development. These goals have been achieved.

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History

Everything started with a very small group of people who saw the future like the founders of a high-tech company. Endovascular development began in the former Soviet Union (now Russia and Ukraine) and continued in Western Europe before spreading to some centers in the United States. We should remember these pioneers, most of whom are still active, who kept in touch over the years, becoming friends, developing techniques and equipment, oftentimes in unofficial settings. In their hands, the procedures are relatively safe and efficient, but the learning curve is not short. Although endovascular techniques are improving, not all aneurysms and AVMs can be treated in this way if we want to offer the best possible treatment for each patient. What happens to patients with adjoining hematomas? Do we offer the best possible therapy by delaying or denying microsurgery? Should we be more concerned with maximal effectiveness than minimal invasiveness? The International Subarachnoid Aneurysm Trial (ISAT), although it has several flaws, has encouraged us to change from microsurgical to endovascular therapy to treat cerebral aneurysms. But we still have to wait for the results in long-term efficacy to avoid recanalization and rupture of the treated aneurysms (8, 11, 12).

Current Technology

The flow of new endovascular products into the market is continuous, and it may be difficult to choose or even compare treatment results with so many different kinds of equipment used to treat the patients with aneurysms. In comparing different treatment modalities of ruptured cerebral aneurysms, we must speak about efficacy: is the aneurysm completely isolated from the circulation? The second question concerning durability: does the treatment permanently remove the aneurysm from the circulation? Further important questions are: what are the morbidity and mortality of the procedure, espe-

cially in whose hands (9, 18)? Where is the aneurysm site, and what is the aneurysm size and structure of the wall? What is the condition of the patient and his/her vessels leading to the aneurysm and brain in relation to the severity of subarachnoid hemorrhage (SAH)? What is the age and somatic condition of the patient?

New products should be thoroughly tested before being made available, as inadequate testing may lead to unexpected adverse effects in the long run. Current products are also quite expensive and often not available in the developing countries with many other health issues than neurovascular disease to take care of. Developing more and more complicated coils that only a few experts can set is not the answer. The techniques should be so easy that almost anyone in the field can use them.

Operative Venues

As the equipment becomes more and more refined and complicated with the need to also treat poor-grade patients, we need close monitoring of the usually anesthetized patients (15). Often, the architecture of the vasculature and the lesion are such that it takes a relatively long time to treat it, often longer than with microsurgery in experienced hands. Together with the expensive endovascular tools, this may make the therapy less cost-effective, especially with the need of close radiological follow-up over the years. And, as the number of patients with endovascular preference is increasing, we would need several endovascular suites in a single department, such as the operating room, to take care of them.

Intracranial Aneurysms (Including Giants)

Small selected case series are very different from unselected population-based aneurysm series with long-term follow-up periods. At our institution, we are obliged to take care of all SAH patients living in the catchment area of two million people. This makes a difference when selecting the patients for clipping and coiling, as you can not preselect the cases. One-third of the ruptured aneurysms show large hematomas or severe hydrocephalus, causing deterioration of the patient and necessitating open surgery. It would be interesting to know where these patients are treated in countries in which close to 90% of the aneurysms are coiled. We strongly believe that these patients with potential possibilities for recovery are left outside any form of treatment and will succumb to diseases. It is good to remember that, in spite of many advances in diagnosis and treatment, the total mortality of aneurysmal SAH all over the world is a sad 50 % and, depending on the selection of patients reporting to the hospital, the management outcome is plagued with a 20 to 30% death rate. Those who report lower figures do not take every patient offered to their neurosurgical care. Depending on how we are selecting the patients for aneurysmal treatment, the surgical or endovascular mortality rates can vary between 1 and 15%. We should also consider those patients who are elderly with multiple diseases, who are in poor condition and have difficult aneurysms, or who present as emergencies with expanding hematomas. By careful selection of the patients, we can report figures with very low mortality and morbidity. But, at the same time, we have left many patients out of our operating rooms or our hospitals, without giving them any chance of useful recovery.

In unselected material of cerebral aneurysms seen in the large Finnish aneurysm centers of Kuopio and Helsinki (with a total experience of 11,000 patients treated; the annual total is nearly 500 patients with cerebral aneurysms treated), more than half of the patients still remain outside endoarterial treatment. We began endovascular therapy as early as 1991 and have found, in agreement with the literature, that giant and complex aneurysms are not suitable for coiling. Also, very small aneurysms are often impossible, and stent-assisted coiling of broad-necked aneurysm are often a problem in regards to complete occlusion (14). As stated, we do not coil aneurysm patients with adjacent intracerebral hemorrhage and often find problems with coiling in patients with severe atherosclerosis or extremely tortuous vessels.

The ISAT study has been criticized and was flawed for many reasons starting with patient and physician (only six experienced endovascular surgeons and 100 less experienced microsurgeons) selection (11, 12), and we only really can tell that, in inexperienced hands, aneurysms should probably be coiled. But the long-term stability of Guglielmi detachable coil occlusion is of concern. Long-term angiographic follow-up (> 5 yr after initial treatment) has been previously suggested for patients with incompletely clipped aneurysms. Given the annual risk of 0.9 to 1.8% of de novo aneurysm formation and the possibility of aneurysm regrowth after apparently complete clipping, late angiographic follow-up might be recommended for young patients, even with complete clipping of the aneurysm.

There is an increased need for bypass surgery, preferably high-flow, as the number of previously unsuccessfully coiled aneurysms is growing. Clipping a coiled aneurysm is like trying to clip a golf ball, and it may be very difficult to remove the coils before clipping, necessitating a bypass.

Vasospasm

The occurrence of vasospasm is similar in patients who have been treated with coiling or clipping. We may decrease vasospasm by systemic administration of Nimodipine or locally by endovascular means. However, these often fail and we would need more potent drugs in our armamentarium. According to some very promising preliminary reports, Nicardipine pellets applied locally after clipping may change the preference for microsurgery.

Cerebral AVMs

One should not consider embolization as a treatment of choice in AVMs because of the relatively high risk of achieving only partial occlusion or ending up with recanalization in the long term. It is at its best when used before microsurgical (or radiosurgical) removal to make surgery safer with less blood loss and reduced operating time. The solution to more effec-

tively and less invasively treated aneurysms and AVMs does not come from developing increasingly complicated coils or stents, but rather by studying their pathobiology and ultimately developing non-invasive means that could be used by anyone in the field.

Vein of Galen Malformations

In no other lesion were neurosurgeons so completely bested by endovascular surgeons. As stated by the authors, historical contributions from the neurosurgical point of view have demonstrated limitations in the management of these difficult lesions, even in the best hands, and have relinquished them to interventional neuroradiology.

Spinal AVMs

It seems that, although some neurosurgeons may have an extensive experience in microsurgical removal of these lesions, there is a growing trend of referring patients with these lesions to endovascular surgeons. The classification suggested by Spetzler's group is very useful.

Atherosclerotic Disease

More and more people in the developed countries consume statins and antioxidants in an effort to prolong their lives. We do not yet know how these affect the occurrence of cerebral aneurysms. Perhaps they will decrease the occurrence or incidence of rupture.

Carotid Atherosclerotic Disease

The immunological mechanisms of atherosclerotic plaque rupture and ulceration have recently been elucidated mainly in the aorta and extracranial carotids. This will eventually lead to pharmaceutical therapy, probably beginning with bioactive stents. The role of atherosclerosis in the growth and rupture of intracranial aneurysms is not well established, but there is still growing evidence on the role of inflammation (16).

Carotid Angioplasty and Stenting

These techniques are already replacing open surgery in selected cases of atherosclerotic carotid stenoses and will probably continue to do so even more in the future.

Stroke

In acute stroke, one may try to remove the clot by endovascular means followed by local administration of some clot lysing agent. However, in some cases, intracranial thrombectomy may only be possible through open microsurgery. The results of emergency bypass surgery for revascularization are not very rewarding.

Neoplasms

We have found preoperative embolization of some vascular neoplasms very helpful in reducing the often massive intraoperative bleeding. Hemangiopericytomas, some giant vascular (shown in MRI scans) meningiomas, juvenile angiofibromas, and hypernephroma metastases are good examples.

Manpower

It is not impossible that a handful of technical masters and groups treat all patients with SAH. For example, in Finland (population, 5.2 million), where this is the highest frequency of aneurysmal SAH in the world, as well as in Japan, one or two large centers (instead of five) could easily treat all patients with ruptured aneurysms. There are new developments in microsurgery of cerebral aneurysms. Nowadays, most aneurysms can be clipped effectively, very quickly, and in a simple way, while preserving the normal anatomy without brain damage and retraction, and without extensive removal of the cranial base (4–7, 13, 19). Because the endovascular surgeons are not touching the brain, this also should not be done by those who treat the aneurysms by open surgery. We should operate cleanly and gently, which results in reduced surgery time, always performing an angiogram after clipping (preferably by intraoperative indocyanine green angiography, which is a breakthrough in neurovascular surgery).

More and more often, unruptured aneurysms and AVMs are going to be detected as incidental findings with improved and increased imaging. According to the International Study of Unruptured Intracranial Aneurysms, small unruptured aneurysms should not be treated at all, which is a contradiction to the clinical practice because, in fact, most of the ruptured aneurysms are relatively small in size. The efficacy of endovascular therapy for unruptured aneurysms is debatable. We need dedicated neurovascular teams with both microsurgeons and endovascular surgeons working together for the benefit of the patients.

Training

The careers of a neurosurgeon and an endovascular surgeon are marathons. Training does not stop once you have passed the board examination. In fact, it is just the beginning and you are required to train all your life. But do we start too late for dexterity to develop? Pianists, for example, begin to practice at the age of 5 to 10 years. Also, not all neurosurgeons and endovascular surgeons are equally skilled; there are some who are much better than others, just as there are violin players who reach a higher level than others. But, who will excell? One who can memorize a biochemistry book by heart or the one who has true motor talent?

Competence in aneurysm surgery (14) means the ability to handle aneurysms at all sites and of all sizes, to manipulate the aneurysm and its base with bipolar coagulation, and to be knowledgeable in clipping and opening of the aneurysm. Furthermore, the competent aneurysm surgeon should be skilled in aneurysm and vessel thrombectomy and in the use of temporary clipping, and should be aware of cerebral protection during this procedure. He or she should be able to treat acute hydrocephalus by ventriculostomy and/or opening of the lamina terminalis. In cases of complex lesions, reconstruc-

tion of arteries with clips or sutures is necessary and the vessel bypassing techniques should be mastered. And lastly, he or she should also be very well aware of the pitfalls and benefits of endovascular treatment.

Competence in endovascular surgery means, in our mind, aneurysm occlusion at all sites with knowledge of the limits of the method. The endovascular surgeon should be involved in clinics, discussions with patients and relatives, and should be aware of cerebral protection. He or she should always be available. By doing that, he or she knows that acute and early aneurysm surgery is a heavy burden because of the high mortality and complication rate in acutely and severely ill patients. These high requirements cannot be achieved only by completing a neurovascular or endovascular fellowship, but by continuing clinical work on daily basis for years. The trend to train so-called hybrids who can manage both clipping and coiling is increasing. The learning curve for coiling is shorter than for clipping. However, it takes a long time to master the details of endovascular techniques and it may be difficult to maintain abilities of both in the long run.

The Future

Instead of fighting over which method is better, clipping or coiling, we should work together not only in the clinics to tailor the treatment accordingly, but also in research. Our group has found different wall types in aneurysms making them more or less prone to rupture (1–3). The next step is to identify and treat them before rupture occurs. Families with a history of aneurysms should be screened (10, 17), and those with the actual gene defect should be followed and treated. We should not forget that the wall of an aneurysm is undergoing continuous destruction and repair processes. We have found evidence of inflammatory process expression of different growth factors behind aneurysm rupture. However, the pathobiology of the aneurysm wall should be elucidated in detail before developing simple bioactive coils that are easier to set even pharmaceutical therapy to prevent aneurysm rupture in a less complicated way.

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Two decades ago, upon witnessing the emerging capabilities of endovascular technology and envisioning its future impact, Dr. Michael L.J. Apuzzo prophesied a "requiem" for conventional cerebrovascular surgery (4). Indeed, neurosur-

gery's response to the evolution of endovascular intervention recites the reaction to death and dying schematized by Elisabeth Kubler-Ross (5). The stages of denial, anger, bargaining, and depression have finally yielded to acceptance, and the publication of this supplement—which confers ultimate credence and validity to endovascular therapy—symbolizes the end of this thanatological journey.

As further proof of this culmination, new mantras have emerged. Annual meeting seminars are now titled "clip and coil," no longer "clip versus coil." Advertisements abound for interdisciplinary "stroke centers" that focus on disease, not on medical specialty. Another sign of maturity is the formation of a new organization, the Society of Endovascular Neurosurgeons (www.SENS-online.com). More than 50 neurosurgeons in the United States have now completed endovascular fellowships that conform to the criteria mutually adopted by the Joint Section of Cerebrovascular Surgery and the American Society of Interventional and Therapeutic Neuroradiology several years ago (3). Within the past few months, however, the Society of Neurological Surgeons has approved guidelines with less stringent requirements, potentially enabling more neurosurgeons to obtain endovascular certification, and the Residency Review Committee has explored models for integrating endovascular training into neurosurgical residency curricula.

Part of this embrace results from recent technical innovations and ongoing instrumentation enhancements, an ever-aging population with commensurate increases in the incidence of diseases best treated by endovascular methods, and the pervasive trend toward therapeutic minimalism (1). Multicenter studies, including the notorious ISAT (6) and Stenting and Angioplasty with Protection in Patients at High Risk for Enderarterctomy (SAPPHIRE) (8) trials, have validated endovascular approaches that complement or, in some cases, replace conventional open surgeries. Although these studies show flaws in methodology and facile oversimplification of the results, their impact on practice patterns is indisputable. They have also caught the attention of the healthcare consumer who, armed with information obtained from the Internet and other sources of questionable veracity, expects to receive only the newest, safest, and purportedly most advanced treatment.

To a large extent, however, much of the shift in attitude reflects the old adage, "if you can't beat them. . . ." Anecdotes about cardiologists performing intracranial stenting, increasing numbers of neurologists obtaining endovascular training, and other trends suggest that cerebrovascular disease will become the domain of specialists from more and more backgrounds. At times, it seems that the neurosurgical community's acceptance of endovascular therapy is as much about turf, paranoia, enfranchisement, and political agenda as it is about optimum patient care.

Ironically, it was a neurologist, Egas Moniz, who pioneered cerebral angiography. Moniz was also awarded the Nobel Prize for development of another surgical procedure, the prefrontal leucotomy (7). In addition to his medical achievements, Moniz led a storied life as a statesman, and the revolutions he initiated in medicine are rivaled only by his political uprisings. A similar revolt occurred when Jacques Moret, the pioneering French interventional neuroradiologist, presented the Schneider lecture at the 1989 American Association of Neurological Surgeons annual meeting. As one of the first expositions of endovascular therapy at a major neurosurgical conference, this address was initially met by some opposition, but proved to be a catalyst for its eventual acceptance by the neurosurgical community.

Currently, endovascular therapy has evolved elegant approaches to a wide array of hemorrhagic and ischemic conditions of the central nervous system, and the insightful articles of this supplement provide an excellent survey of extant strategies to treat blood vessel pathology. Fundamentally, however, the applications are ablative or mechanical. Perhaps the real utility of endovascular technology lies in its capacity to deliver neural progenitor cells, gene therapy vectors, radiosensitizers, neuroprotective drugs, and other novel agents into the brain parenchyma. Intra-arterial delivery circumvents many of the limitations of conventional routes of access and has the advantages of widespread distribution, the ability to deliver large volumes, limited perturbation of neural tissue, and the feasibility of repeated administration (2). Thus, instead of worrying about how to divide the proverbial pie, neurosurgery can inaugurate the era of neurorestoration.

The revolution continues. . . .

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This compilation of personal accounts, conceptual descriptions, reviews, original research, and editorial opinions about the past, present and future of endovascular neurosurgery is a timely and necessary read for all those who will be affected by the explosion of this field. There has been no other period in medicine that has seen such a rapid increase in knowledge. Coupled with and driven by the technological advancement of catheter-based interventions, neuroendovascular procedures are at the forefront of this wave.

The historical perspectives in this issue are an insight into the pioneering nature of the field at its inception. The days of a small collegial group of innovators making devices in their garages have long since passed, as the influences of industry and the potential for personal financial gain have significantly influenced the development of the field.

As one can clearly see from the scientific articles, we have made tremendous strides in our understanding of disease, the sophistication of diagnostic and therapeutic devices, periprocedural care, and in treatment efficacy with a concomitant reduction in morbidity and mortality. Also evident is the fact that many challenges still exist, particularly in giant and wide-neck cerebral aneurysms, cerebral vasospasm, stroke, and intracranial atherosclerosis. Updates on stent-assisted aneurysm techniques, and new embolic agents for cerebral AVMs, and outstanding reviews of vein of Galen malformations, head and neck tumors, spinal vascular malformations, and interventions for brachiocephalic atherosclerotic disease are clinical highlights.

Ironically, the nature in which we will train neurosurgical residents and neurosurgeons in practice has returned to the frontier-like mentality. Each individual and each institution find their own way, and many different pathways are currently available for neuroendovascular training. With the lack of compliance with the Accreditation Council for Graduate Medical Education guidelines, it is left to individual hospital credentialing committees to decide who is qualified to perform these procedures. As the reader will see, attempts are currently underway by various societies to standardize at least neurosurgical endovascular training, but this is still very much a process in evolution. Will there be a day when all graduating neurosurgical residents are qualified to perform these procedures? Perhaps, but what is the future for neurologists, radiologists, cardiologists, vascular surgeons, and cardiothoracic surgeons interested in this field? Equally important to diagnostic and therapeutic development is insuring the quality of the health care professionals involved in neuroendovascular procedures. These concepts are explored by several leaders in the field.

This supplement will go beyond updating the reader about the current status of neuroendovascular surgery. It will also inspire discussion, with a renewed awareness of the past, about the clinical, experimental, and political challenges that remain in possibly the most exciting, rapidly involving subspecialty in medicine.

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Endovascular therapy has seen a tremendous growth in the management of vascular diseases in the central nervous system in the past two decades. As a physician practicing in this field during this time, it has been truly heartening to see how much more we can do for our patients. This collected supplement of 29 chapters provides a timely assessment of where endovascular therapy has been, where it is now and, to some degree, where it is going. The first seven chapters provide personal insights into where the field came from and ideas about where technological advancements may take us, as well as the environment for neuroendovascular work. The next 18 chapters highlight disease-specific topics, concentrating on the management of aneurysms, AVMs and AVFs, ischemic disease, and head and neck tumors. The final four chapters concentrate on training and manpower needs.

Although I do not agree with everything in these articles, this collection of invited chapters is well worth reading. They provide some thoughtful insights into the present state of neuroendovascular therapy. As you read these articles, it is important to keep in mind that, although they are appearing in a peer-reviewed journal, they are invited papers. A major problem that continues to plague our specialty is a paucity of evidence-based data. This series of chapters reflects that weakness. Some of the articles in the collection attempt to provide a summary of clinical data. Others rely more heavily on personal experience. Either type of article may reflect the opinions and biases of the authors and of the editors who invited the essayists. An advantage to a series of invited papers is that it allows the authors more free rein to "editorialize" and express a point of view. The disadvantage of a series of invited papers is that you will be reading articles that may not be scientifically rigorous and that reflect the biases of the essayists.

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PERSONAL ACCOUNTS OF THE EVOLUTION OF ENDOVASCULAR NEUROSURGERY

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My first recollection of the concept "endovascular" was in 1970. After completing medical school in Mexico, while in Israel as a surgical intern, I was impressed that on the right of a road was desert and on the left were palm trees. Because of the lack of water in the desert, a specialized delivery system to conserve water was used, called drop-by-drop irrigation, in which tubing was laid to deliver water directly to the roots. That was also the year I lost a young patient from aplastic anemia secondary to chloramphenicol that was given systemically to treat a multidrug-resistant renal infection. Continuing my education in the United States, again as a surgical intern, I met a radiologist named Harold Moskowitz who would influence me. I had never seen an angiogram, and when I observed him performing a renal angiogram, bingo! I had a thought that if I could put a catheter into the renal artery, inject a potent antibiotic directly into the infected kidney, similar to drop-by-drop irrigation, and pick it up in the vein, then maybe such treatment could have saved the boy. That was the beginning of my journey that would eventually lead to my involvement in the rapidly evolving field of surgical neuroangiography and endovascular neurosurgery.

To recount the history of endovascular therapy, the start was probably in the 17th century with the first blood transfusion through a bird-feather needle to access a vein. At the time of my initial interest, it was known that therapeutic endovascular occlusion, described as early as 1904 by Dawbarn (12), was performed in the external iliac artery using liquid paraffin in a malignant tumor and in 1930 by Brooks in the internal carotid artery using a piece of muscle to treat a cavernous carotid fistula (11). The modern beginnings and multidisciplinary evolution of our field, however, correspond to the development of catheters for more selective catheterization and that provide functional anatomic modifications and the delivery of various embolic agents and infusion of various pharmacologic agents (*Table 1*). As pioneers, in 1960, Luessenhop and Spence (32) initially described embolization of cerebral brain arteriovenous malformations (AVM) by open arteriotomy of the carotid artery followed by placement of small emboli (pellets), originally of methyl methacrylate and then later silicone, that preferentially flowed into the AVM. Mullan et al. (35) were experimenting with electrically induced thrombosis within intracranial aneurysms, a precursor to developments that were to occur decades later. In Russia, in the 1960s and early 1970s, despite the Cold War, it was known that Serbinenko (40–42, 46) had developed a nondetachable, flow-directed balloon that was used to treat cavernous carotid fistulae while preserving the carotid artery. Later, he developed a detachable balloon that, with them, "cavities of arterial aneurysms may also be occluded" (42, 43). In 1968, Doppman et al. (16) described embolization of a spinal cord AVM. In the early 1970s, Djindjian et al. (15) were pioneering endovascular techniques in France in maxillofacial and spinal embolization. The early 1970s was also the time Zanetti and Sherman (48) introduced cyanoacrylate as an adhesive embolic agent, Kerber (24) developed calibrated-leak balloons, and Debrun et al. (13, 14), after visiting Serbinenko, brought detachable balloons to the West. That was the state of the world when I was training.

As a radiology resident at Mount Sinai Hospital in New York, I was performing an emergency aortogram on a bleeding patient who had undergone a splenectomy, and I found a gastric artery pseudoaneurysm. On the angiogram, active extravasation was present, and I called Harold Mitty, my attending, and con-

TABLE 1. Representative multidisciplinary early contributors to the evolution of endovascular neurosurgery

B. Brooks	Surgeon
Alfred J. Luessenhop	Neurosurgeon
Dotter	Radiologist
R. Djindjian	Neurologist
Fedor A. Serbinenko	Neurosurgeon
J.L. Doppman	Radiologist
P.H. Zanetti	Neurosurgeon
C. Kerber	Neuroradiologist
Hilal	Neuroradiologist
Y.N. Zubkov	Neurosurgeon

vinced him that we could stop the bleeding faster than anyone else, and we did. This was my first embolization procedure. At this point, I knew that this was what I wanted to do for my career. During this time, Peng Huang, a diagnostic neuroradiologist, was a major influence. Huang was a brilliant and generous man. From the beginning of residency, I had a surgical impression of what radiology should be, but in the first months, the radiologists were analyzing the radiographs and discussing the nuances of the images, and in the beginning, I did not appreciate what they were talking about. With Huang's mentorship, however, I realized that there was much to learn and master in diagnostic neuroradiology, particularly in cerebral angiography, when thinking and analyzing a problem, which is the strength of a radiological background. He influenced my way of analyzing an angiogram and helped me foster a three-dimensional sense of cerebral angiography. The dedication and creativity I invested in the intellectual aspect of diagnostic neuroangiography would pay dividends later, both technically and clinically.

In my pursuit of a neuroradiology fellowship, I wished to stay in New York and was fortunate to obtain a fellowship position at New York University with neuroradiologists Norman Chase and Irv Kricheff and to later work with the visionary neurosurgeon and chairman Joseph Ransohoff (10, 17, 26), who was to have a tremendous influence on my career. During my 2 years of fellowship, I developed an animal laboratory and started experimenting with all available catheters and embolic agents, plus some others, which led to the publication of some of my early contributions to the field (1–5).

In 1978, C. Kerber organized a meeting in Wiesbaden, Germany, during the Symposium Neuroradiologicum. It was primarily a meeting of the French and North Americans who were performing endovascular procedures. It was the first symposium with a round table discussion that led to heated exchanges. Merland, Debrun, Picard, Manelfe, Lasjaunias, Theron, and Moret were present. It was my first international meeting and I was able to meet many of the important figures in this burgeoning field. Because I thought that the best way to learn was to personally observe the innovators of the field, with the help of Kricheff, I made arrangements to visit other interventionalists.

As I visited Picard, Debrun, Lasjaunias, Moret, and Merland, I was able to see the then state-of-the-art, which was practiced with very limited devices and embolic materials, and observe the way they worked. These early experiences fostered personal creativity and innovation. As an example, at the time, I was developing a new variable stiffness catheter. Catheterization of the common carotid artery was a challenge because the current catheters were too rigid with their use of braided tubing. We were experimenting with a coaxial catheter system for selective catheterization. Kerber, an inventive genius, was using silicone rubber tubing that was secured to make his catheters. He procured hundreds and hundreds of meters of tubing. He was generous enough to give me several rolls to use and experiment with. I came up with the idea to take the stiffly braided catheter, leave it braided except for the last 10 to 15 cm, which would have a smaller outer diameter than the nonbraided segment but would maintain the same inner diameter. In 1978, I developed, with John Aberle, a double lumen balloon catheter with a larger inner diameter for injection, and a moon-shaped lumen to inflate the balloon (2). We never patented it, which was a mistake, but it became the universal shaft for angioplasty balloon-tipped catheters. Using this balloon catheter to block arteries, I realized that when contrast is injected with an occlusive balloon catheter, there comes a point where something washes the contrast out. It was obvious that blood flow could not be completely stopped, except in only a very short proximal segment, and that a ligation was being performed because collaterals eventually would reconstitute the blood supply. As I injected more forcefully, I visualized the collaterals from the external carotid system to the brain; I did not know them by name, but I realized that they were present. And, of course, my thought was that the closer to the cranium, the greater chance of seeing the collaterals.

After the meeting in Wiesbaden, I went to France to observe cases. Djindjian had died before I was able to visit him in France. I never met him, about which I am sorry. He was one of the pioneers of the field and maintains a large influence through the people that he trained, including many in the current strong French contingency. I did, however, have the opportunity to spend a month with Gerard Debrun who was extremely generous and provided housing for me and Josee, my wife, in his daughter's apartment. I observed him and Jacquelyn placing detachable balloons into an intracranial aneurysm. Debrun had improved the technology of the detachable balloon of Serbinenko. I observed Merland as well. He was extremely skillful and elegant. I also visited and established a strong and lasting admiration and friendship with Pierre Lasjaunias in France.

In the United States, a meeting of 13 interventionalists took place in Santa Barbara, California, which was organized by Kerber and included not only myself, but Wolpert, Benson, Hieshima, Merland, Debrun, Moret, Manelfe, Picard, Lasjanias, Theron, and Bank. It was a fabulous meeting. The

meeting was disorganized and complete, but stimulating, chaos, with everybody screaming and shouting, although it was simply a presentation of reports and personal experiences. Prompted by this meeting, I organized a second one in Utah. At that time, we decided that each of us could invite one person. Then, the third and subsequent annual meetings were held in Val d'Isere in France, which became the nucleus of probably the best meeting in medicine, one like no other. As Picard said, "The only rule is that there are really no rules." When we started the working group in interventional neuroradiology, everyone was obliged to present and everyone shared their knowledge, and, in that way, we learned what others were doing. You couldn't just take, you had to give. It was a great forum.

The French emphasis on anatomy is exemplified by Pierre Lasjaunias, who, among other significant contributions, helped describe the blood supply to the cranial nerves (30). Our subsequent partnership and deep respect and friendship started inauspiciously. I was well versed in catheter and embolization techniques, and he was the master of functional anatomy, and we began to disagree and argue, and I was called untruthful regarding a particular embolization technique. I challenged Lasjuanias to come to New York to observe what I said I could do. Suddenly, he showed up. I was working at Bellevue Hospital and was treating a girl with a facial labial AVM that I wanted to embolize while preserving the adjacent normal tissue. Lasjuanias explained the internal maxillary and the facial artery anastomoses. I expanded the thought and argued that if what he was saying was true, then I could put a chunk of gelfoam distal to the labial artery, plug it there to protect the normal lip, and put microparticles into the lip malformation. Lasjuanias was surprised by this application of his functional anatomy, yet he agreed, and the embolization worked. This was the beginning of a career of long collaboration and unique friendship, which includes the authorship of the influential multivolume book *Surgical Neuroangiography* (6–9, 27–29). In the beginning, the best analogy of the relationship between Lasjuanias and myself was that he had a excellent driver in me, with my experience in catheter, materials, and angiographic techniques, and he was the definitive map. Lasjuanias, in my opinion, is the most intellectual of my contemporaries, a true genius.

I then visited Lasjuanias in France on a second trip. He was living near the Museum Pompidou. At his home, Lasjuanias shared with me, "I'm writing a book, on the upper cervical arteries, and I have a preface. Would you mind reading it?" I agreed. I read the preface several times, and I suggested some changes that were amenable to Lasjuanias. Then he said, "Would you read a chapter?" I read a chapter, and so I never made it to the museum. I stayed for 7 days in his house discussing his book. When Lasjuanias' book was printed, he was generous and acknowledged my contribution.

By this time, I had developed a growing clinical practice and was performing more and more cases. Lasjuanias' emphasis was on anatomy and mine was clinical when he suggested, "Why don't we write a book together?" We agreed, and we wrote volume I (Anatomy) and volume II (Clinical) and that was when we decided on the title *Surgical Neuroangiography*, which may have been controversial at the time. The series had to be expanded to five volumes covering functional anatomy and endovascular treatment of craniofacial arteries and functional anatomy and endovascular treatment of cerebral, spine, and spinal cord lesions. Writing these books was a tremendous undertaking, but well worth it. The first book of the series was written when Lasjuanias visited me in Hillsdale, New York. We had a one-bedroom house, so he was sleeping in the living room. My wife, Josee, was pregnant with our first child, Erica, and she was cooking for us while we were discussing and arguing and screaming for 16 hours a day, writing the first book. The second book was written at his house in Paris. We would soon schedule three to four trips a year, usually for 9 days of work and 2 days of traveling. I remember not going out for meals; instead, we would cook for ourselves and dedicated ourselves, like college students during final examinations, to writing the books.

In my opinion, a close interaction has always existed between interventional neuroradiology and neurosurgery. As my career ascended, I benefited from a close relationship with Joseph Ransohoff, chairman of neurological surgery at New York University. Ransohoff, without question, was a visionary for endovascular neurosurgery. He "saw" it long before I did. As an example of Ransohoff's influence and support for the concept of endovascular neurosurgery, I invited Ransohoff to give a lecture on the surgical perspective in interventional neuroradiology at the first New York University course (the first of eight annual meetings) in interventional neuroradiology, developed by Pierre Lasjaunias and me. The night before the meeting, I was frantically arranging slides for several presentations the next day when Ransohoff came by and said, "Gimme a piece of paper!" On a yellow pad of paper, Ransohoff wrote on the left column what interventional neuroradiology had achieved and on the right column where it was going. Even by today's standard, he was ahead of his time, and he would talk about the topics of endovascular transplant, physiological injections as a way to visualize function, etc.

Joseph Ransohoff's influence was enormous and his support for me was unwavering. An example of this occurred at a meeting in neurosurgery called the Senior Society for Academic Neurological Surgery Chairmen. At this meeting, a member can invite one guest, and Ransohoff invited me. During this meeting, I presented a case, my first intracranial catheterization into a middle cerebral artery AVM. I was very nervous, as you could imagine, because I was still a fellow. After my talk, Robert Rand, who had described the treatment of cerebral aneurysms by stereotaxic ferromagnetic silicone (38), stood up and said, "Neurosurgeons have to wake up. This is not a radiology procedure. This is a neurosurgical procedure!" Luessenhop affirmed this and said, "Yes, we have to bring this back into neurosurgery." Ransohoff was all the way at the end of the meeting hall with his tie untied and a cigarette in his mouth. He responded, "You see this guy? You

are a surgeon with a knife. This guy is a surgeon with a catheter. And he's doing it better than we are! Why neuroradiologists? Because they're thinking about the problems, trying to understand them, attacking the problems. The man that should do this is the better one. If we neurosurgeons want to do it, we better learn from these guys." That is the type of leader and visionary Ransohoff was. But, it showed what was obvious, that for neurosurgeons who had done it, such as Luessenhop and Rand, they felt that it was a neurosurgical procedure and that angiography was a surgical procedure.

I am fortunate to know M. Gazi Yaşargil, a legend, a brilliant, intellectual man who is critical and does not accept mediocrity. I was very young and was invited to give a talk at a national neurosurgery meeting. Yaşargil was the invited speaker for the surgery of AVMs, Steiner the speaker for radiosurgery, and I for the endovascular treatment of AVMs. I was in the speaker-ready room preparing my slides when I heard this gentleman with a heavy German accent showing some slides. As I looked from behind, he explained, "This is impossible to treat! No neurosurgeon in the world can treat that!" I realized that it was a case that was similar to one that I was to present. Yaşargil showed another case, a vein of Galen (VOG) malformation, and said, "Impossible! Nobody can do this. It is a challenge for neurosurgery." My second case! After realizing we had several similar cases and that I was to speak after him, I had to meet Yaşargil. At a break, I said, "Excuse me, Professor Yaşargil. My name is Alex Berenstein and I would like to show you some cases." Yaşargil replied, "You're Berenstein? You're a child!" I responded, "Yes, I'm quite young, but I have to show you something." I was very assertive and I showed him slides of the cases I was to present after his talk. He looked at me and said, "Thank you very much." The symposium started, and he went before me and started his amazing presentation. "For years, throughout my entire career, I have been looking how to climb Mount Everest. I have tried so hard to climb Mount Everest. Today we are going to see how to get there. What this young Berenstein is going show us later today is how to reach Mount Everest in a funicular!" He started his lecture like that. Then Yaşargil proceeded to show masterful microsurgical cases that, even today, we cannot perform endovascularly.

In the 1980s and 1990s, tremendous technical innovation occurred from the variable stiffness microcatheter to the Guglielmi detachable coil (20, 21, 25, 45). I was fortunate to be a part of this innovation, both in the industry and in its clinical application. During this time, I helped develop, among other inventions, different catheters, including diagnostic catheters, the Fastealth low-profile angioplasty balloon, and the Berenstein liquid coil. Clinically, my practice grew tremendously, and I started a fellowship program, starting with In Sup Choi, my first official fellow. I also introduced alcohol as a sclerosing agent in facial venous malformations.

My road to VOG malformation embolization (19, 39) started with adults. As I do now, during that time, I was treating patients with brain AVMs with glue. I will never forget one of the first patients who I "cured" with glue embolization in a single session. She was a patient who presented with seizures. Immediately after the embolization, she was doing well, and Ransohoff was pleased and congratulated me. Then an hour later, the patient deteriorated from a delayed hemorrhage and died. At the time, I attributed the hemorrhage to perfusion pressure breakthrough or venous outlet obstruction. Pierre Lasjuanias and Vallo Benjamin, one of the most intellectual neurosurgeons I know, argued against perfusion pressure breakthrough. After this case, I saw brain AVMs as a dynamic disease and decided to embolize in stages. I also decided to refrain from treating patients with brain AVM who had not presented with a hemorrhage. There was a period in my career when I only treated brain AVMs that bled or VOG malformations. I thought that younger patients with VOG would all die and that surgery was not a good option; therefore, I was aggressive and soon had some successes, not going for a "cure," but embolizing in stages. Now, there is a generation of patients with VOG who I treated in their youth and are surviving into adulthood. I think that transarterial glue embolization of VOG malformations and variants has changed the history of this disease and will be one of my lasting contributions (18, 39). Pierre Lasjaunias visited me and I shared my experience with VOG patients. He later made significant contributions with his own series of endovascularly treated VOG patients and in their classification (31).

The invention of the variable stiffness microcatheter was a key event. Immediately, the microcatheter gave us access to the middle meningeal beyond foramen spinosum and the petrosal branch that supplies the facial nerve. Then, we were able to gain more distal access into brain and spinal vessels. This allowed greater use of liquid embolic agents. From our first variable stiffness microcatheter came the Target Therapeutics Tracker catheter. Now we had access, embolic agents, and an understanding of anatomy, which were all happening together with contributions from fantastic people. Each one had an important part to play.

After the microcatheter and cyano-acrylate liquid embolic agent, the detachable balloon, first developed by Serbenenko, advanced by Debrun, and later pioneered by Hieshima, was an important advance. We treated more fistulas then than we do now. And we treated aneurysms with detachable balloons. Grant Hieshima and I visited each other a few times. I think Grant's main contribution to the field was mastery of the detachable balloon (22), and his group shared their embolization experience with us in numerous publications during this time. Hieshima was extremely skillful and ingenious, and most of all, he had incredible intuition. In those days, two schools of thought were already developing. On one side, there was the French school, which emphasized the anatomy, and on the other, there were people, such as Hieshima, who would say, "It's a bad one!" and intuitively know how to best treat the lesion. He would know how to get himself out of trouble. Grant also published a spiritual article addressing the physician's hidden feelings after a bad experience, illustrating Hieshima's great sensitivity, which I share.

In the 1990s, a key event was the invention and development of the Guglielmi detachable coil invented by Guglielmi and clinically pioneered by Viñuela and his group at University of California, Los Angeles (20, 21, 45). The history of the Guglielmi detachable coil has been previously described (44). Coil technology continues to evolve today in the treatment of cerebral aneurysms and other diseases. Advances include a balloon remodeling technique introduced by Moret et al. (34), three-dimensional coil shapes, and, more recently, in this new decade, bioactive coils such as Viñuela and Murayama's Matrix coil (33, 36, 37) and the new self-expanding Hydrocoils (47). The advent of intracranial stents, such as Neoform, are leading the next advance. The endovascular treatment of intracranial aneurysms during the past decade has led to a renaissance in vascular neurosurgery, which has added endovascular training and therapy as part of the armamentarium to treat aneurysms and other diseases.

The only way we are to survive as a specialty is to transmit accumulated knowledge and experience. Therefore, the fellows we train are our legacy (*Table 2*). Some great surgeons disagree with this philosophy and really train no one, which, in my opinion, hurts the field in the long run. My principle goal of fellowship is to teach the trainees how to think, to understand the consequences of what they do, and to learn the best of radiology and the best of surgery to the benefit of the patients and the emerging new specialty. I have been fortunate to have trained more than 40 fellows. It is rewarding to see former fellows contributing to the field, such as Joe Eskridge in balloon angioplasty for vasospasm and Robert Rosenwasser, a vascular neurosurgeon, in aneurysm treatment, with many of them becoming leaders in their own right and training their own fellows. From the beginning, with my first fellow, In Sup Choi, I stressed the need to train the fellows clinically, particularly the neuroradiologists. This emphasis came from Joseph Ransohoff. He told me that this new field is surgical, and I knew that. The first neurosurgeon I trained was Yasunari Niimi in 1988. The first American neurosurgeon I trained was Robert Rosenwasser in 1992. I was impressed that Rosenwasser, although he was already an attending neurosurgeon for many years, was willing to become a fellow again. His philosophy is that he is a neurosurgeon who can bring all treatment modalities to the disease. He can do the surgery, the radiosurgery, and the embolization. Along with Nick Hopkins, Rosenwasser has led the way for the younger generation of neurosurgeons to have a better infrastructure to pursue endovascular training. This new generation may have a better chance to advance the field because they will not have to fight so many battles as in the past and current generations of interventional neuroradiologists.

When I started in this field, many people thought I was crazy. Today, everybody wants to do it. If everybody wants to do it, neuroradiologists, neurosurgeons, vascular radiologists, vascular surgeons, cardiologists, neurologists, it must mean that we are doing something right. However, I am concerned about the fragmentation that is occurring. Because these people come from different backgrounds and have different areas of interest, I do not see how broadness is to be maintained in this small field. To prevent fragmentation, a solution may be to create a specialty of

TABLE 2. Fellows

Name	Years
Eric Russell, M.D.[a]	1979–1980
In Sup Choi, M.D.	1981–1982
Ira Braun, M.D.[a]	1981–1982
Makoto Negoro, M.D.[a]	1983–1984
Charles Jungreis, M.D.	1983–1984
Doug Koenig, M.D.	1983–1984
John Scott, M.D.	1984–1985
Joseph Eskridge, M.D.	1985–1986
Lucie Brazeau-Lamontagne, M.D.	1985–1986
Douglas Graeb, M.D.	1980–81, 1985–86
John Pile-Spellman, M.D.	1986–1987
John Jacobs, M.D.	1986–1988
Yasunari Niimi, M.D.	1988–1989
Paul Rosel, M.D.[a]	1988–1989
Nolan Kagetsu, M.D.	1988–1990
Avi Setton, M.D.	1990–1992
Graham Lee, M.D.	1989–1990
David Kumpe, M.D.	1989–1990
Mario Hebert, M.D.	1989–1990
Robert W. Hurst, M.D.	1990–1991
Andrew Ku, M.D.	1990–1991
Peter Kim Nelson, M.D.	1991–1992
Buckley Terpenning, M.D.	1991–1992
Dong Ik Kim, M.D.	1991–1992
Robert Rosenwasser, M.D.	1992–1993
Thomas Marotta, M.D.	1992–1993
Gary Spiegel, M.D.	1992–1994
James Manzione, M.D.	1993–1994
John Agola, M.D.	1993–1994
Adam Davis, M.D.	1994–1996
Arani Bose, M.D.[a]	1995–1996
Lynette Master, M.D.	1995–1997
Johnny Pryor, M.D.	1996–1997
Toshifumi Kamiryo, M.D.[a]	1996–1997
Howard Riina, M.D.	1997–1998
Claudia Kirsch, M.D.[a]	1997–1998
Jonathan Hartman, M.D.	1998–1999
John Wong, M.D.	1999–2001
Charles Prestigiacomo, M.D.	2000–2002
Daniel Walzman, M.D.[a]	2001–2002
Razvan Buciuc, M.D.	2002–2004
Patricia Fernandez, M.D.	2002–2004
Jonathan Brisman, M.D.	2002–2004
Katsunari Namba, M.D.[a]	2004–2006
Navraj Heran, M.D.[a]	2004–2006
Rafael Ortiz, M.D.[a]	2006–2008

[a]Trained prior to full fellowship program, visiting fellows for more than 6 months, or did not complete the fellowship, and current fellows.

endovascular surgery with a separate residency and board certification. However, this is a major political enterprise.

An important part of our evolution was also brought on by the development of experimental models and protocols, pioneered by people such as Charles Strother, a true scientist and thinker among us, and the force behind the formation of the American Society of Interventional and Therapeutic Neuroradiology (ASITN). Two organizations that have helped define our specialty are the World Federation of Interventional and Therapeutic Neuroradiology and the ASITN, organizations for which I have served as president in the past. The World Federation of Interventional and Therapeutic Neuroradiology was formed in Val D'Isere to meet the needs of interventionalists in different parts of the world other than Europe and North America to help people with local problems. At this meeting, we discussed standardized training and ways to promote a new specialty, precursors to the guidelines for Accreditation Council for Graduate Medical Education accreditation in the United States (23). With great neurosurgeons such as Bill Bachay, Hopkins, and others, we started the process that, more than a decade later, would lead to a special competence in "Endovascular Surgical Neuroangiography," which is today recognized by the Accreditation Council for Graduate Medical Education.

ASITN was created as a result of our disagreements with the neuroradiology society. In a meeting, the American Society of Neurology did not want to separately recognize interventional neuroradiologists. An older generation thought they could be very good diagnostic and very good interventional neuroradiologists, as they had been during the era of silicone spheres. But, we were way beyond silicone spheres and the old ways, and needed to be more clinical. In response, Charles Strother suggested that we create our own society. We created the ASITN with approximately 60 members. We chose to host a meeting with another society. There were those who thought that we should partner with the Society of Interventional Radiology. However, my opinion was that it would be better to partner with neurosurgery. The others who were performing most of the cases agreed that we had to align with neurosurgery. Therefore, I approached Nick Hopkins and others to discuss the possibilities. We agreed that they would make us members of the American Association of Neurological Surgeons/Cerebrovascular Section, and we would make them members of ASITN. Strother, Kerber, and I accepted the arrangements. Viñeula and Hieshima, who were also very involved, agreed as well. From the beginning, this partnership has been important. The evolution of endovascular neurosurgery continues, and the greatest advancements are yet to come.

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History of Endovascular Neurosurgery: A Personal View

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"What's pass't is prologue."
—*The Tempest*, William Shakespeare

We in the neurosciences are blessed to stand on the shoulder of giants, giants whose interesting stories come to light through their scientific writings. Too many histories rely simply upon dry facts. For example, we read of battle sites and outcomes, the names of kings and presidents, the dates of redrawing of national boundaries, and, perhaps not surprisingly, we find little of interest. But, through our forefathers' writings, we can see between the lines, to see the frustrations and their eventual successes. How much better and more interesting it would be to hear more literally the human side, to learn of their struggles, failures, and eventual triumphs. Sadly, today we can rarely do more than infer. But infer we must, for knowing the past, we may perhaps avoid our fathers' failures and see even more clearly toward our future. Besides, the development of endovascular neurosurgery is really a fascinating story.

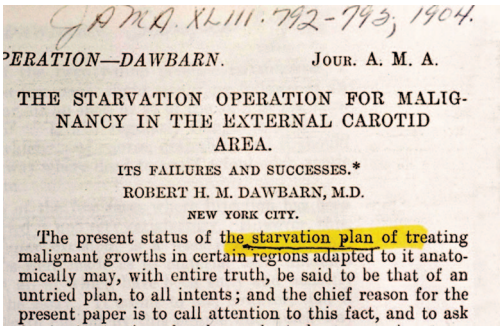
This history is the one time that we cannot begin with a pithy Hippocrates quote. Hippocrates simply didn't do endovascular work; the discovery of the circulatory system was a few millennia away.

Our story begins with James Dawbarn, a general surgeon, who presented the results of his "starvation plan" for head and neck malignancies at the American Medical Association meeting in 1904 (6) (*Fig. 1*). He directly exposed branches of the external carotid artery and injected a mixture of beeswax and other organic materials. Because nothing more was heard from him or his technique thereafter, we must assume that his article did not go over well.

The next mention of embolic therapy, we find buried in an article by Brooks (23) in 1930. He described traumatic fistulas and was able to treat a cavernous carotid fistula by muscle embolization. The technique was chancy, but he made it work (*Fig. 2*).

The first treatment of a brain lesion, an arteriovenous malformation, is described in 1960 by Luessenhop and Spence (24). These surgeons exposed the internal carotid artery, made small methacrylate spheres by hand, rolling the polymerizing plastic between their fingers and then introducing those spheres directly into the internal carotid artery, which allowed the flow of blood to carry the emboli into the nidus. The surgeons then ligated the internal carotid artery. When I saw this patient more than 20 years later, he said that he had been one of their earliest cases (*Fig. 3*). Though having a recurrence, he had received 20 years of palliation after his hemorrhage. An observation from this patient helped us to develop the first rule of therapeutic embolization: the malformation fills from a posterior communicating artery after injection of the vertebral artery; the internal carotid artery is totally occluded. So that first rule is *never sacrifice an afferent artery*. The carotid artery gone, we were unable to perform more embolization. But we must not be too critical—20 years of palliation is significant.

In the early 1960s, Alskne and Fingerhut (1) began to treat cerebral berry aneurysms. They placed a magnet at the dome of the aneurysm and introduced iron filings into the aneurysm, sometimes endovascularly and sometimes through a needle placed through the center of the magnet. The system worked remarkably well, but the surgeons were hampered by lack of equipment. At the time, there was no good image amplification, so they were unable to judge the adequacy of treatment, nor did they have a good delivery microcatheter or balloon microcatheter to limit the escape of the particles. Consequently, some of the iron filings found their way into the general circulation and ended up in the reticuloendothelial system. Alksne thus abandoned the procedure. I performed follow-up angiography on his patient more than 25 years later, and this aneurysm, a difficult paraophthalmic lesion, was still perfectly occluded (*Fig. 4*). The diagnosis: Alksne was too far ahead of his time.


JAMA. XLIII. 792-793, 1904.

PERATION—DAWBARN. JOUR. A. M. A.

THE STARVATION OPERATION FOR MALIGNANCY IN THE EXTERNAL CAROTID AREA.

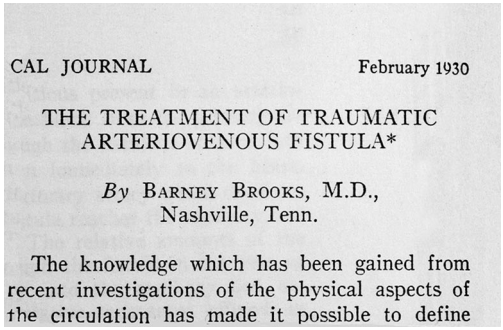
ITS FAILURES AND SUCCESSES.*

ROBERT H. M. DAWBARN, M.D.

NEW YORK CITY.

The present status of the starvation plan of treating malignant growths in certain regions adapted to it anatomically may, with entire truth, be said to be that of an untried plan, to all intents; and the chief reason for the present paper is to call attention to this fact, and to ask

FIGURE 1. *Dawbarn's original article.*


CAL JOURNAL February 1930

THE TREATMENT OF TRAUMATIC ARTERIOVENOUS FISTULA*

By BARNEY BROOKS, M.D., Nashville, Tenn.

The knowledge which has been gained from recent investigations of the physical aspects of the circulation has made it possible to define

FIGURE 2. *The Brooks article.*

SOME SPECIFICS

We now move to another facet of our story. We could perform few endovascular procedures today without the next two critical inventions. First, we must recognize our debt to Seldinger (30) for his developing the universally used percutaneous arterial entry technique, which he described in a modest and short article in 1953. The second evolution is much less well documented. It is the widespread adoption of catheter-based angiography. Following Forssmann's proving that he could catheterize his own heart in 1929 (12), interest in using intravascular catheters spread slowly and cautiously. Radner (prudently in a human other than himself) seems to have been the first to use a catheter for intracerebral diagnosis (29). Attempting to catheterize the heart from a right radial artery approach, he was surprised to find his catheter tip in the right vertebral artery.

The value of catheter cerebral angiography was not well appreciated, however, and the technique remained primarily utilized by Scandinavian abdominal angiographers, not finding its way to America until the mid 1960s. That introduction is not well documented in the literature, but was led by Amundsen (2), a visiting professor at the University of California, San Francisco, and almost contemporaneously by Hanafee (16) at the University of California, Los Angeles. For years thereafter, catheter cerebral angiography remained a phenomenon that grew at only a few centers (34) and was performed exclusively by radiologists. Neurosurgeons, for the most part, continued to perform their diagnostic studies via direct needle puncture of the carotid artery, reserving catheter diagnosis for lesions supplied by the vertebral arteries. That radiologists became more than secondary film readers was an important and seminal bifurcation event for this nascent specialty.

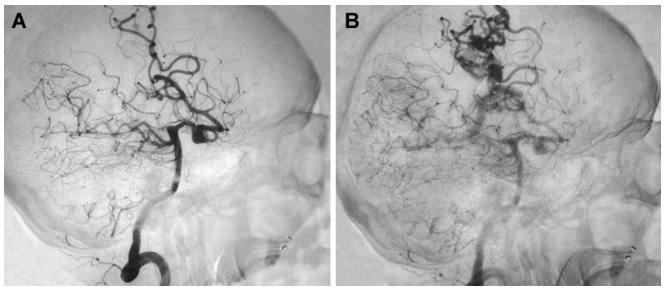


FIGURE 3. *A patient presented with seizures more than 20 years after receiving treatment by Luessenhop and Spence for a brain malformation. He had originally experienced a parenchymal hemorrhage. Their technique consisted of a cut down into the internal carotid artery, creating small methacrylate spheres by hand, then introducing those spheres into the internal carotid artery and allowing downstream flow to carry the particle preferentially into the nidus.* A, *first image.* B, *0.5 seconds later. Notice that flow into the residual AVM nidus occurs through a poster communicating artery, as their technique sacrificed the internal carotid artery.*

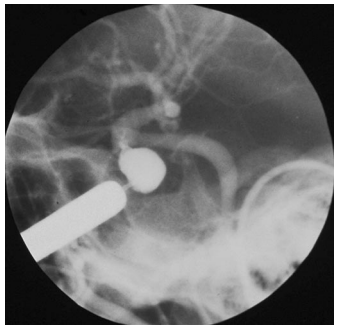


FIGURE 4. *John Alksne performed iron filing obliteration of this paraophthalmic aneurysm. The magnetic probe enters from the 8 o'clock position, its tip lying adjacent to the aneurysm. The radio dense, nearly spherical mass is iron filings within the aneurysm. The repeat examination more than 20 years later showed continued obliteration.*

CATHETERS AND WIRES

Unlike the tools for operative neurosurgery, endovascular devices developed slowly. The reasons were explained in 1970 by William Cook, president of Cook, Inc. The expected volume of sales was small, whereas legal liability was perceived to be unacceptably high (Cook W, personal communication).

Slowly though, diagnostic catheters and guide wires improved, led by demand from peripheral, abdominal, and cardiac angiographers, groups having much larger numbers of practitioners, and, thus, more economic clout.

Although the early diagnostic catheters were primitive, we were able to perform some interventions. Radiologists began to introduce barbiturates to localize language foci (the Wada test), Djindjian (9) described the nonselective embolization of facial vascular malformations, Newton and Adams (26) treated spinal cord malformations, and Boulos et al. (5) embolized brain arteriovenous malformations from a catheter in the internal carotid artery. This latter technique depended for its success upon the sump effect of the arteriovenous malformation nidus. Increased blood flow leading to the malforma-

tion would theoretically suck the particles (silicone spheres, pieces of dura, or polyvinyl alcohol foam particles) into the nidus. Unfortunately, a point would come in every treatment where flow into the nidus had been reduced to a volume and velocity less than that of flow to the remaining normal brain, and then the subsequently introduced particles would pass into critical arteries, often with disastrous results (*Fig. 5*). The judgment to know when to stop was often gained in retrospect, after the infarct occurred. Djindjian et al. (8), Kricheff et al. (21), and Wolpert and Stein (35) expanded the utility and safety of this nonselective technique.

In 1968, Doppman et al. (10) published a seminal article showing the necessity of filling the entire nidus of an arteriovenous malformation, rather than blocking only the feeding vessels (*Fig. 6*). This article directed most subsequent attempts to design a better AVM therapy.

During the seminal years of the 1960s, it was generally recognized that placing a somewhat stiff diagnostic catheter above the second cervical vertebra often caused iatrogenic dissection and subsequent infarction. In 1973, I developed a small silicone catheter ending in a balloon with a calibrated leak (*Fig. 7*) (17, 18). The microcatheter could be introduced into the brain via a larger guiding catheter and flow directed peripherally into even fourth and fifth order cerebral branches. Contemporaneously, Pevsner (27) developed an almost identical system.

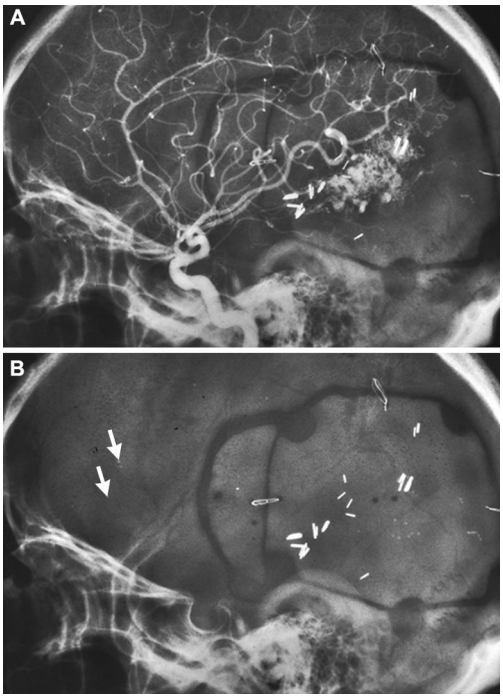


FIGURE 5. *An example of silicone sphere embolization of a recurrent posterior temporal arteriovenous malformation.* A, *angiographic image 0.5 seconds after injection.* B, *numerous small spheres are evident within the nidus. Unfortunately, the patient was becoming inappropriately happy, developing frontal lobe signs. The spheres within the anterior cerebral artery circulation are shown by* arrows.

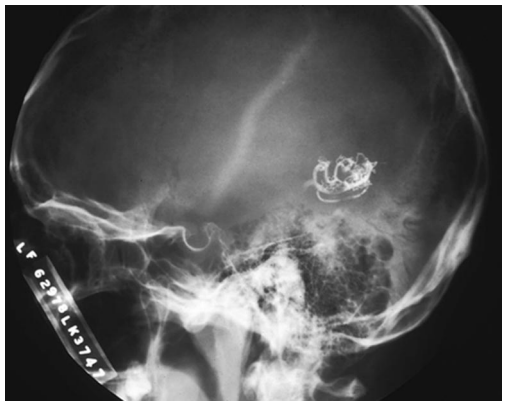


FIGURE 6. *The Doppman ideal: filling of the AVM nidus with embolic material rather than occlusion of the afferent artery.*

A year later, a patient presented with hemorrhage from a recurrent thalamic and occipital arteriovenous malformation. With this catheter, she received the first human treatment of intra-arterial cyanoacrylate (1974) (*Fig. 8*).

At the time, we thought this was the first intracranial exploration and treatment with a microcatheter, but Serbinenko had published his experience in the Russian literature in 1971 (31). In 1974, his first English report appeared in a neurosurgical journal (*Fig. 9*) (32). The imagination and hopes of the English speaking neuroscience community were now engaged.

Treatments for carotid cavernous fistula matured quickly, with durable occlusion by latex detachable balloon described not only by Serbinenko, but also by Lacour and Debrun (22), Debrun et al. (7), and Berenstein and Kricheff (4). Suddenly, an extensive surgical procedure taking the better part of the day was reduced to a few hours of work (*Fig. 10*). It had taken about 40 years, but we had come a long way from Brooks' tethered muscle therapy. This development is seminal, particularly because it offered a clear cure that was, by all admissions, significantly better than open surgery.

Those primitive small silicone and polyethylene catheters, coming to be known as microcatheters, although improving the

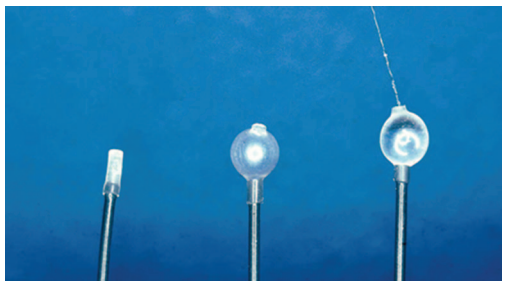


FIGURE 7. *The calibrated leak balloon microcatheter. Inflating the balloon slightly allowed the sump effect to carry the catheter toward areas of increased blood flow, for example, an AVM nidus. Further expansion of the balloon, especially when limited by an arterial wall, allowed fluid (either contrast agent or cyanoacrylate) to leak from the tip and further inhibited blood flow during the injection.*

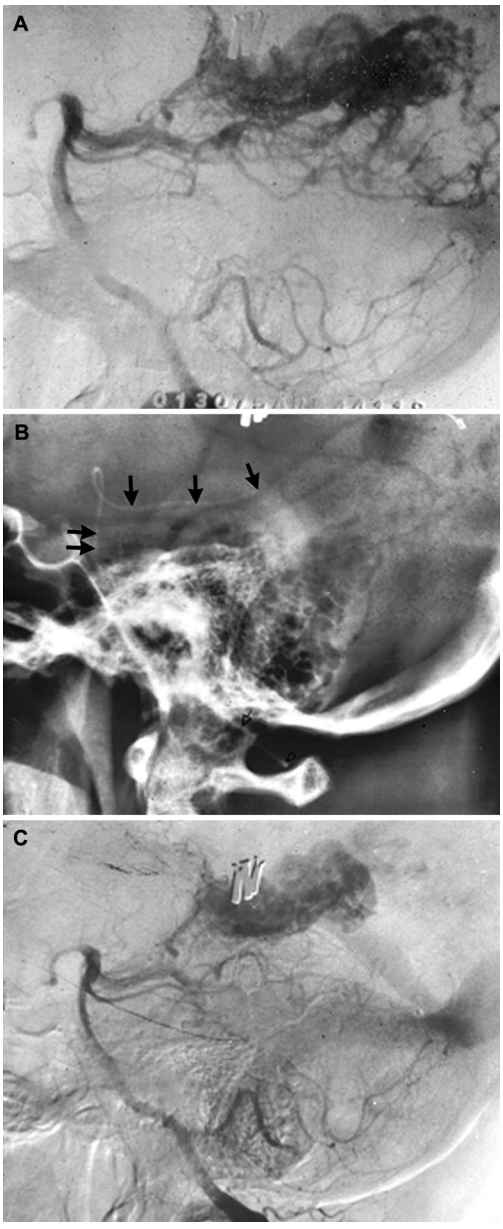


FIGURE 8. *The first intracranial AVM treatment with the calibrated leak balloon microcatheter. Twelve years earlier, the patient had excision of a deep thalamic and mesial temporal/occipital arteriovenous malformation. She presented with recurrent hemorrhage, in coma.* A, *initial angiographic image.* B, *the silicone Micro catheter in position* (arrows). C, *after treatment. Though not a cure, the patient awoke the following day. I have always wondered whether she would have awakened anyway.*

specialty's reach, were difficult to use and were unreliable. In October 1986, Target Therapeutics introduced their Tracker microcatheter and associated Microguide wire (Boston Scientific/Target, Fremont, CA), and the utility, effectiveness, and safety of cranial vessel exploration improved by a quantum step (*Fig. 11*).

WHAT TO INTRODUCE

Unfortunately, although microcatheter and guide wire development were proceeding rapidly, embolic material remained inadequate (*Fig. 12*). From the 1960s to the 1980s, the complaint heard most often was that, although there were better delivery devices, what we had to put through them was inadequate. Djindjian had cut slivers of gelfoam as a temporary occluding device for the external circulation and slivers of dry dura for injection when he needed a more permanent occlusion. (Incidentally, Djindjian is an important godfather on three levels: first, he trained an entire generation of French interventionalists; second, he introduced practical external carotid embolic techniques to the field; and, perhaps most importantly, he was the first interventionalist to publicly show his complications and to describe what he had learned from them.)

Gelfoam was well known in the operating room and so was, in general, a readily available occlusive agent when temporary blockage was needed, such as for a nosebleed or when a patient was to be taken soon after treatment to the operating room. Bank and Kerber (3) developed a technique to create sterile prepackaged gelfoam particles. This increased their utility and uniformity, and decreased the chance of infection.

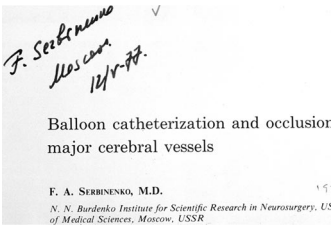
It remained for Tadavarthy et al. (33) to introduce a more permanent agent. They hand cut slivers of polyvinyl alcohol foam, injecting or pushing them through the delivery catheter. Shortly thereafter, we showed how to make polyvinyl alcohol foam particles uniform, sterile, and in a form that we could reconstitute in the angio suite (19). Despite this article's publication, it was almost 15 years before the manufacturers brought the device to market.

Arteriovenous malformations of the brain are difficult lesions to treat under any circumstance. Luessenhop and Spence's technique required a cut down on the internal carotid artery, a few methacrylate spheres introduced by hand, and then a ligation of the internal carotid artery. Silicone spheres (and occasionally liquid silicone) soon came to be a practical palliative device, introduced nonselectively, as with the previous, technique; but, because a catheter was used, the internal carotid artery remained open. As mentioned previously, the fatal flaw in the theory was that, as flow dynamics changed and the sump disappeared, particles tended to go to critical brain arteries.

An article by Zannetti and Sherman (36) in 1968 provided a clue to a better embolic device. Paul Zanetti had directly injected Bucrylate, a pure 4–carbon cyanoacrylate specifically invented to be used as a suture substitute by the Ethicon Corporation, into both arteriovenous malformations and aneurysms. What a superior example of lateral thinking. *Figure 13* shows the before and after treatment of an anterior communicating artery aneurysm he directly injected with Bucrylate in 1967.

In 1971, Zanetti (we had been residents together at the University of Pittsburgh) sent samples of his Bucrylate (*Fig. 14*) for use with the silicone calibrated leak catheter. It was a time in medicine when innovation was actively encouraged. For exam-

ple, the Human Use Committee at the University of Oregon did not want to know about *innovative* medicine (a physician developing a new treatment technique), only *experimental* medicine (a physician using a control group). When Charles Dotter was the chairman at the University of Oregon, Rosch, and other innovative abdominal interventionalists, introduced the idea that radiologists used devices to treat, rather than just diagnose, disease, an initiative that was actively encouraged within the radiology department. It remains amusing to this day to remember seeing requests for consultation with large black block printing saying, "diagnose, DO NOT TREAT." I should add that these requests invariably came from vascular surgeons, not neurosurgeons.


Balloon catheterization and occlusion major cerebral vessels

F. A. SERBINENKO, M.D.

N. N. Burdenko Institute for Scientific Research in Neurosurgery, US of Medical Sciences, Moscow, USSR

FIGURE 9. *Serbinenko's original article.*

After extensive laboratory testing and development of technique, we used bucrylate on a female patient, 1974 (*Fig. 8*) (17). Our patient presented with hemorrhage from her residual (or recurrent) deep arteriovenous malformation. Encouraged by my neurosurgical colleagues who thought they had little to offer operatively, we guided the silicone catheter into thalamic arteries, and injected as much bucrylate as we could. Though not a cure, she awoke in a few days and left the hospital a week later. She did well for 12 years until she finally experienced an ovarian malignancy. Modified by the addition of oily contrast agents and acetic acid to make it radiopaque and modify behavior and polymerization time, the 4–carbon monomer remains in use today, unchanged (and, unfortunately, unimproved).

ON TO ANEURYSMS

Alksne's and Zanetti's innovative work from the 1960s was ahead of its time, but lacked administrative and industry support. As years passed and detachable latex balloons became more widely available for the treatment of carotid cavernous fistulas, attempts to treat aneurysms by primarily filling them with a latex detachable balloon were attempted (7, 32). Unfortunately, few aneurysms are spheres or oblate spheroids, forms that an inflated balloon would take. The technique never became widely accepted.

Guido Guglielmi and Ivan Sepetka's development of the detachable platinum coil in 1991 changed aneurysm therapy forever (14, 15). For the first time, vascular therapists had a clinically effective, relatively easy to use device that would protect patients from aneurysmal rerupture, and, in a vast majority, primarily treat the aneurysm. It is only fair to say at this point that there is not universal acceptance of the value of coil obliteration of berry aneurysms. Nonetheless, many think that our aneurysm treatment paradigm had progressed from Walter Dandy's *clip it,* through *exclude it from the circulation,* to *pack it.* We can only guess at and hope for the next step in aneurysm therapy.

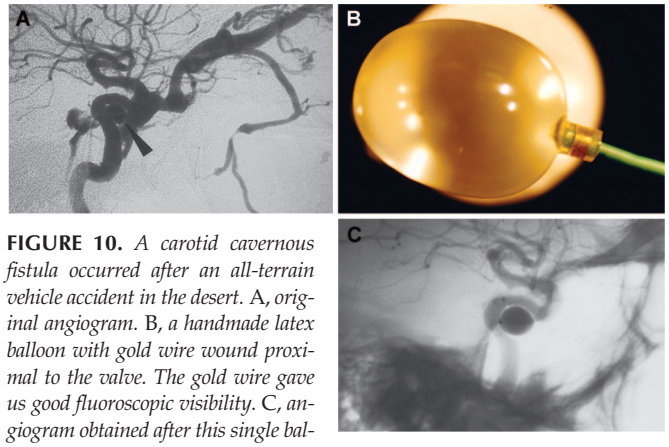


FIGURE 10. *A carotid cavernous fistula occurred after an all-terrain vehicle accident in the desert.* A, *original angiogram.* B, *a handmade latex balloon with gold wire wound proximal to the valve. The gold wire gave us good fluoroscopic visibility.* C, *angiogram obtained after this single balloon's detachment. The carotid artery is preserved. The entire procedure took less than an hour.*

ENHANCING FLOW

At this point, we have thought only of blocking blood flow to various arterial abnormalities, hypervascular tumors, fistulae, arteriovenous malformations, and aneurysms. But the brain is exquisitely sensitive to an interruption of blood flow. What about the opposite side of the coin: enhancing cerebral flow to treat or prevent stroke?

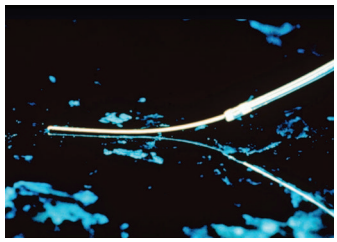


FIGURE 11. *A Target Therapeutics Tracker microcatheter and guidewire. Whereas the calibrated leak microcatheter was flow guided, this catheter could be pushed and rotated to a desired location, giving the therapist much better control and access to the intracranial third and fourth order vessels.*

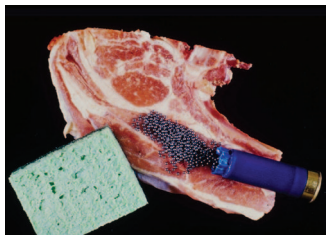


FIGURE 12. *The early embolic materials were primitive and generally not particularly safe. We used pieces of the patient's own muscle and fat, ground up sponge, and, although it's difficult to believe, we actually disassembled shotgun shells to use the lead pellets.*

In the early 1960s, radiological diagnosis had progressed far beyond our feeble attempts at therapy. Charles Dotter (11), thinking that catheters could do more than diagnose arterial illness, performed an angioplasty on an elderly woman in January 1964 who was bedridden because of a cold ulcerated foot. Dotter used coaxial stiff catheters to perform his successful dilatation, and she walked out of the hospital soon thereafter. On many levels, this development was revolutionary. It was a disruptive technique. Compared with the central nervous system disease, atherosclerosis was a huge problem involving large numbers of patients,

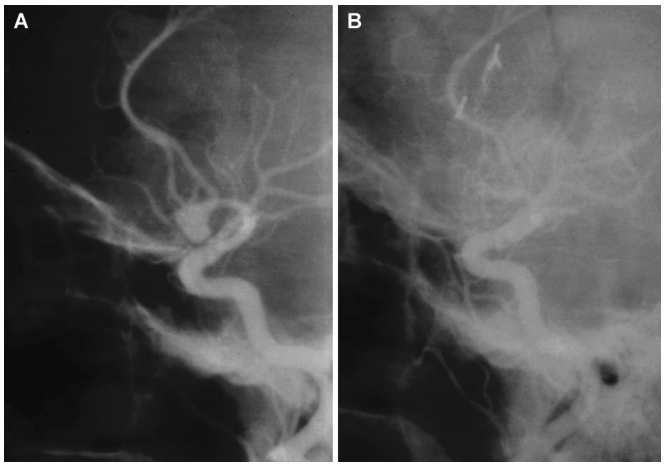


FIGURE 13. *One of Zanetti's early patients. He directly injected Bucrylate into this anterior communicating artery aneurysm (*A*), completely obliterating the aneurysm while preserving all distal branches (*B*).*

and the disruption of newly developed (but immediately perceived as traditional) surgical procedures and thought paradigms caused distress in the surgical communities. There was time for the surgeons to adapt, as this technique was to mature slowly. There were few radiologists trained and able to perform the procedure, and the Dotter technique left a hole and the artery's entry site as large as the dilatation catheter. The occasional need for surgical consult to close that arteriotomy was inevitable and was not always furnished with collegial goodwill.

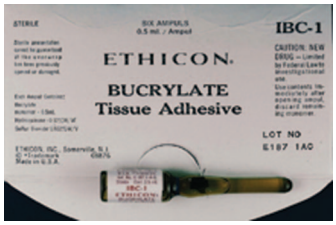


FIGURE 14. *For many years, bucrylate, although never approved by the Food and Drug Administration, was our only cyanoacrylate-based embolic material. Originally designed as a suture substitute by Ethicon Corporation, Zanetti successfully treated both berry aneurysms and arteriovenous malformations with bucrylate.*

Nonetheless, the idea spread rapidly, but it was not until the development of firm, effective dilatation balloons that the procedure became well accepted and efficacious.

In 1973, Porstmann (28) recognized that simple latex balloons could not provide the axial strength needed to open atherosclerotic plaques. He developed a caged balloon which he called his "korsett balloon catheter." It worked, but was slow, with each forward passage being spherical, irregularly dilated the plaque.

It remained for Andreas Gruntzig, in a gently understated letter in *Lancet*, to solve the problem and effectively dilate arteries using a firm, sausage-shaped balloon of polyvinylchloride (13). Few letters to the editor have had such an impact, and his technique spread rapidly, although it was used extensively by both coronary and peripheral angiographers, but not by neuroradiologists.

In the 1960s, carotid endarterectomy to treat transient cerebral ischemia had come of age, and the significant complication rate fell below 10%. Even a cursory examination of the surgically removed endarterectomy plaque with its ulcerations, exposed grumous material, and small clots adhering to the denuded surface was enough to give most neurointerventionalists pause. We knew the brain's poor tolerance of embolic material and concluded, incorrectly in retrospect, that carotid bifurcation disease was best left to the surgeons.

In 1974, we performed the first carotid dilation using the Dotter technique (20). The patient had two serious stenoses: one at the bifurcation and a more proximal stenosis at the common carotid artery origin. After the bulb endarterectomy, we passed the Dotter catheter down toward the heart, expecting that any dislodged plaque would pass harmlessly out of the endarterectomy site. It was a cautious and conservative first attempt. As balloon dilation catheters became more widely available, primarily fibrotic narrowings, fibromuscular disease of the internal carotid artery, Takayasu's arteritis, and post surgical bulb restenosis was treated, but it remained for Mathias et al. (25) to prove our intuition wrong when they performed the first carotid bulb dilatations for primary atherosclerosis. Since then, larger series have proven the value of this therapy, and now, reliable stents and distal protection devices are routinely used.

A SERIOUS DEFICIENCY

What is missing in our short history? We see only the names of physicians, colleagues who brought devices to clinical utility. To be sure, in the early days it was, of necessity, the physician who was also engineer, inventor, and fabricator. But devices did not attain their present level of effectiveness, uniformity, and reliability until the might of the primarily United States-based industry was brought to bear on our problems. The engineers working in commercial laboratories remain essentially unsung, but deserve our deepest gratitude.

OUR PRIMARY TOOL

Above all, the safety of endovascular therapy comes from our ability to see, to see finer anatomy, with wider gray scales, to subtract away bones and other soft tissue electronically, and especially to be able to manipulate planar images into visual constructs that the human mind can understand.

Imaging Chain

The development of grayscale and color Doppler ultrasound, and, more recently, the coupling of computer manipulation to computed tomographic (CT) scan and magnetic resonance imaging scan axial images has certainly piqued the attention of our diagnostic colleagues. The utility of a CT angiographic movie showing rotating vessels and the relationships of those vessels to the neck of an aneurysm cannot be underestimated. This kind of image manipulation provides both surgeons and interventionalists a three-dimensional percept that allows appropriate and safer therapy. With these computer-generated images, our diagnostic colleagues have

chided us about the demise of catheter angiography, a not unexpected jibe. But then the manufacturers surprised us all: the marriage of the computer with rotational angiography has provided incredibly useful moving images, with the computer allowing us to subtract, for example, radiopaque clips, the mesh of stents, and even superimpose images from other modalities, such as magnetic resonance imaging scans. Moreover, the manufacturers have recently brought us flat-panel technology, with its greater reliability, less image degradation during the life of the machine, wider dynamic range, and the ability to obtain CT scan soft tissue imaging on the angiography table. What a time to be in practice.

OUR FAILURES

Throughout the 50-year saga, we must critically ask what we have *not* done (or not done well enough). Compare our journals through the past decade to the cardiology journals, and we must reluctantly conclude that we have not brought enough scientific evaluation to our field. We have not done adequate outcomes analyses. For example, despite thousands of cases treated with combined embolization and surgery, who can unequivocally say that preoperative embolization of an AVM actually works in the patient's best interests? There are other basic science questions that also need to be answered. Why do aneurysms form where they do? If atherosclerosis is a systemic disease, why does the plaque deposit at predictable sites? (Have you seen any atherosclerosis in an arm lately?)

PUTTING IT ALL TOGETHER

In these times of overregulation and poor reimbursement, it is tempting to look back with certain nostalgia at the freedom we had, but there were no "good old days." The early days of this history were dreary, plagued by poor or nonexistent equipment, resistance from colleagues, and awful complications.

So, why study history? Is it not to predict the future, as Shakespeare pointed out eloquently at the beginning of this article? I am somewhat reluctant to do so now, remembering the words of three painfully foolish futurists: the General Motors executive, who in 1952 dismissed the Volkswagen invasion with the following words, "They imported 50,000 cars? Well, we *lose* that many each year." Or the IBM Vice President who, only decades ago, said "I expect there will be a market for, maybe, 11 home computers." And finally, Bill Gates himself who said, "The computer will certainly make this a paperless world."

So, maybe we cannot predict specifics, but studying history does allow us to see critical large and general movements, and oftentimes those movements are more clearly appreciated in retrospect. For example, to try to hold back the expansion of endovascular interventions is much like trying to hold back the tides.

Of course, there is the other reason to study history: its entertainment value. We can laugh at the big egos, dumb mistakes, lost opportunities, and can congratulate ourselves for not having so similarly fallen—and *maybe* be more cautious about not making those same mistakes.

NOT REPEATING MISTAKES IS THE VALUE OF HISTORY

These are wonderful, heady times for us in interventional neuroradiology or endovascular neurosurgery. Each month seems to bring new advances, new techniques, better tools. But a caution: Dr. Penfield, one of our pioneers who, in 1948, said, "Elaboration of surgical technique is an important mechanical achievement. But beware of vainglory; for it may be that our intellectual maturity is yet far off, and only to be acquired after years of further pioneering."

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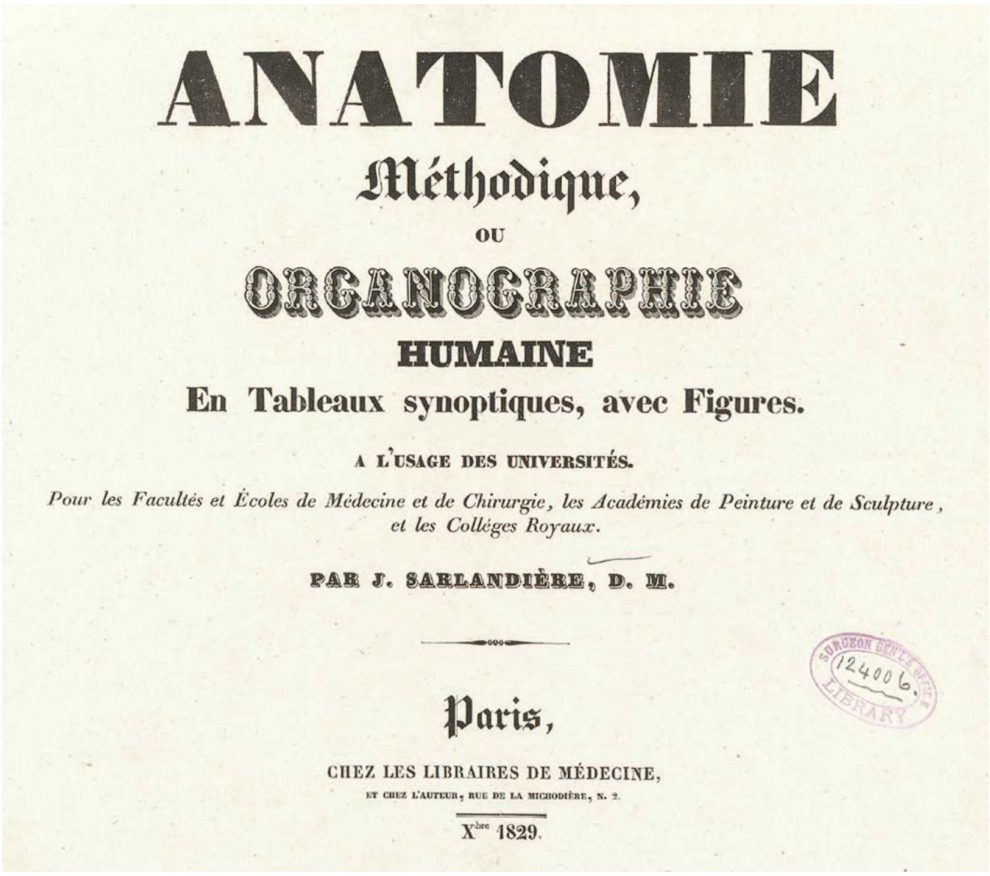

ANATOMIE

Méthodique,

OU

ORGANOGRAPHIE

HUMAINE

En Tableaux synoptiques, avec Figures.

A L'USAGE DES UNIVERSITÉS.

Pour les Facultés et Écoles de Médecine et de Chirurgie, les Académies de Peinture et de Sculpture, et les Colléges Royaux.

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HISTORICAL PERSPECTIVES: THE MICROSURGICAL AND ENDOVASCULAR TREATMENT OF ANEURYSMS

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THE HISTORY OF aneurysm therapy is rich in parallelisms that exist between the once-fledgling field of aneurysm surgery and the now-growing field of endovascular aneurysm treatment. The treatment of aneurysms has had a cyclic progression. The indirect and safest approach to the treatment of aneurysms was seen in the development and use of Hunterian ligation in the 19th century. During the past few decades, nascent technology and a better understanding of the pathophysiology of aneurysms resulted in a more direct intracranial, extravascular approach to aneurysm therapy, with the focal point being the use of the aneurysm clip to secure an aneurysm at its neck. Interestingly, alternative and, arguably, even more direct approaches to aneurysm therapy developed in the surgical suites. These techniques became the seeds for the birth of direct endovascular aneurysm treatment in particular and endovascular surgery in general. As endovascular technology continues to develop, somewhat more sophisticated, indirect approaches to aneurysm therapy (the use of stents to modify flow, for example) are being investigated. The treatment of intracranial aneurysms has a rich history. First thought to be inoperable lesions, aneurysms have challenged neurosurgeons and their colleagues since they were first recognized in the 18th century. Treatment for these lesions did not begin until the 19th century with the use of Hunterian ligation. This review describes the many milestones in the field of aneurysm surgery and endovascular surgery, tracing the many parallelisms contained within the birth and growth of each field and their respective significance.

KEY WORDS: Aneurysm, Endovascular, History, Surgery

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The history of intracranial aneurysms is an extremely rich story of parallels that continues through the present day. Despite the tremendous advances in understanding some aspects of the pathophysiology and in the technology required to safely treat these lesions, the overall morbidity and mortality of this disease remains unacceptably high. The many parallels that exist in aneurysm treatment reflect the neurosurgical community's struggle in trying to understand why aneurysms develop and why they rupture. It is also a struggle to determine how to best treat these lesions with the technology of the times and a vision towards the technology of the future. At times, when the technology did not exist, alternatives were chosen that seemed to be somewhat effective. However, as technology developed, the philosophy changed. Or rather, as technology "caught up" to the ideas, the overall philosophy of aneurysm treatment changed.

This has resulted in an almost cyclic evolution in aneurysm treatment with parallels being seen between the microsurgical and endovascular treatment of lesions. It began with an indirect attack on the parent vessel (Hunterian ligation) and matured to the more direct surgical approaches of trapping, wrapping, and subsequently direct clipping of the aneurysm (*Fig. 1*).

The dawn of endovascular treatment, in essence, grew at the height of direct microsurgical approaches to aneurysms, although historical roots existed well before that (*Fig. 2*). The concept of a "direct attack" on the aneurysm in the operating room was then translated to a direct "transfundal" or "transaneurysmal" approach and matured from endosaccular balloon occlusion to current coil technologies. Further developments in endovascular therapy now look back to the original concepts of aneurysm surgery. Once again, interventional neuroradiologists and surgeons introduced the concept of flow reversal (Hunterian ligation) and trapping as a means of treating otherwise untreatable aneurysms. Interestingly, whereas the indirect approach to aneurysm treatment was all that could be accomplished with the technology of the early 20th century, the concept of flow diversion with stents without endosaccular filling reflects a more sophisticated and elegant approach to the concept of an "indirect" attack on aneurysms at the beginning of the 21st century.

The history of intracranial aneurysm treatment does not limit itself to the technical advances within the operating room or endovascular suite. It is quite expansive. Much has been, and can be, written on the historical aspects of the pre- and postoperative management of aneurysm patients. Although interesting in their own right, these aspects of aneurysms will not be discussed. Instead, the focus will remain on the direct technological advances in the instrumentation used to treat aneurysms and the rationale behind their development and use. In order to better understand the rationale behind the development of endovascular techniques, a sound basis on the historical roots of aneurysm surgery is necessary. This review is by no means meant to be an exhaustive historical account of the origins of the microsurgical clipping of aneurysms, which, in and of itself, is abundant and rich in its complexity. Thus, references to very important individuals who brought aneurysm surgery to its present status must be admittedly brief in order to bring focus to the endovascular history.

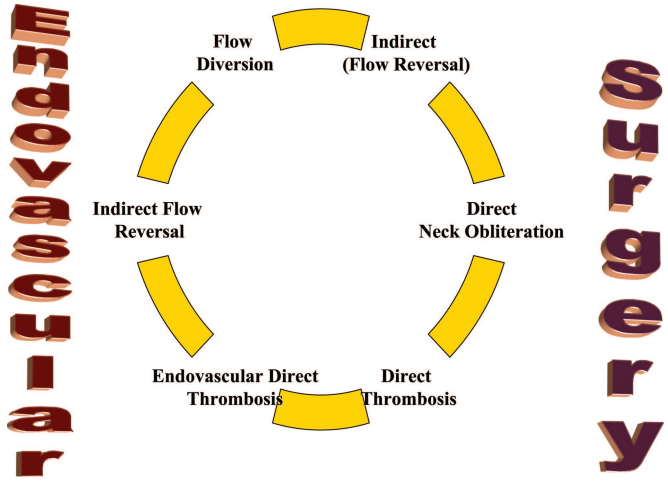

FIGURE 1. *Diagram representing of the cyclic phases of the surgical and endovascular treatment of aneurysms.*

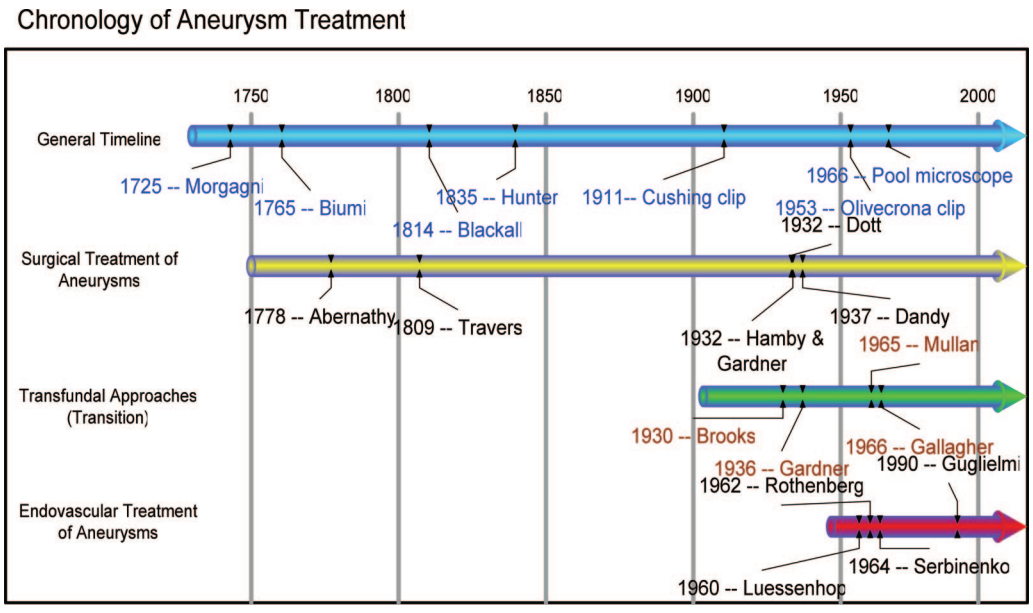

FIGURE 2. *Chronology of important events in the recognition and treatment of aneurysms. Refer to text for details.*

THE EARLY HISTORY OF ANEURYSM SURGERY

Intracranial aneurysms were first thought to be a cause of subarachnoid hemorrhage (SAH) in the 17th century (11, 106). Morgagni (71) likewise emphasized the concept that intracranial aneurysms could be the cause of hemorrhage. He was also the first to report the presence of incidental "dilatations" of both posterior cerebral arteries in 1725, possibly making this the first description of an intracranial aneurysm. The first documented account of an unruptured intracranial aneurysm did not occur until 1765 by Francesco Biumi (9) in Milan. In 1814, the first verified account of an aneurysmal rupture was reported by Blackall (10).

Despite recognizing these lesions during the mid-18th century, there is no mention of any treatment being offered. Indeed, the reports at this time were based on postmortem findings. Treatment of vascular lesions of the head and neck did not begin until the late 19th century, several years after Hunter's description of proximal femoral artery ligation for popliteal aneurysms as an alternative to leg amputation (45, 52).

Building upon the success of Hunterian ligation in the peripheral circulation, the concept of carotid artery ligation for intracranial vascular pathology began to take form. Although Jean Luis Petit was the first to report that the brain may survive when deprived of contribution of one artery, Hebenstreit was the first to ligate the carotid artery for injury in 1793 (19). There is substantial literature to describe John Abernathy (1) as being the first individual to deliberately ligate the carotid artery for injury in 1778 or 1779 (reported in 1798) (39). The first successful carotid sacrifice for an indication other than hemorrhage was by Cooper (15) in 1808 for an aneurysm of the left cervical internal carotid artery (Cooper's first carotid ligation in 1805 was unsuccessful). Cooper, interestingly, surmised at the time that the partial resolution in pulsations was attributed to retrograde filling from distal collateral circulation. Benjamin Travers (99) first reported successful treatment of an intracranial lesion (carotid cavernous fistula) in 1809.

The years that followed were filled with clinical reports of carotid ligation for numerous nontraumatic indications. A full century after Hunterian ligation was first

described, carotid occlusion for an intracranial aneurysm was performed. During surgery for resection of a middle fossa tumor in a 48-year-old woman, Victor Horsley identified a pulsating tumor, most likely an aneurysm. Horsley subsequently ligated her right common carotid artery. She was reported to be doing well 5 years later (54).

The following years were then devoted to developing more sophisticated methods of carotid occlusion. Progress in ligature began with simple occlusion methods involving various suture materials. Because of a high infection rate at that time, most methods involved applying a circumferential ligature with the sutures coming out of the wound. After approximately 2 to 3 weeks, the sutures would "come away" and the vessel would be presumed thrombosed. More sophisticated techniques were then developed to allow for thrombosis of the parent vessel while minimizing clot propagation into the intracranial circulation. Methods, such as Poppen's sequential placation of the carotid artery over a 3 to 4 cm length, were reported as successful and safe methods of carotid occlusion (83, 84). Halstead (44) and Matas (63) evaluated the use of aluminum strips that allowed for progressive tightening of the band or complete removal if the patient did not tolerate the procedure. Nassette (22) and Perthes (78) began the use of a fascial band to minimize the intimal damage from the suture. Proponents of this technique, such as Dandy (24), argued that this could be performed as a staged procedure, thus allowing for collateral circulation to develop and consequently would be better tolerated. However, its success was variable, as complete occlusion was not often noted.

A rather ingenious device invented and later perfected by Neff (75) allowed for gradual arterial occlusion with the need for a single stage operation that allowed for the development of collateral circulation while occluding and dividing the vessel. The Neff clamp consisted of two metal bands secured at both ends by rubber bands. Absorbable catgut was wrapped around the one end of the bands to prevent the blades from completely crushing the vessel. As the catgut was absorbed, the rubber bands would slowly squeeze the metal bands together, thus gradually, but progressively, occluding the artery. By 1904, independent reports of the success of this clamp were published (17).

Further advances in carotid occlusion were in the simplification and mechanization of the technique. The introduction of the Dott, Crutchfield, Selverstone and Kindt clamps (among others) allowed the surgeons to place the clamp around the artery and to gradually tighten the clamps over a period of days (16, 31, 40, 89, 90). In reviewing the literature between 1933 and 1960, Tonnis and Walter (98) found a 3 to 41% mortality and significant morbidity from carotid ligation. The high death rate in some of the reported literature, however, was due to the high rate of infection and thrombosis. Later reports demonstrated mortality rates generally below 20% (25, 84, 88). Unfortunately, successful obliteration of the aneurysm was low, with success usually occurring for aneurysms of the internal carotid artery (ICA) itself. Winn's (105) report evaluating the rehemorrhage rate in 34 patients with posterior communicating artery aneurysms essentially found no difference between those treated with carotid occlusion and the conservatively managed nonoperative group.

Because of the difficulties noted and because of significant concerns regarding delayed thrombotic/embolic events from cervical carotid occlusion, the methods of cervical carotid occlusion were superseded by intracranial methods. The first successful intracranial carotid occlusion was described by Hamby and Gardner (46) in 1932. Zeller (110) was the first to attempt this procedure in 1911, but his patient died from hemorrhage after an assistant accidentally avulsed the ligated artery by pulling the ligature. In 1935, Dandy (20) introduced the use of the Cushing silver clip (developed in 1911) to achieve proximal supraclinoid ICA occlusion for the treatment of intracranial aneurysms.

DIRECT APPROACHES TO ANEURYSM TREATMENT

By the early 1900s, it was clear that, although a significant amount of knowledge had been gained on the pathology of aneurysms and some technical advances toward the treatment of these lesions had taken place, the overall outcomes were still dismal. Indeed, Harvey Cushing (18) thought that the aneurysm was "a lesion having such remote surgical bearings, . . .whether there are surgical indications. . .further experience alone can tell." Ayer (7) later echoed these sentiments by stating that subarachnoid hemorrhage "has little interest from a standpoint of active surgical procedure."

Because of the many difficulties encountered with the indirect approaches of cervical carotid ligation, intracranial carotid ligation, and trapping, more direct approaches were sought. Although there were real concerns with a direct attack on the neck of an aneurysm, there were significant benefits. The technology in the 1930s made securing an aneurysm at the neck rather dangerous, as ligatures and silver clips were the only devices developed at the time. Thus, risks of exsanguination secondary to avulsion of the aneurysm at the neck were quite real. However, preservation of the parent vessel and a higher chance of cure for aneurysms beyond the carotid terminus was sufficient reason to embolden surgeons in their quest for new techniques.

Norman McComish Dott (30), a pupil of Cushing's and one of several men to help found neurosurgery in Great Britain, was the first surgeon to be credited with the first direct attack on an intracranial aneurysm. On April 22, 1932, in treating a middle-aged man who had sustained three subarachnoid hemorrhages secondary to an aneurysm of the ICA terminus at the origin of the proximal middle cerebral artery, Dott encountered "formidable" bleeding during the exposure. He harvested muscle from the patient's thigh and placed it on the exposed aneurysm dome. He reported that hemorrhage stopped after approximately 12 minutes. He applied further muscle pledgets in the region and surrounding the parent artery. The patient was reported to have made an excellent

recovery with no further hemorrhagic events. Additional reports by Tonnis (97), Dandy (25), and Jefferson (53) added to the early literature of wrapping.

The next advance in aneurysm treatment was aneurysm trapping, which was initially described by Walter Dandy (22) in 1936. He performed cervical internal carotid ligation and clipping of the supraclinoid carotid artery for a cavernous aneurysm. Logue (58) clipped the A1 segment to trap an anterior communicating artery aneurysm in 1956 and Tindall et al. (96) added contralateral common carotid artery narrowing to assist in thrombosis.

THE ANEURYSM CLIP

On March 23, 1937, a new era in cerebrovascular surgery began. Walter Dandy (21) reported exposing an aneurysm of the posterior communicating artery via his hypophyseal approach in a 43-year-old man presenting with a third nerve palsy. Having identified the neck of the aneurysm, he placed a silver clip across its neck and cauterized its dome. By 1944, he had amassed sufficient cases that he published his observations and results in the first monograph of aneurysm surgery, *Intracranial Arterial Aneurysms* (25).

This first clip used by Dandy was a malleable Cushing or Mackenzie type silver clip (22). Simple, yet important, modifications to the concept followed with the development of a U-shaped clip to allow the tips of the clip to approximate first and essentially trap the vessel within the clip, thus obliterating the vessel (34).

Further modifications to the clip came quickly. The next important step in the development of the aneurysm clip was the development of an adjustable clip that could be reopened and repositioned. The Olivecrona clip was essentially a recurved metal strip with proximal "wings" projecting above the fulcrum of the clip to allow the clip to be reopened if the wings were compressed (76). This began a flurry of modifications to a basic concept that provided safer and more controlled application of the aneurysm clip, with Housepian's clip being the embodiment of clip technology at that time (35).

Schwartz developed the cross-action alpha clip originally intended for use in temporary occlusion in the 1950s (64). Although excellent in concept, the Schwartz clip was difficult to use in the setting of intracranial aneurysm surgery. Mayfield and Kees (64) then modified these concepts on a smaller scale and changed the applier to improve the ergonomics of clip placement. The Mayfield-Kees clip became the most popular clip of the 1950s and 1960s. Subtle, but important, improvements in several aspects of clip technology took place, with the most important being the development of better biocompatible metals, wider blade openings, different configurations, and the bayoneted clip to allow better visualization of the clip as it was being placed on the aneurysm (93). Although George Smith initially developed a clip that allowed the surgeon to treat aneurysms on the opposite side of the vessel wall (35), it was not until Drake's modification of the Mayfield-Kees clip that the fenestrated clip was developed (27). In treating many posterior circulation aneurysms, Drake noted the need to develop a clip that would allow him access to the neck of an aneurysm without compromising vessels that were in the way. By developing the fenestration, the aneurysm clip could be safely placed along the neck of an aneurysm without displacing and potentially compromising other vessels in the field. Sundt's encircling clip-graft was another significant innovation in aneurysm clip technology that allowed for repair of vessel tears or small irregularities that are untreatable by ordinary clipping methods (94).

Currently, modifications to the aneurysm clip are based on metallurgy and different design configurations. Concurrent with the development of the aneurysm clip came many other developments in techniques and parallel technologies that helped improve the surgical treatment of patients with cerebral aneurysms (12). The introduction of the surgical microscope revolutionized the approach to treating aneurysms (81, 82). The elegant microsurgical techniques of Yaşargil and Fox (107) and Yaşargil (108) helped to redefine the surgical approaches to aneurysms, emphasizing the importance of understanding cisternal anatomy and microvascular anatomy in maximizing patient results. During this period, others, such as Drake (32), set the standards for surgery of posterior circulation aneurysms, along with the development and use of the first fenestrated aneurysm clip.

ENDOSACCULAR ALTERNATIVES TO CLIPPING

As aneurysm clip technology continued to develop, surgeons continued to reflect on alternative techniques for the management of aneurysms. The concept that aneurysms could be treated endoluminally was serendipitous. In 1936, Gardner (38) opened a giant ICA aneurysm, thinking it to be a large tumor. He subsequently packed it with five cotton sponges. The patient did well until 2 years later when the sponges were removed because of infection.

Several years later, Walter Dandy (22, 23) attempted an endosaccular cure for an unclippable aneurysm by inserting eight silk sutures into the sac of a giant cavernous sinus aneurysm. Reoperation 5 days later demonstrated continued filling of the aneurysm and the patient subsequently underwent surgical trapping.

In 1941, Werner et al. (104) described a 15-year-old girl with a giant ICA aneurysm eroding through the orbital roof. Several attempts at Hunterian ligation were ineffective. Consequently Werner, working in conjunction with Blakemore and King, who had studied this technique for aortic aneurysms, approached the aneurysm transorbitally by gently retracting the globe medially and identifying the sac of the aneurysm. He then passed 30 feet of 34 gauge silver enameled wire into the aneurysm fundus and heated it for 40 seconds to 80 degrees centigrade. The patient survived the procedure, reportedly with no further recurrence.

Mullan became quite interested in the endosaccular approach to aneurysm treatment and subsequently published several studies evaluating the use of 33-gauge berryliumcopper wire and copper wire as a means to promote thrombosis without need for electric current (73). In a series of 15 patients, Mullan et al. (72) documented 12 patients with good results. Mullan also explored the use of direct current in the thrombosis of aneurysm in 1965 and stereotactically placed wire electrodes into exposed aneurysms and subjected them to an electric current. Although partially successful, the complications from the procedure were higher than those from clipping.

Gallagher (37) developed a technique of injecting horse or hog hair into the dome of an aneurysm as a means of inducing thrombosis (pilojection). In his series of 15 cases, Gallagher noted only partial thrombosis in most patients.

In 1966, Alksne et al. (2) and Rosomoff (86) independently developed methods by which iron suspensions could be injected via the internal carotid artery and collected in the aneurysm dome by placing a stereotactically guided magnet near the aneurysm. Although a fair degree of thrombosis was noted, the embolic risk by this technique was too great. Therefore, Alksne et al. (3) modified the technique by inserting the iron suspension by a stereotactic transfundal approach, using the magnet to keep the suspension within the dome of the aneurysm while thrombosis took place.

Except for a few select procedures, the aforementioned techniques all involved transcranial approaches to the aneurysm. The technology for safe navigation intravascularly was not far behind. By 1962, Rothenberg et al. (87) developed an intravascular catheter that could release an expandable sleeve and occlude an aneurysm in an experimental animal model. Two years later, modern endovascular therapy for aneurysms was born.

ENDOVASCULAR TREATMENT OF ANEURYSMS

The concept of endovascular aneurysm treatment has grown from attempts to treat aneurysms endovascularly since the 19th century. Careful observations and subsequent experiments in animals by Velpeau (100) suggested that metallic objects, such as needles, could result in local thrombosis sufficient to occlude an artery. Independently, Phillips (79) demonstrated that the use of a needle with an electric current applied also resulted in thrombosis within a vessel. These concepts were first studied in humans for the treatment of aortic aneurysms. It wasn't until approximately a century later that the technique was attempted for intracranial lesions (104).

The development of angiography was essentially an extension of the search for means of better diagnosing intracranial lesions. Before 1927, plain cranial x-rays, pneumoencephalography, and myelography were the basic methods of imaging the central nervous system. Egas Moniz, inspired by Sicard's work on the use of iodized oil myelography (92), set out to develop a technique that would improve the diagnosis of intracranial tumors. On June 28, 1927, after several frustrating attempts on cadaver heads and dogs, Moniz (66) successfully demonstrated the displacement of the anterior and middle cerebral arteries in a 20-year-old man with a pituitary adenoma after a direct surgical exposure of the carotid artery. By 1931, Moniz (67) was able to perform a complete angiogram which included arterial and venous phases. Angiography's preeminence as a diagnostic tool came in 1936 with Loman and Myerson's (59) percutaneous carotid puncture technique. Interestingly, the *Lancet* foreshadowed the potential of angiographic techniques as early as 1931, when it commented that not only might it be able to diagnose aneurysms, but also that "its possibilities as an avenue for therapeutics should not be lost sight of in the future" (5).

As previously discussed, neuroendovascular therapy has an extensive history. Although there were many approaches at endosaccular occlusion of aneurysms as described in the previous section, true catheter-based endovascular approaches to vascular diseases of the central nervous system did not take place until 1960 (60).

Prior to Luessenhop, the direct intravascular approach to treatment of vascular pathology preceded Gardner's resourceful, yet inadvertent, "intravascular" approach to intracranial vascular pathology. Brooks (14) is credited with the first such attempt when he placed a piece of muscle intravascularly to obliterate a traumatic carotid fistula in 1930. Arutiunov and Burlutsky (6) expanded upon Brooks' procedure in the ensuing years and presented their important findings in 1964.

Catheter technology had developed sufficiently by 1960, such that Luessenhop and Spence (60) were able to intraoperatively cannulate the internal carotid artery. They were the first to successfully deposit silastic spheres into the internal carotid circulation to treat an arteriovenous malformation in the operating room. Two years later, Rothenberg et al. (87) introduced the concept of using balloons in the treatment of intracranial aneurysms when he developed the angiotactic balloon. A polyester sleeve wrapped around a neoprene balloon was attached to a 4-French delivery system. This sleeve could then be deployed in situ, with inflation of the balloon, as was demonstrated in their animal model, substantiating that the intravascular use of balloons might be helpful in the treatment of intracranial vascular disease—a concept that would become important in endovascular therapy.

Several years later, Luessenhop and Velasquez (61) demonstrated that balloons could be safely introduced into the internal carotid artery and actually demonstrated temporary exclusion of an aneurysm from the circulation during balloon inflation. In 1966, further advances in endovascular navigation were made by Frei et al. (36), who developed a magnetic silicone catheter. In 1967, Yodh et al. (109) developed a method by which a magnet could be endovascularly guided to an aneurysm using an external magnet. Subsequently, iron filings could then be injected intravascularly and would be attracted to the endosaccular magnet, thereby producing thrombosis, in a way paralleling Mullan's work both in concept and in time.

The art and technique of selective catheterization continued to grow when Driller et al. (33) and Hilal (49) published two articles based on their work at the Neurological Institute of New York, which described selective catheterization for the treatment of vascular lesions of the external carotid artery. In 1970, Kessler and Wholey (55) presented a series of two patients in whom they placed nondetachable balloons within the carotid artery to treat internal carotid aneurysms, resulting in persistent thrombosis. By 1974, Hilal et al. (51) were the first to describe the endovascular electrothrombosis of a basilar aneurysm.

During this period, a tremendous amount of research in the field of materials science enabled biomedical engineers to bond soft shapeable tubing of different compositions in such a way as to provide proximal catheter support with distal catheter flexibility and softness, resulting in a vast improvement in the navigation properties of the catheter. With the birth of the microcatheter, endovascular surgery's explosive growth paralleled that which was seen with the advent of the aneurysm clip.

Unlikely to have been greatly influenced by work in the Western Hemisphere, Serbinenko began searching for the endovascular treatment of intracranial vascular disease as a young neurosurgeon training at the N. N. Burdenko Institute in the mid-1950s. Kikut and Serbinenko (57) were the first to report several different "zones" of circulation within aneurysms and their parent vessels, providing our first systematic reports various "flow zones" within aneurysms. They surmised that, by reducing the flow of blood within a parent artery and increasing the coagulability of blood within the aneurysm, successful and stable thrombosis of an aneurysm might ensue. This was further emphasized by Khilko and Zubkov (56) in 1969 when they demonstrated that stable thrombus can be formed within an aneurysm by saturation with coagulants and reduction of flow to the aneurysm by temporary parent vessel constriction.

Serbinenko began to research and develop skills and techniques for the use of balloons in earnest. By 1974, Serbinenko (91) reported the use of selective catheterization to deliver and deploy detachable balloons filled with a hardening agent (liquid silicone) for the treatment of a variety of vascular lesions in 300 patients at the Burdenko Institute. He began in 1963 with balloon exploration of the intracranial circulation and first occluded the internal carotid artery with a balloon via an approach through the external carotid artery in 1964. Most important to this historical review, he reported the successful detachment of balloons within a basilar tip aneurysm and supraclinoid carotid aneurysm.

Encouraged by this, Debrun et al. (26) made minor modifications to Serbinenko's concept by introducing contrast into the balloon and an elastic band at its neck, which tightened to prevent leakage of contrast upon detachment. DiTullio et al. (28, 29) developed the one-way valve for balloons, whereby contrast injection opened the valve, and the internal hydrostatic balloon pressure, once inflated, would prevent outflow of contrast.

In 1982, Romodanov and Shcheglov (85) reported their results in the treatment of 119 patients with detachable, silicone-filled latex balloons. They reported 108 occlusions with 93 parent vessel preservation and four deaths. Higashida et al. (47, 48) and Moret et al. (68) used hydroxyethyl methacrylate as the filling solution for the balloon, further refining this technique. Although initially promising, significant complications were reported with this technique, which included intraoperative and delayed rupture, as well as recanalization (47).

The use of coils for endovascular vessel occlusion began in earnest almost a century after its initial use for aortic aneurysms, with the introduction of the Gianturco coil (41, 62). In 1985, Braun et al. (13) reported the first intracranial aneurysm treated with coil embolization. Interestingly, the use of coils in this setting was the result of an unsuccessful balloon occlusion for a giant internal carotid artery aneurysm. The introduction of platinum coils with Dacron (E.I. duPont de Nemours and Co., Wilmington, DE) fiber to induce thrombosis for the treatment of vascular malformations and aneurysms was reported by Hilal et al. (50) in 1988. Although some successes were reported, the inability to precisely control these pushable coils resulted in a significant incidence of parent vessel occlusion and distal embolization. A controllable delivery system with the ability to retrieve, reposition, and redeploy the coil to a satisfactory configuration prior to detachment was necessary to increase the safety of the procedure.

Intrigued by Mullan's work on electrothrombosis and Serbinenko's endovascular techniques, Guido Guglielmi began developing techniques that would combine these concepts. Guglielmi first constructed a microwire with a small magnet that would be introduced endovascularly within an aneurysm. He then developed a technique whereby a suspension of iron microspheres would be injected into the circulation and be attracted to the small magnet within the aneurysm, thus inducing thrombosis. The magnet would then be electrolytically detached from the microwire and left in situ (77).

Approximately 1 year later, Guglielmi began working with Ivan Sepetka of Target Therapeutics and developed the first generation electrolytically detachable coil (42). In 1990, the first coil was introduced in a patient for a traumatic carotid cavernous fistula who failed balloon occlusion (95). One month later, the first aneurysm was treated with this electrolytically detachable coil (43). Interestingly, the initial reports suggested that aneurysmal thrombosis was a consequence of the thrombogenic properties of the coils in conjunction with electrothrombosis during detachment. This was later found not to be the case.

Since that time, the tremendous explosion in endovascular technology and techniques has challenged the role of microsurgery in the treatment of aneurysms. Early endovascular studies revealed that, although small aneurysms with small necks and a 2 to 1 dome-to-neck ratio had excellent long-term results, outcomes for large aneurysms or those with broad necks (>4 mm) had a significant recanalization rate (101). To

address this, Moret et al. (69) introduced the balloon remodeling technique. By placing a balloon across the neck of the aneurysm during coil deployment from a second microcatheter, better packing was achieved with less risk of coil protrusion into the parent artery.

Because of the limitations of coil embolization for aneurysm treatment, additional advances have been made in an attempt to reduce the recurrence rate of endovascular aneurysm therapy. Numerous studies have been published, evaluating the role of endovascular aneurysm therapy (65).

Similar to the explosion in the various kinds of aneurysm clips in the 1960s and 1970s, this past decade has seen the development of several different generations of the original coil along with variations in basic coil morphology (80). The addition of bioactive coatings on or within the coil has resulted in a new direction of aneurysm treatment (74). Such technology may increase the healing at the aneurysm neck, thereby reducing aneurysm recurrence.

Endovascular Hunterian ligation, aneurysm trapping or parent vessel occlusion have all been reevaluated since being introduced in the early 20th century (4, 8, 70). Similar to its surgical predecessors, endovascular Hunterian ligation has a limited role in the current armamentarium of aneurysm therapy.

As with open surgical techniques, these concepts of "indirect" aneurysm therapy have been reintroduced with greater sophistication. Whereas at first the indirect approaches to aneurysm therapy involved flow reversal and trapping of aneurysms, now the indirect approach involves the use of stents for diversion of flow away from the aneurysm inflow zones (70). First used as adjuncts for broad necked aneurysms, stents are now being evaluated for their ability to alter flow along the aneurysm neck and, thus, influence recanalization (102).

CONCLUSION

The technologies of the future are, in many ways, built upon the successes and failures of the techniques and technologies that preceded them. Indeed, one cannot study the past without thinking about the future. The treatment of aneurysms has a long and rich history filled with innovative and bold ideas, albeit with variable successes. The concepts of how to best treat aneurysms have evolved over many generations. Treatments for these lesions began with the safest and potentially least successful operations of that time. As technology improved, surgeons were emboldened to pursue more direct means of treating aneurysms, with excellent results. The endovascular treatment of aneurysms owes much to its surgical roots. Indeed, biographical studies of most of the pioneers in endovascular surgery have some form of neurosurgical background. Of course, the field of radiology has been instrumental in its growth as well. Although many parallels exist in its history, the unique advantage of approaching these lesions from within has resulted in a reassessment of the "old" concept of the indirect attack on the aneurysm.

Recalling the pessimism that revolved around the treatment of aneurysms less than 100 years ago (18, 103), the current state of aneurysm treatment serves as a testament to the perseverance and ingenuity of the pioneers in microsurgical and endovascular techniques. Although Walton's 1956 comment that "this advance [in surgery] may require considerable recasting of the commonly accepted views on management" (103) reflected recent advances in aneurysm clip technology, this very same statement is just as applicable in today's world. Both the endovascular and surgical armamentarium reduce the number of aneurysms that are deemed "inoperable." It is this cyclic, parallel growth of surgical and endovascular techniques for aneurysm therapy that continues to educate the field of neurosurgery, demonstrating how the seemingly unachievable milestones need only be examined from a different perspective to achieve results. New technology will, at times, beget a better understanding of the pathophysiology, which, in turn, will further bolster new techniques and perhaps entirely new fields of study. The treatment of intracranial aneurysms has achieved and will continue to achieve just that.

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HISTORICAL PERSPECTIVES: THE MICROSURGICAL AND ENDOVASCULAR TREATMENT OF ANEURYSMS

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THE HISTORY OF aneurysm therapy is rich in parallelisms that exist between the once-fledgling field of aneurysm surgery and the now-growing field of endovascular aneurysm treatment. The treatment of aneurysms has had a cyclic progression. The indirect and safest approach to the treatment of aneurysms was seen in the development and use of Hunterian ligation in the 19th century. During the past few decades, nascent technology and a better understanding of the pathophysiology of aneurysms resulted in a more direct intracranial, extravascular approach to aneurysm therapy, with the focal point being the use of the aneurysm clip to secure an aneurysm at its neck. Interestingly, alternative and, arguably, even more direct approaches to aneurysm therapy developed in the surgical suites. These techniques became the seeds for the birth of direct endovascular aneurysm treatment in particular and endovascular surgery in general. As endovascular technology continues to develop, somewhat more sophisticated, indirect approaches to aneurysm therapy (the use of stents to modify flow, for example) are being investigated. The treatment of intracranial aneurysms has a rich history. First thought to be inoperable lesions, aneurysms have challenged neurosurgeons and their colleagues since they were first recognized in the 18th century. Treatment for these lesions did not begin until the 19th century with the use of Hunterian ligation. This review describes the many milestones in the field of aneurysm surgery and endovascular surgery, tracing the many parallelisms contained within the birth and growth of each field and their respective significance.

KEY WORDS: Aneurysm, Endovascular, History, Surgery

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The history of intracranial aneurysms is an extremely rich story of parallels that continues through the present day. Despite the tremendous advances in understanding some aspects of the pathophysiology and in the technology required to safely treat these lesions, the overall morbidity and mortality of this disease remains unacceptably high. The many parallels that exist in aneurysm treatment reflect the neurosurgical community's struggle in trying to understand why aneurysms develop and why they rupture. It is also a struggle to determine how to best treat these lesions with the technology of the times and a vision towards the technology of the future. At times, when the technology did not exist, alternatives were chosen that seemed to be somewhat effective. However, as technology developed, the philosophy changed. Or rather, as technology "caught up" to the ideas, the overall philosophy of aneurysm treatment changed.

This has resulted in an almost cyclic evolution in aneurysm treatment with parallels being seen between the microsurgical and endovascular treatment of lesions. It began with an indirect attack on the parent vessel (Hunterian ligation) and matured to the more direct surgical approaches of trapping, wrapping, and subsequently direct clipping of the aneurysm (*Fig. 1*).

The dawn of endovascular treatment, in essence, grew at the height of direct microsurgical approaches to aneurysms, although historical roots existed well before that (*Fig. 2*). The concept of a "direct attack" on the aneurysm in the operating room was then translated to a direct "transfundal" or "transaneurysmal" approach and matured from endosaccular balloon occlusion to current coil technologies. Further developments in endovascular therapy now look back to the original concepts of aneurysm surgery. Once again, interventional neuroradiologists and surgeons introduced the concept of flow reversal (Hunterian ligation) and trapping as a means of treating otherwise untreatable aneurysms. Interestingly, whereas the indirect approach to aneurysm treatment was all that could be accomplished with the technology of the early 20th century, the concept of flow diversion with stents without endosaccular filling reflects a more sophisticated and elegant approach to the concept of an "indirect" attack on aneurysms at the beginning of the 21st century.

The history of intracranial aneurysm treatment does not limit itself to the technical advances within the operating room or endovascular suite. It is quite expansive. Much has been, and can be, written on the historical aspects of the pre- and postoperative management of aneurysm patients. Although interesting in their own right, these aspects of aneurysms will not be discussed. Instead, the focus will remain on the direct technological advances in the instrumentation used to treat aneurysms and the rationale behind their development and use. In order to better understand the rationale behind the development of endovascular techniques, a sound basis on the historical roots of aneurysm surgery is necessary. This review is by no means meant to be an exhaustive historical account of the origins of the microsurgical clipping of aneurysms, which, in and of itself, is abundant and rich in its complexity. Thus, references to very important individuals who brought aneurysm surgery to its present status must be admittedly brief in order to bring focus to the endovascular history.

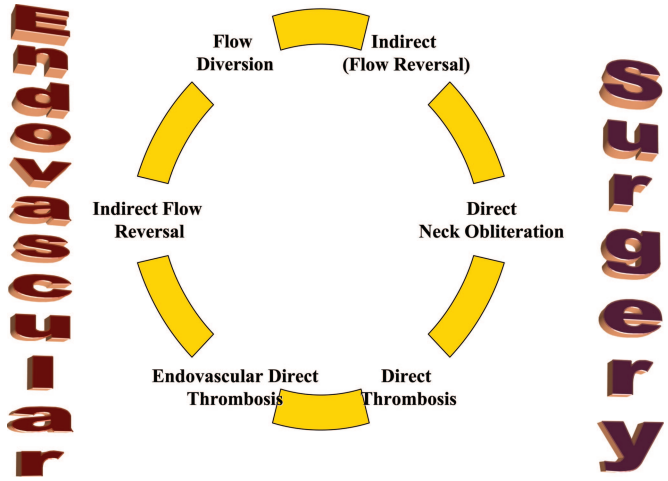

FIGURE 1. *Diagram representing of the cyclic phases of the surgical and endovascular treatment of aneurysms.*

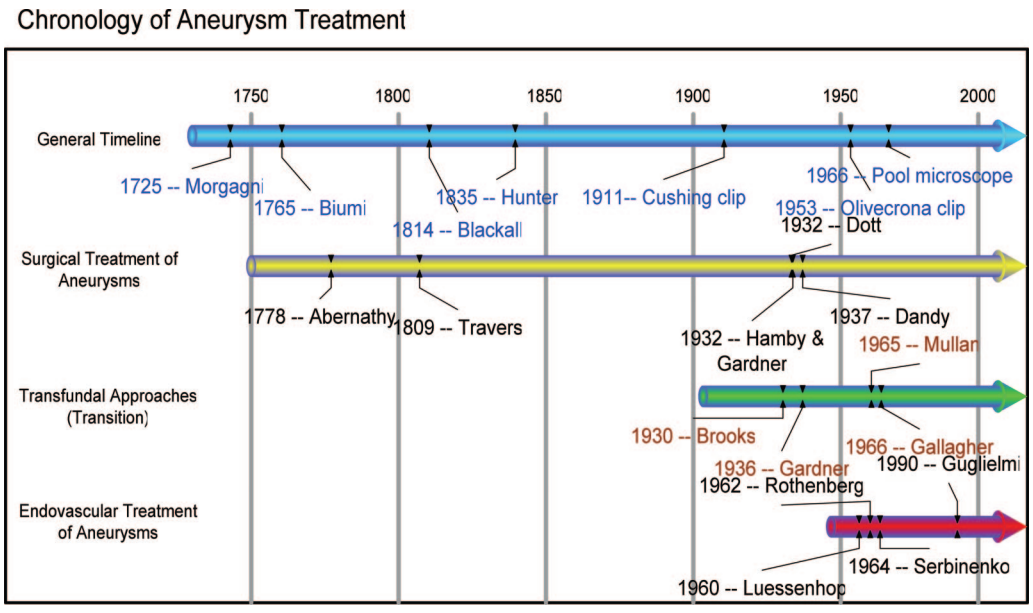

FIGURE 2. *Chronology of important events in the recognition and treatment of aneurysms. Refer to text for details.*

THE EARLY HISTORY OF ANEURYSM SURGERY

Intracranial aneurysms were first thought to be a cause of subarachnoid hemorrhage (SAH) in the 17th century (11, 106). Morgagni (71) likewise emphasized the concept that intracranial aneurysms could be the cause of hemorrhage. He was also the first to report the presence of incidental "dilatations" of both posterior cerebral arteries in 1725, possibly making this the first description of an intracranial aneurysm. The first documented account of an unruptured intracranial aneurysm did not occur until 1765 by Francesco Biumi (9) in Milan. In 1814, the first verified account of an aneurysmal rupture was reported by Blackall (10).

Despite recognizing these lesions during the mid-18th century, there is no mention of any treatment being offered. Indeed, the reports at this time were based on postmortem findings. Treatment of vascular lesions of the head and neck did not begin until the late 19th century, several years after Hunter's description of proximal femoral artery ligation for popliteal aneurysms as an alternative to leg amputation (45, 52).

Building upon the success of Hunterian ligation in the peripheral circulation, the concept of carotid artery ligation for intracranial vascular pathology began to take form. Although Jean Luis Petit was the first to report that the brain may survive when deprived of contribution of one artery, Hebenstreit was the first to ligate the carotid artery for injury in 1793 (19). There is substantial literature to describe John Abernathy (1) as being the first individual to deliberately ligate the carotid artery for injury in 1778 or 1779 (reported in 1798) (39). The first successful carotid sacrifice for an indication other than hemorrhage was by Cooper (15) in 1808 for an aneurysm of the left cervical internal carotid artery (Cooper's first carotid ligation in 1805 was unsuccessful). Cooper, interestingly, surmised at the time that the partial resolution in pulsations was attributed to retrograde filling from distal collateral circulation. Benjamin Travers (99) first reported successful treatment of an intracranial lesion (carotid cavernous fistula) in 1809.

The years that followed were filled with clinical reports of carotid ligation for numerous nontraumatic indications. A full century after Hunterian ligation was first

described, carotid occlusion for an intracranial aneurysm was performed. During surgery for resection of a middle fossa tumor in a 48-year-old woman, Victor Horsley identified a pulsating tumor, most likely an aneurysm. Horsley subsequently ligated her right common carotid artery. She was reported to be doing well 5 years later (54).

The following years were then devoted to developing more sophisticated methods of carotid occlusion. Progress in ligature began with simple occlusion methods involving various suture materials. Because of a high infection rate at that time, most methods involved applying a circumferential ligature with the sutures coming out of the wound. After approximately 2 to 3 weeks, the sutures would "come away" and the vessel would be presumed thrombosed. More sophisticated techniques were then developed to allow for thrombosis of the parent vessel while minimizing clot propagation into the intracranial circulation. Methods, such as Poppen's sequential placation of the carotid artery over a 3 to 4 cm length, were reported as successful and safe methods of carotid occlusion (83, 84). Halstead (44) and Matas (63) evaluated the use of aluminum strips that allowed for progressive tightening of the band or complete removal if the patient did not tolerate the procedure. Nassette (22) and Perthes (78) began the use of a fascial band to minimize the intimal damage from the suture. Proponents of this technique, such as Dandy (24), argued that this could be performed as a staged procedure, thus allowing for collateral circulation to develop and consequently would be better tolerated. However, its success was variable, as complete occlusion was not often noted.

A rather ingenious device invented and later perfected by Neff (75) allowed for gradual arterial occlusion with the need for a single stage operation that allowed for the development of collateral circulation while occluding and dividing the vessel. The Neff clamp consisted of two metal bands secured at both ends by rubber bands. Absorbable catgut was wrapped around the one end of the bands to prevent the blades from completely crushing the vessel. As the catgut was absorbed, the rubber bands would slowly squeeze the metal bands together, thus gradually, but progressively, occluding the artery. By 1904, independent reports of the success of this clamp were published (17).

Further advances in carotid occlusion were in the simplification and mechanization of the technique. The introduction of the Dott, Crutchfield, Selverstone and Kindt clamps (among others) allowed the surgeons to place the clamp around the artery and to gradually tighten the clamps over a period of days (16, 31, 40, 89, 90). In reviewing the literature between 1933 and 1960, Tonnis and Walter (98) found a 3 to 41% mortality and significant morbidity from carotid ligation. The high death rate in some of the reported literature, however, was due to the high rate of infection and thrombosis. Later reports demonstrated mortality rates generally below 20% (25, 84, 88). Unfortunately, successful obliteration of the aneurysm was low, with success usually occurring for aneurysms of the internal carotid artery (ICA) itself. Winn's (105) report evaluating the rehemorrhage rate in 34 patients with posterior communicating artery aneurysms essentially found no difference between those treated with carotid occlusion and the conservatively managed nonoperative group.

Because of the difficulties noted and because of significant concerns regarding delayed thrombotic/embolic events from cervical carotid occlusion, the methods of cervical carotid occlusion were superseded by intracranial methods. The first successful intracranial carotid occlusion was described by Hamby and Gardner (46) in 1932. Zeller (110) was the first to attempt this procedure in 1911, but his patient died from hemorrhage after an assistant accidentally avulsed the ligated artery by pulling the ligature. In 1935, Dandy (20) introduced the use of the Cushing silver clip (developed in 1911) to achieve proximal supraclinoid ICA occlusion for the treatment of intracranial aneurysms.

DIRECT APPROACHES TO ANEURYSM TREATMENT

By the early 1900s, it was clear that, although a significant amount of knowledge had been gained on the pathology of aneurysms and some technical advances toward the treatment of these lesions had taken place, the overall outcomes were still dismal. Indeed, Harvey Cushing (18) thought that the aneurysm was "a lesion having such remote surgical bearings, . . .whether there are surgical indications. . .further experience alone can tell." Ayer (7) later echoed these sentiments by stating that subarachnoid hemorrhage "has little interest from a standpoint of active surgical procedure."

Because of the many difficulties encountered with the indirect approaches of cervical carotid ligation, intracranial carotid ligation, and trapping, more direct approaches were sought. Although there were real concerns with a direct attack on the neck of an aneurysm, there were significant benefits. The technology in the 1930s made securing an aneurysm at the neck rather dangerous, as ligatures and silver clips were the only devices developed at the time. Thus, risks of exsanguination secondary to avulsion of the aneurysm at the neck were quite real. However, preservation of the parent vessel and a higher chance of cure for aneurysms beyond the carotid terminus was sufficient reason to embolden surgeons in their quest for new techniques.

Norman McComish Dott (30), a pupil of Cushing's and one of several men to help found neurosurgery in Great Britain, was the first surgeon to be credited with the first direct attack on an intracranial aneurysm. On April 22, 1932, in treating a middle-aged man who had sustained three subarachnoid hemorrhages secondary to an aneurysm of the ICA terminus at the origin of the proximal middle cerebral artery, Dott encountered "formidable" bleeding during the exposure. He harvested muscle from the patient's thigh and placed it on the exposed aneurysm dome. He reported that hemorrhage stopped after approximately 12 minutes. He applied further muscle pledgets in the region and surrounding the parent artery. The patient was reported to have made an excellent

recovery with no further hemorrhagic events. Additional reports by Tonnis (97), Dandy (25), and Jefferson (53) added to the early literature of wrapping.

The next advance in aneurysm treatment was aneurysm trapping, which was initially described by Walter Dandy (22) in 1936. He performed cervical internal carotid ligation and clipping of the supraclinoid carotid artery for a cavernous aneurysm. Logue (58) clipped the A1 segment to trap an anterior communicating artery aneurysm in 1956 and Tindall et al. (96) added contralateral common carotid artery narrowing to assist in thrombosis.

THE ANEURYSM CLIP

On March 23, 1937, a new era in cerebrovascular surgery began. Walter Dandy (21) reported exposing an aneurysm of the posterior communicating artery via his hypophyseal approach in a 43-year-old man presenting with a third nerve palsy. Having identified the neck of the aneurysm, he placed a silver clip across its neck and cauterized its dome. By 1944, he had amassed sufficient cases that he published his observations and results in the first monograph of aneurysm surgery, *Intracranial Arterial Aneurysms* (25).

This first clip used by Dandy was a malleable Cushing or Mackenzie type silver clip (22). Simple, yet important, modifications to the concept followed with the development of a U-shaped clip to allow the tips of the clip to approximate first and essentially trap the vessel within the clip, thus obliterating the vessel (34).

Further modifications to the clip came quickly. The next important step in the development of the aneurysm clip was the development of an adjustable clip that could be reopened and repositioned. The Olivecrona clip was essentially a recurved metal strip with proximal "wings" projecting above the fulcrum of the clip to allow the clip to be reopened if the wings were compressed (76). This began a flurry of modifications to a basic concept that provided safer and more controlled application of the aneurysm clip, with Housepian's clip being the embodiment of clip technology at that time (35).

Schwartz developed the cross-action alpha clip originally intended for use in temporary occlusion in the 1950s (64). Although excellent in concept, the Schwartz clip was difficult to use in the setting of intracranial aneurysm surgery. Mayfield and Kees (64) then modified these concepts on a smaller scale and changed the applier to improve the ergonomics of clip placement. The Mayfield-Kees clip became the most popular clip of the 1950s and 1960s. Subtle, but important, improvements in several aspects of clip technology took place, with the most important being the development of better biocompatible metals, wider blade openings, different configurations, and the bayoneted clip to allow better visualization of the clip as it was being placed on the aneurysm (93). Although George Smith initially developed a clip that allowed the surgeon to treat aneurysms on the opposite side of the vessel wall (35), it was not until Drake's modification of the Mayfield-Kees clip that the fenestrated clip was developed (27). In treating many posterior circulation aneurysms, Drake noted the need to develop a clip that would allow him access to the neck of an aneurysm without compromising vessels that were in the way. By developing the fenestration, the aneurysm clip could be safely placed along the neck of an aneurysm without displacing and potentially compromising other vessels in the field. Sundt's encircling clip-graft was another significant innovation in aneurysm clip technology that allowed for repair of vessel tears or small irregularities that are untreatable by ordinary clipping methods (94).

Currently, modifications to the aneurysm clip are based on metallurgy and different design configurations. Concurrent with the development of the aneurysm clip came many other developments in techniques and parallel technologies that helped improve the surgical treatment of patients with cerebral aneurysms (12). The introduction of the surgical microscope revolutionized the approach to treating aneurysms (81, 82). The elegant microsurgical techniques of Yaşargil and Fox (107) and Yaşargil (108) helped to redefine the surgical approaches to aneurysms, emphasizing the importance of understanding cisternal anatomy and microvascular anatomy in maximizing patient results. During this period, others, such as Drake (32), set the standards for surgery of posterior circulation aneurysms, along with the development and use of the first fenestrated aneurysm clip.

ENDOSACCULAR ALTERNATIVES TO CLIPPING

As aneurysm clip technology continued to develop, surgeons continued to reflect on alternative techniques for the management of aneurysms. The concept that aneurysms could be treated endoluminally was serendipitous. In 1936, Gardner (38) opened a giant ICA aneurysm, thinking it to be a large tumor. He subsequently packed it with five cotton sponges. The patient did well until 2 years later when the sponges were removed because of infection.

Several years later, Walter Dandy (22, 23) attempted an endosaccular cure for an unclippable aneurysm by inserting eight silk sutures into the sac of a giant cavernous sinus aneurysm. Reoperation 5 days later demonstrated continued filling of the aneurysm and the patient subsequently underwent surgical trapping.

In 1941, Werner et al. (104) described a 15-year-old girl with a giant ICA aneurysm eroding through the orbital roof. Several attempts at Hunterian ligation were ineffective. Consequently Werner, working in conjunction with Blakemore and King, who had studied this technique for aortic aneurysms, approached the aneurysm transorbitally by gently retracting the globe medially and identifying the sac of the aneurysm. He then passed 30 feet of 34 gauge silver enameled wire into the aneurysm fundus and heated it for 40 seconds to 80 degrees centigrade. The patient survived the procedure, reportedly with no further recurrence.

Mullan became quite interested in the endosaccular approach to aneurysm treatment and subsequently published several studies evaluating the use of 33-gauge berryliumcopper wire and copper wire as a means to promote thrombosis without need for electric current (73). In a series of 15 patients, Mullan et al. (72) documented 12 patients with good results. Mullan also explored the use of direct current in the thrombosis of aneurysm in 1965 and stereotactically placed wire electrodes into exposed aneurysms and subjected them to an electric current. Although partially successful, the complications from the procedure were higher than those from clipping.

Gallagher (37) developed a technique of injecting horse or hog hair into the dome of an aneurysm as a means of inducing thrombosis (pilojection). In his series of 15 cases, Gallagher noted only partial thrombosis in most patients.

In 1966, Alksne et al. (2) and Rosomoff (86) independently developed methods by which iron suspensions could be injected via the internal carotid artery and collected in the aneurysm dome by placing a stereotactically guided magnet near the aneurysm. Although a fair degree of thrombosis was noted, the embolic risk by this technique was too great. Therefore, Alksne et al. (3) modified the technique by inserting the iron suspension by a stereotactic transfundal approach, using the magnet to keep the suspension within the dome of the aneurysm while thrombosis took place.

Except for a few select procedures, the aforementioned techniques all involved transcranial approaches to the aneurysm. The technology for safe navigation intravascularly was not far behind. By 1962, Rothenberg et al. (87) developed an intravascular catheter that could release an expandable sleeve and occlude an aneurysm in an experimental animal model. Two years later, modern endovascular therapy for aneurysms was born.

ENDOVASCULAR TREATMENT OF ANEURYSMS

The concept of endovascular aneurysm treatment has grown from attempts to treat aneurysms endovascularly since the 19th century. Careful observations and subsequent experiments in animals by Velpeau (100) suggested that metallic objects, such as needles, could result in local thrombosis sufficient to occlude an artery. Independently, Phillips (79) demonstrated that the use of a needle with an electric current applied also resulted in thrombosis within a vessel. These concepts were first studied in humans for the treatment of aortic aneurysms. It wasn't until approximately a century later that the technique was attempted for intracranial lesions (104).

The development of angiography was essentially an extension of the search for means of better diagnosing intracranial lesions. Before 1927, plain cranial x-rays, pneumoencephalography, and myelography were the basic methods of imaging the central nervous system. Egas Moniz, inspired by Sicard's work on the use of iodized oil myelography (92), set out to develop a technique that would improve the diagnosis of intracranial tumors. On June 28, 1927, after several frustrating attempts on cadaver heads and dogs, Moniz (66) successfully demonstrated the displacement of the anterior and middle cerebral arteries in a 20-year-old man with a pituitary adenoma after a direct surgical exposure of the carotid artery. By 1931, Moniz (67) was able to perform a complete angiogram which included arterial and venous phases. Angiography's preeminence as a diagnostic tool came in 1936 with Loman and Myerson's (59) percutaneous carotid puncture technique. Interestingly, the *Lancet* foreshadowed the potential of angiographic techniques as early as 1931, when it commented that not only might it be able to diagnose aneurysms, but also that "its possibilities as an avenue for therapeutics should not be lost sight of in the future" (5).

As previously discussed, neuroendovascular therapy has an extensive history. Although there were many approaches at endosaccular occlusion of aneurysms as described in the previous section, true catheter-based endovascular approaches to vascular diseases of the central nervous system did not take place until 1960 (60).

Prior to Luessenhop, the direct intravascular approach to treatment of vascular pathology preceded Gardner's resourceful, yet inadvertent, "intravascular" approach to intracranial vascular pathology. Brooks (14) is credited with the first such attempt when he placed a piece of muscle intravascularly to obliterate a traumatic carotid fistula in 1930. Arutiunov and Burlutsky (6) expanded upon Brooks' procedure in the ensuing years and presented their important findings in 1964.

Catheter technology had developed sufficiently by 1960, such that Luessenhop and Spence (60) were able to intraoperatively cannulate the internal carotid artery. They were the first to successfully deposit silastic spheres into the internal carotid circulation to treat an arteriovenous malformation in the operating room. Two years later, Rothenberg et al. (87) introduced the concept of using balloons in the treatment of intracranial aneurysms when he developed the angiotactic balloon. A polyester sleeve wrapped around a neoprene balloon was attached to a 4-French delivery system. This sleeve could then be deployed in situ, with inflation of the balloon, as was demonstrated in their animal model, substantiating that the intravascular use of balloons might be helpful in the treatment of intracranial vascular disease—a concept that would become important in endovascular therapy.

Several years later, Luessenhop and Velasquez (61) demonstrated that balloons could be safely introduced into the internal carotid artery and actually demonstrated temporary exclusion of an aneurysm from the circulation during balloon inflation. In 1966, further advances in endovascular navigation were made by Frei et al. (36), who developed a magnetic silicone catheter. In 1967, Yodh et al. (109) developed a method by which a magnet could be endovascularly guided to an aneurysm using an external magnet. Subsequently, iron filings could then be injected intravascularly and would be attracted to the endosaccular magnet, thereby producing thrombosis, in a way paralleling Mullan's work both in concept and in time.

The art and technique of selective catheterization continued to grow when Driller et al. (33) and Hilal (49) published two articles based on their work at the Neurological Institute of New York, which described selective catheterization for the treatment of vascular lesions of the external carotid artery. In 1970, Kessler and Wholey (55) presented a series of two patients in whom they placed nondetachable balloons within the carotid artery to treat internal carotid aneurysms, resulting in persistent thrombosis. By 1974, Hilal et al. (51) were the first to describe the endovascular electrothrombosis of a basilar aneurysm.

During this period, a tremendous amount of research in the field of materials science enabled biomedical engineers to bond soft shapeable tubing of different compositions in such a way as to provide proximal catheter support with distal catheter flexibility and softness, resulting in a vast improvement in the navigation properties of the catheter. With the birth of the microcatheter, endovascular surgery's explosive growth paralleled that which was seen with the advent of the aneurysm clip.

Unlikely to have been greatly influenced by work in the Western Hemisphere, Serbinenko began searching for the endovascular treatment of intracranial vascular disease as a young neurosurgeon training at the N. N. Burdenko Institute in the mid-1950s. Kikut and Serbinenko (57) were the first to report several different "zones" of circulation within aneurysms and their parent vessels, providing our first systematic reports various "flow zones" within aneurysms. They surmised that, by reducing the flow of blood within a parent artery and increasing the coagulability of blood within the aneurysm, successful and stable thrombosis of an aneurysm might ensue. This was further emphasized by Khilko and Zubkov (56) in 1969 when they demonstrated that stable thrombus can be formed within an aneurysm by saturation with coagulants and reduction of flow to the aneurysm by temporary parent vessel constriction.

Serbinenko began to research and develop skills and techniques for the use of balloons in earnest. By 1974, Serbinenko (91) reported the use of selective catheterization to deliver and deploy detachable balloons filled with a hardening agent (liquid silicone) for the treatment of a variety of vascular lesions in 300 patients at the Burdenko Institute. He began in 1963 with balloon exploration of the intracranial circulation and first occluded the internal carotid artery with a balloon via an approach through the external carotid artery in 1964. Most important to this historical review, he reported the successful detachment of balloons within a basilar tip aneurysm and supraclinoid carotid aneurysm.

Encouraged by this, Debrun et al. (26) made minor modifications to Serbinenko's concept by introducing contrast into the balloon and an elastic band at its neck, which tightened to prevent leakage of contrast upon detachment. DiTullio et al. (28, 29) developed the one-way valve for balloons, whereby contrast injection opened the valve, and the internal hydrostatic balloon pressure, once inflated, would prevent outflow of contrast.

In 1982, Romodanov and Shcheglov (85) reported their results in the treatment of 119 patients with detachable, silicone-filled latex balloons. They reported 108 occlusions with 93 parent vessel preservation and four deaths. Higashida et al. (47, 48) and Moret et al. (68) used hydroxyethyl methacrylate as the filling solution for the balloon, further refining this technique. Although initially promising, significant complications were reported with this technique, which included intraoperative and delayed rupture, as well as recanalization (47).

The use of coils for endovascular vessel occlusion began in earnest almost a century after its initial use for aortic aneurysms, with the introduction of the Gianturco coil (41, 62). In 1985, Braun et al. (13) reported the first intracranial aneurysm treated with coil embolization. Interestingly, the use of coils in this setting was the result of an unsuccessful balloon occlusion for a giant internal carotid artery aneurysm. The introduction of platinum coils with Dacron (E.I. duPont de Nemours and Co., Wilmington, DE) fiber to induce thrombosis for the treatment of vascular malformations and aneurysms was reported by Hilal et al. (50) in 1988. Although some successes were reported, the inability to precisely control these pushable coils resulted in a significant incidence of parent vessel occlusion and distal embolization. A controllable delivery system with the ability to retrieve, reposition, and redeploy the coil to a satisfactory configuration prior to detachment was necessary to increase the safety of the procedure.

Intrigued by Mullan's work on electrothrombosis and Serbinenko's endovascular techniques, Guido Guglielmi began developing techniques that would combine these concepts. Guglielmi first constructed a microwire with a small magnet that would be introduced endovascularly within an aneurysm. He then developed a technique whereby a suspension of iron microspheres would be injected into the circulation and be attracted to the small magnet within the aneurysm, thus inducing thrombosis. The magnet would then be electrolytically detached from the microwire and left in situ (77).

Approximately 1 year later, Guglielmi began working with Ivan Sepetka of Target Therapeutics and developed the first generation electrolytically detachable coil (42). In 1990, the first coil was introduced in a patient for a traumatic carotid cavernous fistula who failed balloon occlusion (95). One month later, the first aneurysm was treated with this electrolytically detachable coil (43). Interestingly, the initial reports suggested that aneurysmal thrombosis was a consequence of the thrombogenic properties of the coils in conjunction with electrothrombosis during detachment. This was later found not to be the case.

Since that time, the tremendous explosion in endovascular technology and techniques has challenged the role of microsurgery in the treatment of aneurysms. Early endovascular studies revealed that, although small aneurysms with small necks and a 2 to 1 dome-to-neck ratio had excellent long-term results, outcomes for large aneurysms or those with broad necks (>4 mm) had a significant recanalization rate (101). To

address this, Moret et al. (69) introduced the balloon remodeling technique. By placing a balloon across the neck of the aneurysm during coil deployment from a second microcatheter, better packing was achieved with less risk of coil protrusion into the parent artery.

Because of the limitations of coil embolization for aneurysm treatment, additional advances have been made in an attempt to reduce the recurrence rate of endovascular aneurysm therapy. Numerous studies have been published, evaluating the role of endovascular aneurysm therapy (65).

Similar to the explosion in the various kinds of aneurysm clips in the 1960s and 1970s, this past decade has seen the development of several different generations of the original coil along with variations in basic coil morphology (80). The addition of bioactive coatings on or within the coil has resulted in a new direction of aneurysm treatment (74). Such technology may increase the healing at the aneurysm neck, thereby reducing aneurysm recurrence.

Endovascular Hunterian ligation, aneurysm trapping or parent vessel occlusion have all been reevaluated since being introduced in the early 20th century (4, 8, 70). Similar to its surgical predecessors, endovascular Hunterian ligation has a limited role in the current armamentarium of aneurysm therapy.

As with open surgical techniques, these concepts of "indirect" aneurysm therapy have been reintroduced with greater sophistication. Whereas at first the indirect approaches to aneurysm therapy involved flow reversal and trapping of aneurysms, now the indirect approach involves the use of stents for diversion of flow away from the aneurysm inflow zones (70). First used as adjuncts for broad necked aneurysms, stents are now being evaluated for their ability to alter flow along the aneurysm neck and, thus, influence recanalization (102).

CONCLUSION

The technologies of the future are, in many ways, built upon the successes and failures of the techniques and technologies that preceded them. Indeed, one cannot study the past without thinking about the future. The treatment of aneurysms has a long and rich history filled with innovative and bold ideas, albeit with variable successes. The concepts of how to best treat aneurysms have evolved over many generations. Treatments for these lesions began with the safest and potentially least successful operations of that time. As technology improved, surgeons were emboldened to pursue more direct means of treating aneurysms, with excellent results. The endovascular treatment of aneurysms owes much to its surgical roots. Indeed, biographical studies of most of the pioneers in endovascular surgery have some form of neurosurgical background. Of course, the field of radiology has been instrumental in its growth as well. Although many parallels exist in its history, the unique advantage of approaching these lesions from within has resulted in a reassessment of the "old" concept of the indirect attack on the aneurysm.

Recalling the pessimism that revolved around the treatment of aneurysms less than 100 years ago (18, 103), the current state of aneurysm treatment serves as a testament to the perseverance and ingenuity of the pioneers in microsurgical and endovascular techniques. Although Walton's 1956 comment that "this advance [in surgery] may require considerable recasting of the commonly accepted views on management" (103) reflected recent advances in aneurysm clip technology, this very same statement is just as applicable in today's world. Both the endovascular and surgical armamentarium reduce the number of aneurysms that are deemed "inoperable." It is this cyclic, parallel growth of surgical and endovascular techniques for aneurysm therapy that continues to educate the field of neurosurgery, demonstrating how the seemingly unachievable milestones need only be examined from a different perspective to achieve results. New technology will, at times, beget a better understanding of the pathophysiology, which, in turn, will further bolster new techniques and perhaps entirely new fields of study. The treatment of intracranial aneurysms has achieved and will continue to achieve just that.

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SURGICAL ENDOVASCULAR NEURORADIOLOGY IN THE 21ST CENTURY: WHAT LIES AHEAD?

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FEW COULD HAVE imagined the tremendous growth of endovascular surgery over the past 40 years. Endovascular therapy has greatly enhanced the care of the patient in neurosurgery, spine surgery, and head and neck surgery. Progress in technology and techniques continue to push forward the boundaries of what is deemed "treatable," assuming acceptable risk. This article will briefly review the current state of endovascular surgery and speculate about what its role will be in the near and far future. Endovascular therapy provides a minimally invasive approach to the central nervous system and other systems via natural and, at times, highly selective pathways. Maximizing the accessibility of these routes to highly specific regions of the central nervous system provides an elegant and minimalist approach to treating diseases of the central nervous system with almost no "footprints" of ever having accessed the region. In the future, safe, efficient and intelligent delivery systems that may enhance or alter the tissue's response may result in successful treatment of cerebrovascular diseases, as well as other diseases of the craniospinal axis. The growth of nanotechnology, metallurgy, synthetic polymers, imaging, and training will all combine to help grow the technology and the science that is surgical endovascular neuroradiology.

KEY WORDS: Endovascular, Innovations, Technology

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"... [angiography's] possibilities as an avenue for therapeutics should not be lost sight of in the future." *Lancet, 1931* [5]

Although early in the discipline's growth, endovascular neurosurgery has had a rich and colorful history brought about, in part, by numerous important advances in technique and technology. Taken together, these advances represent a revolutionary leap in the treatment of cerebrovascular disease, just as the introduction of the operating microscope revolutionized the entire field of neurological surgery in the 1960s. Current research in laboratories throughout the world's hospitals, universities, and industry continue to pursue novel methods for treating cerebrovascular disease by endovascular means. Clinicians continue to develop and apply novel techniques to provide safer and more effective therapies to patients with cerebrovascular disease. More importantly, the role of endovascular therapy continues to expand its horizons by applying fundamental techniques to the diagnosis and treatment of nonvascular targets and by taking advantage of the endovascular access to study the in situ environment to obtain a better understanding of the pathobiology of central nervous system disease.

The technologies of the future are built upon the successes and failures of technologies of the past. Review of the history of endovascular neurosurgery's birth clearly demonstrates a strong influence from numerous disciplines along with substantial technological advances in materials science. Although the concepts for endovascular treatment have existed since the early days of angiography, the necessary technological advances did not yet exist. In other words, technology had not yet "caught up" to the innovators' ideas. With the advent of material and polymer science, vast improvements in imaging, and a better understanding of the pathophysiology of cerebrovascular disease, "old" ideas are being revisited.

This article will briefly review the current status of the devices used in endovascular neurosurgery for the treatment of various diseases of the central nervous system and then, because of the sensitive nature of future developments, only briefly present several broad concepts on the possible future directions for this fascinating discipline (*Fig. 1*).

ACCESS DEVICES (CATHETERS, MICROCATHETERS, AND WIRES)

Current catheters and microcatheters depend on the ability to fuse different polymers almost seamlessly to create a catheter or microcatheter that possesses substantially different physical characteristics along its length. Subsequently, micro-

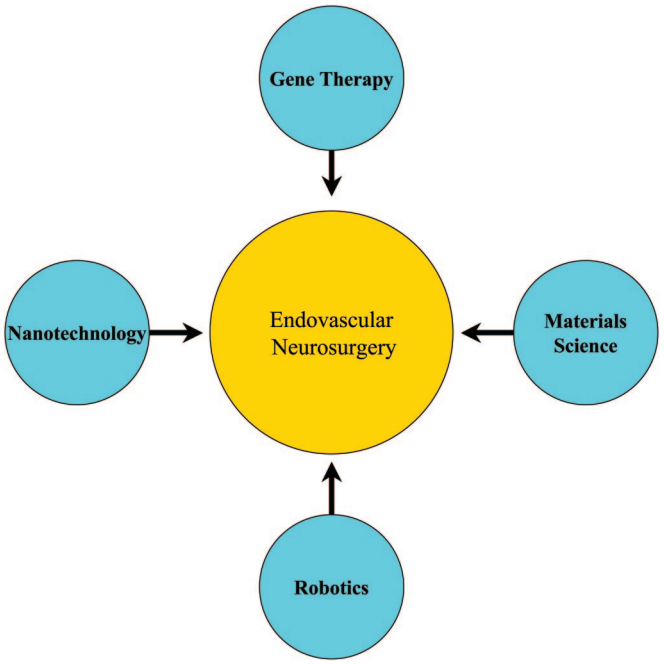

FIGURE 1. *Influence diagram conceptualizing a few of the various fields that endovascular surgery should embrace to continue its astronomical growth.*

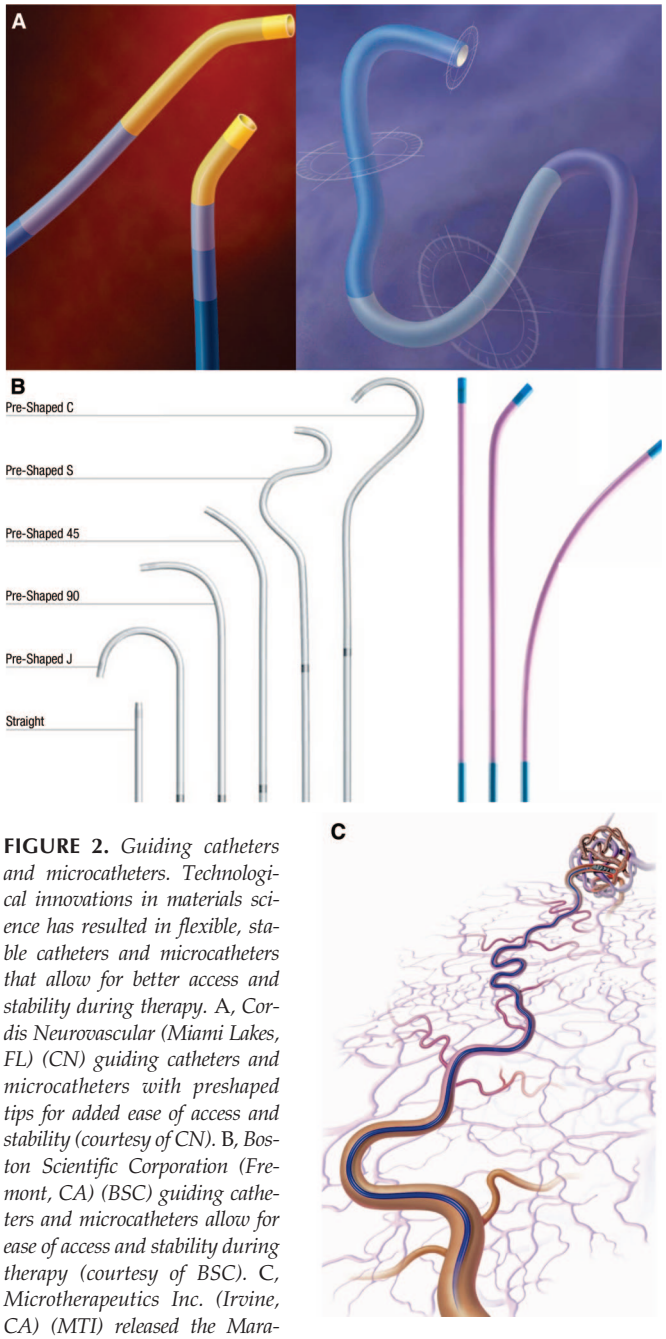

FIGURE 2. *Guiding catheters and microcatheters. Technological innovations in materials science has resulted in flexible, stable catheters and microcatheters that allow for better access and stability during therapy.* A, *Cordis Neurovascular (Miami Lakes, FL) (CN) guiding catheters and microcatheters with preshaped tips for added ease of access and stability (courtesy of CN).* B, *Boston Scientific Corporation (Fremont, CA) (BSC) guiding catheters and microcatheters allow for ease of access and stability during therapy (courtesy of BSC).* C, *Microtherapeutics Inc. (Irvine, CA) (MTI) released the Marathon microcatheter as a flow-guided microcatheter with characteristics that allow for over-the-wire guidance (courtesy of MTI).*

catheters may have a rather stiff proximal portion that allows the necessary "pushability" and "torquability" to navigate proximally tortuous vessels, yet progressively softens to the extent that it may well reach the most distal segments of the anterior, middle, and posterior cerebral arteries without substantially altering the vessel's geometry. The proprietary lubricious coatings present on the surface of these microcatheters assure a less traumatic passage of the microcatheter through tortuous vessels (*Fig. 2*).

Many advances in microguidewire technology have brought endovascular navigation to new frontiers (*Fig. 3*) (9). For several years, the apparent limit of a "functional" microwire, that is one which was useful in tracking a microcatheter to the distal cerebral circulation, seemed to be at the diameter of 0.010 inch. By bonding a soft, platinum-wound coil to the wire's tip, a very soft, shapeable, and trackable wire with excellent radiographic properties was created. The introduction of the 0.008 inch in diameter microwire (Microtherapeutics, Inc., Irvine, CA), and the introduction of the nitinol hypotube, (Boston Scientific, Natick, MA), with its complex laser-cut, machined slots to "soften" the hypotube, has resulted in a highly responsive, torquable microwire with excellent tracking properties.

The future in wires and catheters lies in "smart technology." As in the 1960s when clinicians were attempting to navigate embolic materials or catheters into the brain vasculature through the use of an externally placed magnetic source, current research may focus on microcatheters with realtime, *in situ* shape-changing characteristics (4, 20, 34, 44). Such "dynamorphic" catheters would change shape at each segment of the vessel, allowing for easier tracking and easier access to branches of interest. The advances will take place in steps, most likely beginning with mechanical or electromechanical modifications to microcatheters that allow distal shape changes. As nanotechnology continues to improve, perhaps the use of nanogears embedded within the microcatheter or

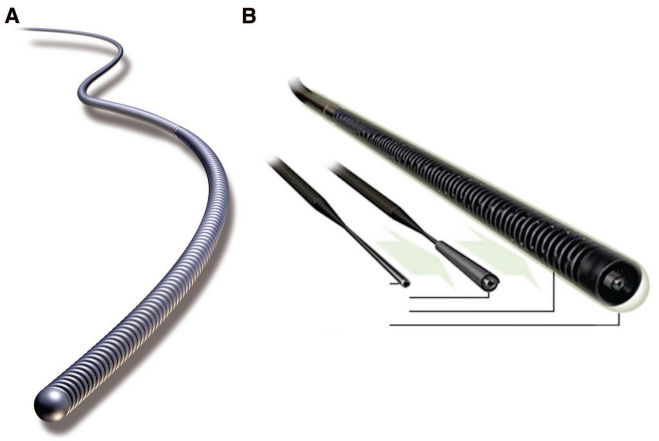

FIGURE 3. *Advances in microguidewire technology.* A, *MTI created the 0.008 Mirage microguidewire with its soft platinum-wound tip and good torquability and pushability (courtesy of MTI).* B, *BSC's Synchro microguidewire is the first nitinol, laser-cut, hypotube that allows for one-to-one torquability in the distal cerebral vasculature (courtesy of BSC).*

microwire, preprogrammed for navigation through a specific patient's vasculature would provide the necessary shape-shifting characteristics and ease the access to the target vessel with minimal human input.

Continued research in the field of access devices should not just focus on endovascular catheters. Focused, targeted access to the subarachnoid space should be studied as an additional means of possible therapeutic and diagnostic access. Developing future generations of catheters that can be guided into any subarachnoid space for pharmacotherapy or gene therapy may result in the birth of a new subspecialty, marrying the skills of the neuroendoscopic and the neuroendovascular surgeon.

IMAGING, NAVIGATION, AND ROBOTICS

The impact cerebral angiography had on the treatment of cerebrovascular disease was foreshadowed in 1931 (5). Since angiography's inception, the most current advances related to imaging in endovascular surgery remain within single-plane and bi-plane angiographic techniques. The rise of three–dimensional (3-D) angiography for the brain and spinal cord has enabled clinicians to better evaluate patients with cerebrovascular disease while reducing overall radiation to the patient (*Fig. 4*) (1, 6, 21, 29, 38, 40). The immediate future will focus on the use of a single-plane, 3-D roadmapping capability that would allow navigation of microcatheters to the target vessel with minimal doses of radiation. Fusion technology, allowing for multiple modalities (such as computed tomography or magnetic resonance imaging sequences and reconstructions) to be coregistered with angiographic images, might not only aid in identification of disease, but also may serve as the building blocks for future semiautomated navigation systems for endovascular surgery (*Fig. 5*).

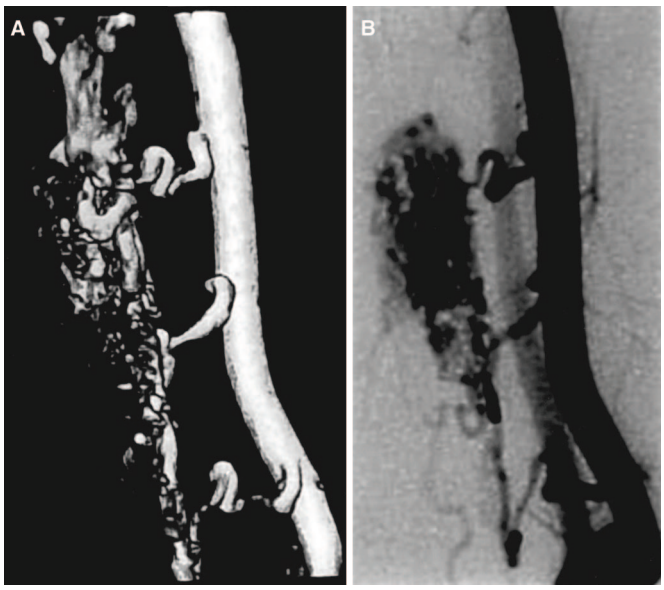

FIGURE 4. *3-D spinal angiography for a spinal vascular malformation.* A, *3-D rotational angiogram depicting several vertebral artery feeding branches which are confirmed on conventional lateral angiogram (*B*). Note the tortuosity of these feeding pedicles, which is easily recognized on the rotational image, allowing for potentially safer microcatheter navigation. Additionally, such a rotational image reduces the overall radiation to patient and staff by determining the best orientation of the image intensifier without repeated acquisitions in preparation for the use of the microcatheter.*

Although endovascular neurosurgery is currently defined by its use of x-ray technology, endovascular surgery need not be dependent upon this modality as its sole means for navigation and imaging. Vertebroplasty and kyphoplasty, for instance, are being performed in some institutions with the use of computer-assisted techniques (22, 27, 42). Granted, although still technically an x-ray-based technology, computed tomographic-guided vertebroplasty and kyphoplasty serve to demonstrate this discipline's ability to embrace and adapt to new concepts and new techniques. Indeed, further evidence of the field's desire to expand beyond the limits of x-ray-based modalities is seen in the development of interventional magnetic resonance imaging in several institutions (7, 31, 36, 41).

The ability to successfully cannulate a target vessel deep in the cerebral circulation depends on microcatheter technology as well as the full understanding of the 3-D aspects required to navigate and engage the vessel of interest. Techniques that would further facilitate vessel selection would certainly improve overall outcomes in patients, as they might substantially reduce vessel injury and total time of radiation exposure for the patient and staff. Thus, specially engineered microcatheters that would be guided by variable magnetic fields to the target vessel of interest are currently being evaluated. As previously mentioned, future technology might include "preprogramming" microcatheters or microwires to a patient-specific destination of a particular vessel, through the use of nanogears placed in specified regions of the microcatheter.

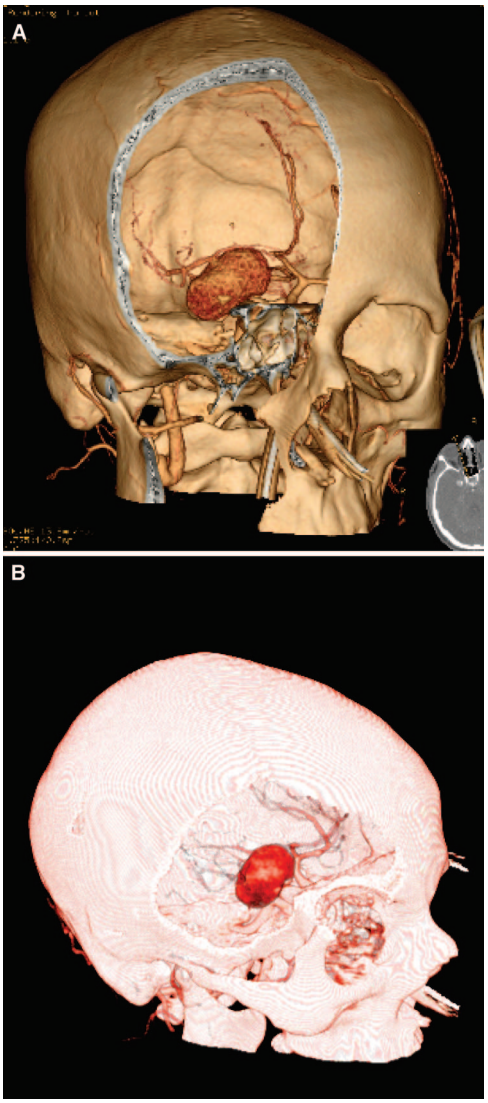

FIGURE 5. *Advances in imaging.* A, *computed tomographic angiogram of a giant right ICA aneurysm in this young patient with subarachnoid hemorrhage.* B, *dextroscope imaging of this same patient can be used to determine the surgical accessibility of the proximal and distal carotid artery for a trapping or bypass procedure.*

As with nearly every other specialty, the field of robotics is being assessed as an important adjunct in endovascular surgery. A "robot" is, by engineering standards, defined as a device with sensors, integrator, and actuators. Thus, a robot is able to sample or receive input from the external environment, process this information, and then produce an effect on the environment. By this strict definition, robotics can take on a multitude of appearances and functions. Robotic surgery is a logical result of the progress in minimally invasive surgery (17, 33). With the ever-increasing precision of robotic arms that drastically reduce or eliminate the physiological tremor, smaller incisions can be used with video assistance for proper illumination and visualization. Such devices can increase precision from the 70 μm demonstrated by some microsurgeons to under 10 μm (11, 25). In the endovascular field, robotics would not only be used for the gentle manipulation of catheters and microcatheters. Development of endovascularly deployed microrobots or nanorobots combined with gene therapy or other forms of tissue engineering could be used to effect local repair in the setting of disease.

DISEASE-SPECIFIC TECHNOLOGIES

One of the main advantages endovascular neurosurgery enjoys is its potential to leave a very small "footprint" after the appropriate therapy has been delivered. Ideally, such an advantage should be embraced and developed to its fullest capacity, such that treatment of any vascular or nonvascular lesion by endovascular means would ultimately result in restitution of normal tissue. Granted, although seemingly impossible to achieve, genetic engineering and stem cell research do provide us with some of the fundamental tools required to ultimately "leave no footprints." Furthermore, this "low-profile" approach to the central nervous system provides an avenue to explore these environments in an almost unobtrusive way, providing the opportunity to better understand the pathobiology of central nervous system disease and ultimately design the appropriate, targeted therapies.

Atherosclerotic Disease

As the understanding of intracranial and supraaortic atherosclerotic disease continues to expand, novel methods for the treatment of this disease are being explored. Novel drug-eluting stents currently being used in the coronary circulation are being evaluated for the intracranial circulation (8, 23, 26, 35, 43). Because of concern that placement of a balloon-expandable stent itself may contribute to delayed in-stent restenosis, a new, self-expanding nitinol stent (Wingspan; Boston Scientific Corporation, Fremont, CA) has recently been approved for the treatment of intracranial atherosclerosis in patients who are refractory to maximal medical therapy (*Fig. 6*).

What does the future hold in the treatment of atherosclerotic disease? Although drug-eluting stents hold promise, as is demonstrated in the cardiac literature, the pathophysiology of intracranial atherosclerosis may not necessarily mimic that of cardiac disease in that the surrounding milieu is biomechanically and biochemically different. As further progress is made in the understanding of intracranial and supraortic atherosclerotic disease, appropriate technological innovations will certainly follow. The growth of gene therapy may result in the ability to locally reverse atherosclerotic disease with appropriately coated stents.

Thromboembolic Disease

The approach to the successful treatment of cerebral thromboembolic disease involves the marriage of many disciplines

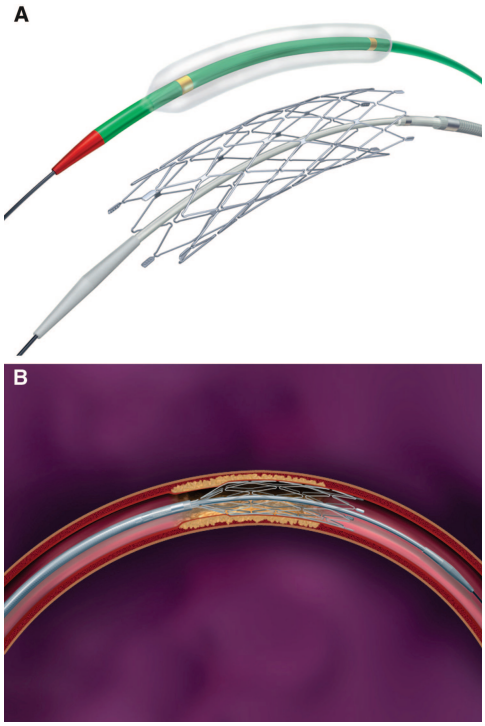

FIGURE 6. *Intracranial stents for atherosclerotic disease.* A, *the introduction of the first Food and Drug Administration-approved self-expanding stent for use in intracranial atherosclerotic disease (Wingspan, BSC) is currently under evaluation (courtesy of BSC).* B, *artistic concept of the placement of the stent within an atherosclerotic lesion after angioplasty.*

and many technologies that work synergistically to reestablish blood flow to ischemic areas, while simultaneously trying to preserve vital brain tissue. Although current concepts in the endovascular treatment of acute thrombosis revolve around the restitution of blood flow to an ischemic region via chemical or mechanical devices, perhaps focus should also be directed at restitution or preservation of brain function once blood flow has been successfully reestablished. Current limitations in the field of endovascular revascularization for thromboembolism are secondary to the complications attributed to the aforementioned pharmaceuticals and devices. Nanotechnology lends itself to the treatment of thromboembolic disease in that devices could be designed to selectively lyse clot in distal territories with little risk of injury to the vessel wall. Furthermore, once revascularization has taken place, the endovascular access to the injured region should then be used to potentially set the stage for repair and potential regeneration of tissue.

Aneurysm Therapy

The successful, permanent obliteration of aneurysms with elimination, or at least substantial reduction, in treatment risk is the primary goal in the endovascular treatment of aneurysms. Most of the technologies for the treatment of aneurysms involve the use of coils to fill the saccular portion of the aneurysm with variable detachment mechanisms. Irrespective of their techniques for detachment and their varying shapes, endovascular coils serve to fill the aneurysm, permit thrombosis and subsequent fibrosis within the aneurysmal sac, and, thus, promote healing. Recent advances in aneurysm coils focus on the use of adjuncts to the coil in an effort to accelerate healing, some of which exhibit bioactive properties. These implants with varying surface modifications seem to engineer accelerated tissue responses (*Fig. 7*).

How will aneurysms be treated 15 to 20 years from now? Such a question depends, in part, on what will be known about aneurysm formation and aneurysm rupture within the next several years. Understanding the biomolecular predisposition to aneurysm formation involves exploring the many factors that we now know contribute to aneurysm formation, not the least of which being the inflammatory response and

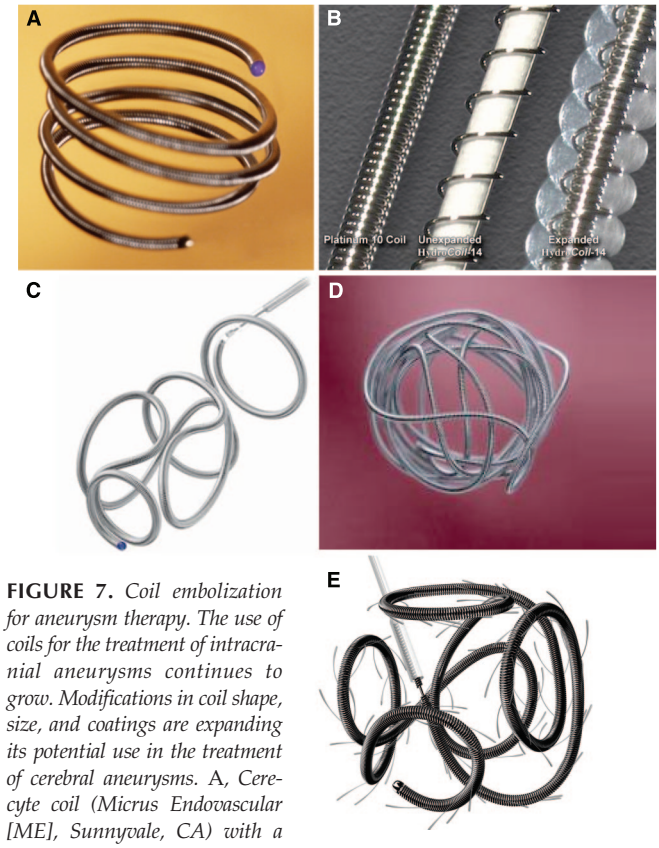

FIGURE 7. *Coil embolization for aneurysm therapy. The use of coils for the treatment of intracranial aneurysms continues to grow. Modifications in coil shape, size, and coatings are expanding its potential use in the treatment of cerebral aneurysms.* A, *Cerecyte coil (Micrus Endovascular [ME], Sunnyvale, CA) with a polyglycolic acid central core is one of several types of "bioactive" coils in current use that may enhance the conversion of thrombus to fibrosis within the aneurysm and its ostium (courtesy of ME).* B, *Hydrocoils (Microventions) employ the use of a self-expanding polymer that increases the filling volume within an aneurysm (courtesy of Microventions).* C, *matrix coils (BSC), such as this 360 coil, have an outer polylactic acid/polyglycolic acid coating that accelerates and potentially enhances the conversion of thrombus to fibrosis within the aneurysm and its ostium (courtesy of BSC).* D, *the Orbit coils (CN) consist of a random complex shape that can be used for endovascular occlusion of an aneurysm (courtesy of CN).* E, *the Nexus Tetris coil (MTI) uses multiple fibers emanating from the coil to enhance thrombus conversion to fibrosis (courtesy of MTI).*

leukocyte infiltration, mechanisms of remodeling, heredity, smoking, flow dynamics, sex, and age (14, 15).

The best way to heal an aneurysm is not necessarily to create a collagen-laden cicatrix at the neck of the aneurysm, but rather to permit regeneration or reconstruction of the intima and media at the site of the aneurysm ostium. Surgical clipping of the aneurysm partly achieves this result in that it approximates what is assumed to be normal intima and media at the site of the aneurysm ostium. Recurrences, although rare, may be secondary to the fact that these regions may lack completely normal intima and media in addition to associated increases in shear stress secondary to the local hemodynamics.

Thus, several approaches can be used to affect healing at the site of the aneurysm. The first involves biological modification by inciting a tissue response, similar in concept to the potential benefits reported in the use of current modified coils. Future technology may include endovascular implantation of engineered genes, proteins, or cells that would promote the reconstruction—or more likely, regeneration—of the vessel's intima and media.

The second approach to healing aneurysms involves principles similar to those of Hunterian ligation (18, 19). Hunter's insightful procedure of proximal ligation of the popliteal artery as an alternative to leg amputation for carriage drivers with popliteal aneurysms demonstrated the concept that eliminating direct pressure to a weakened vessel might promote spontaneous healing. This technique was subsequently applied to the intracranial circulation with variable results. The concept of balloon occlusion therapy or reversal of flow in the treatment of intracranial aneurysms is a current rendition of the technique. Future treatment of aneurysms may apply the principles in a slightly more elegant fashion.

It is postulated that aneurysms grow at a bifurcation because this area of maximal impact, deflection, and separation of flow represents the site of maximal shear stress for the vessel wall (16). When compounded by the histological absence or focal degeneration of the internal elastic lamina, aneurysm formation can occur. In vitro models and biomathematical computer simulations suggest that diversion of flow away from the point of maximal shear stress might allow for spontaneous vessel remodeling and healing. Current use of stents in the clinical setting along with in vitro experiments and some animal models suggest that modifications in stent structure, strut diameter, and configuration may sufficiently redirect flow such that the aneurysm might be excluded from the flow patterns and result in aneurysm healing (2). Another approach to "flow diversion" or "flow redirection" might be to deploy low profile "flow diversion devices" proximal to the site of the aneurysm. In certain situations, the use of covered stents may be deployed to effectively obliterate the aneurysm's orifice without compromising parent vessel patency and without changing the flow dynamics within the parent vessel. Currently, the industry is working to develop intracranial stent technology that will allow for safe navigation through the intracranial vasculature that will not lose its flexibility when coated with occlusive materials. Coating stents with bioactive substances that can induce collagen/fibrin formation and subsequent endothelialization are being explored. By coating alloy or biodegradable stents with compounds that can induce controlled smooth muscle proliferation, the aneurysm orifice would undergo a remodeling that would effectively reconstruct the intima and media.

Several years ago, L'Heureux et al. (24) published the in vitro synthesis of vessels. Expanding on such technology might result in the implantation of vessel precursors at the site of the aneurysm where the microenvironment might allow for de novo vessel wall development.

Future technology need not limit itself to the obliteration of the aneurysm or the reconstruction of the parent vessel (32). Endovascular techniques may be used to deliver novel compounds to combat and even prevent vasospasm after subarachnoid hemorrhage. Microcatheter technology will allow endovascular surgeons to deliver embolic agents in a more controlled, directed fashion. The use and modification of novel liquid embolic agents for the treatment of aneurysms will continue.

The use of virtual endoscopic views of the aneurysm orifice and its dome is starting to play a role in decision making regarding the choice in coil size and shape, and may become the standard as technology continues to improve. Current research in virtual reality approaches to aneurysm treatment are being investigated as a means of determining the a best approach or best treatment option for a given lesion. The use of endovascular ultrasound is being explored and may further enhance endovascular therapy by increasing our understanding of the hemodynamic stresses present at the aneurysm's ostium and dome (13, 30).

Arteriovenous Malformations

The introduction of the liquid embolic agents in the treatment of arteriovenous malformations (AVMs) was an important technological advancement. Liquid embolics, such as *n*-butylcyanoacrylate, ethanol, and ethylene vinyl alcohol, have allowed deeper penetration into the nidus with better occlusion of the feeding pedicle (*Fig. 8*) (3, 28, 39). Each modality, including embolization with particles and coils, is not without risks, which can include vessel rupture, vein occlusion, or embolization of normal parenchymal branches.

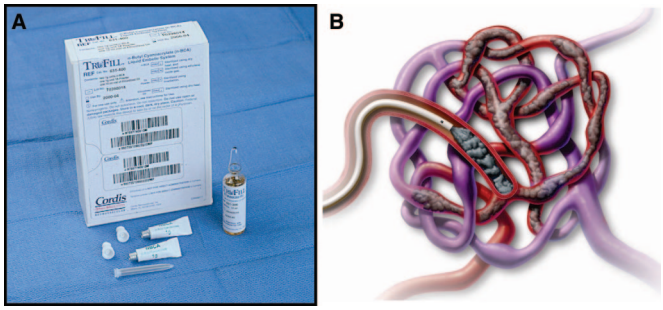

FIGURE 8. *Liquid embolic agents have changed the treatment of arteriovenous malformations.* A, *histoacryl (n-butyl cyanoacrylate) is used for the preoperative treatment of cerebral arteriovenous malformations (courtesy of CN).* B, *MTI's recent release of Onyx (ethylene vinyl alcohol copolymer in dimethyl sulfoxide) has recently been approved for use in presurgical cerebral arteriovenous malformations (courtesy of MTI).*

Although catheter technology has resulted in successful navigation to the most distal, tortuous branches of the cerebral circulation, accurate deposition of the embolic agent remains difficult at times.

Future embolic agents should be 1) adhesive so as to bind the vessel wall and stimulate scar formation at that site; 2) cohesive so as to deliver a continuous column and not fracture and embolize distally; 3) low viscosity to penetrate deep into the nidus and obliterate multiple compartments; and 4) controllable so as to avoid venous outflow obstruction until the entire AVM is obliterated. Although such a compound may not exist at present, perhaps developing a compound that can be delivered to the AVM nidus and then activated by adjuvant treatments, such as radiation, may result in a highly selective, accelerated focal thrombosis and fibrosis of the AVM without affecting normal surrounding tissue. Furthermore, a better understanding of the biology of AVMs (as with all other disease processes) may allow for better-designed therapies. For instance, a better understanding of the functions of the numerous genes expressed in arteriovenous malformations might help in producing agents that recognize the malformation, bind to the malformation, and then help stimulate or suppress specific genes that permit the involution or regression of the malformation (37).

Nonvascular Targets

At present, there is limited selectivity in the various cidal agents used to treat tumors, as is evidenced by the common side effects. Superselective targeting of lesions by embolic agents, whether they be viral vectors, targeted liposomes, or nanotechnology-derived agents, would be most applicable for the endovascular treatment of tumors. Specific antigen targeting might be possible, with subsequent deposition of cidal factors attached to antibodies specific to the tumor and then activated by a focused external source. Only those molecules with the necessary conformational change from binding with the target surface protein on the tumor can be activated. Thus, a highly specific cidal therapy for the tumor may be possible.

TRAINING

The safe, effective training of individuals in the field of endovascular surgery is of paramount importance to ensure the longevity of the subspecialty. Current training standards are similar to other specialties, with a combination of didactics and hands-on experience. The introduction of simulator training for specific endovascular procedures is currently being evaluated (10, 12). Just as cadaveric dissections are still part of residency training in some academic institutions, simulator training in endovascular surgery will be used to not only assist the trainee in learning angiographic anatomy and fundamental angiographic skills, but also with proper haptics and visual feedback, complex patient-specific procedures may be "rehearsed" in advance so as to minimize patient complications.

CONCLUSION

The past century has seen a tremendous revolution in technology. From the birth of aviation and space travel to the explosive growth of the information age, the exponential growth of technology was hardly imaginable in the early parts of the 20th century. Among the many fields that have benefited from this growth, medicine has been a prominent beneficiary, contributing in no small part to the increase in life expectancy for men, women, and children.

Each subspecialty has witnessed its own growth in understanding disease-specific mechanisms and the treatment of specific disorders, some of which were unimaginable at the turn of the past century. It is, therefore, difficult to envision what the future of medicine, or a specific subdiscipline thereof, would be like by the end of this new century or beyond. As an example, the relatively "mature" field of neurological surgery, although technically in existence since prehistory, is practiced quite differently now than a mere 50 years ago. Endovascular surgery, or interventional neuroradiology, not really more than 40 years old, is being practiced in a different way than in its nascent years during the 1960s and 1970s.

What lies ahead for endovascular surgery in the 21st century? Although substantial progress has been documented in the literature, academic laboratories and industry continue to push forward the boundaries of technology. This brief review has primarily focused on the technological achievements and potential future technological advances that are in endovascular neurosurgery's horizon. Such a focus reflects the limitation in revealing the current, up-to-the-minute research and development that is ongoing in many of academia and industry's laboratories around the world. However, it is imperative to recognize that the future of this field is defined not by the technology, but by what is in the minds of the individuals that contribute to the growth of the field, i.e., the clinicians' conceptualization of what the field's potential can or should be. Further developments may mimic or incorporate perhaps some of the concepts brought out in this brief review. Ideally, in keeping with the concept that our attempts to heal should be focused on providing therapy via the smallest possible footprint, endovascular therapy may no longer require catheter-based navigation and approach to the central nervous system. Perhaps, preprogrammed "packages" can be deposited intravenously to find their way to the specific target and deliver the appropriate therapy or permissive framework for healing. Most importantly though, the limits of the field and its future do not rest with the imagination of only one or several individuals. Just as the clinicians of the early 1930s were just learning about the potential of angiography, so too a review of neuroendovascular surgery 50 years hence will most likely reveal many unexpected accomplishments made by bold clinicians and scientists with the vision and foresight to think beyond the current boundaries of this nascent field.

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THE ENDOVASCULAR OPERATING ROOM AS AN EXTENSION OF THE INTENSIVE CARE UNIT: CHANGING STRATEGIES IN THE MANAGEMENT OF NEUROVASCULAR DISEASE

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TECHNOLOGICAL ADVANCES WITHIN the field of endovascular neurosurgery have influenced the management of the neurovascular patient within the intensive care unit (ICU). The endovascular operating room has, in fact, become an extension of the ICU in certain cases. Given the rapid development of new endovascular technologies, it is more important than ever for neurosurgeons to remain intimately involved with the care of their patients within the ICU. This article offers an overview of the evolution in ICU management of neurovascular disease and provides a framework for the incorporation of the endovascular operating room in the intensive care management of patients with this disease.

KEY WORDS: Endovascular operating room, Neurocritical care, Neurovascular disease, Subarachnoid hemorrhage

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The management of patients in a critical care environment has traditionally been a multidisciplinary effort. With respect to neurocritical care, neurosurgeons, or those with neurocritical care specialization, usually direct the treatment course for all critical care issues in their patients. However, the critical care culture has recently changed from an open source with clear influence from the surgical teams to one promoting closed hospital units with dedicated critical care teams that relegate surgical teams to the role of consultants (9, 10, 56, 64). Although this approach may be feasible or even desirable in a setting in which a dedicated neurocritical care unit is present, it may not necessarily be appropriate where dedicated neurocritical care is unavailable. The continuously evolving care of the neurovascular patient exemplifies the problematic nature of this issue. The rate and volume of advancement in neuroendovascular techniques mandates constant education. For example, algorithmic approaches to the management of patients with aneurysmal subarachnoid hemorrhage (SAH) should now include endovascular methods to rapidly deal with severe medically intractable vasospasm. Additional examples include the use of thrombolytics in early thrombotic stroke, stenting of the extra- and intracranial internal carotid arteries, tumor and arteriovenous malformation (AVM) embolization, and coil embolization of cerebral aneurysms.

The purpose of this article is to provide an overview of the current management trends of the neurovascular/endovascular patient within the intensive care unit (ICU). Specifically, a general guide will be provided for incorporating the endovascular operating room into ICU management algorithms. The argument for direct neurosurgical involvement in the ICU will be made. Because many of the techniques have been outlined in other sources, specific interventions will be discussed in detail only where considered "off-label" or relatively new.

SAH

The treatment of patients with aneurysmal SAH can be influenced by multiple variables. These include the neurological status of the patient, the status of the aneurysm (location, secured or unsecured), the presence or absence of vasospasm or hydrocephalus, and the systemic response of the patient to the imposed medical and surgical treatments.

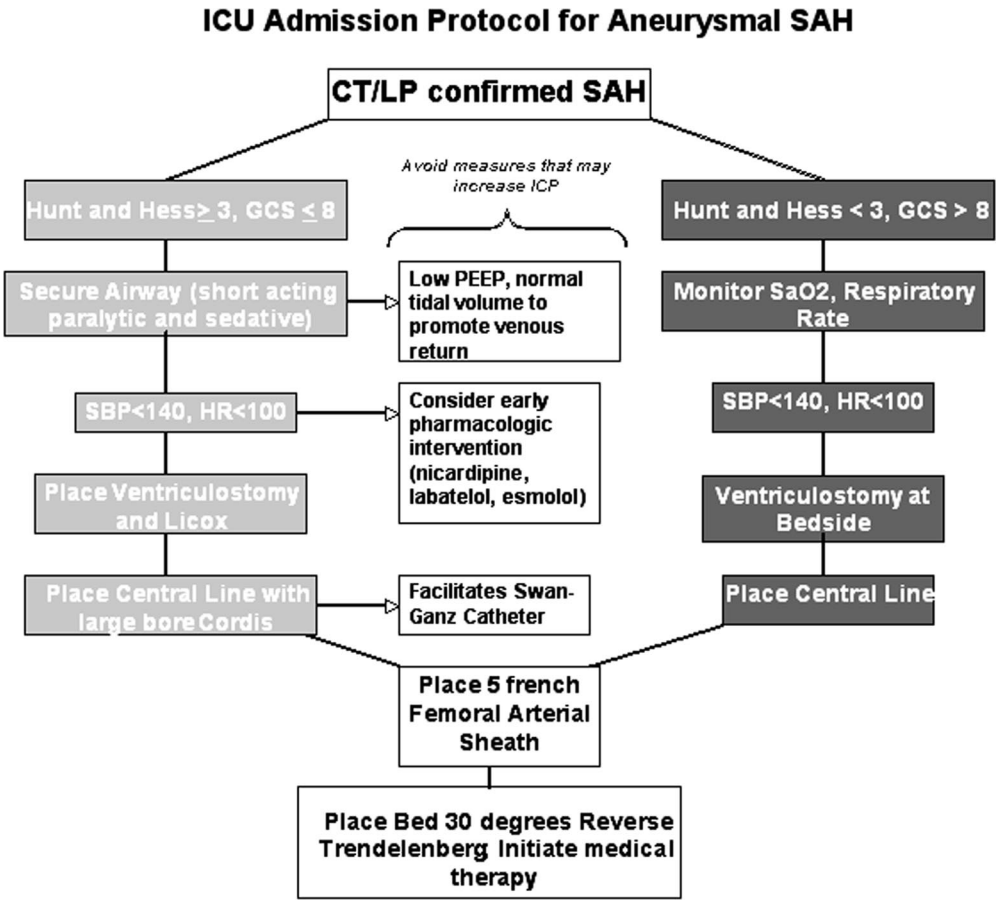

FIGURE 1. *Schematic diagram of ICU admission algorithm for aneurysmal SAH.*

Initial Evaluation and Securing the Aneurysm

The patient with aneurysmal SAH is ideally suited for care within the ICU. Initial presentation can vary from severe headache, nausea, vomiting, photophobia, and nuchal rigidity to frank coma and posturing (18, 91). Initial workup should include a computed tomographic (CT) scan of the head. If blood is not identified on the CT scan, a lumbar puncture is required. Gradient recovery echo and fluid attenuation–inversion recovery magnetic resonance imaging sequences may also be used if the patient is stable. Once SAH has been confirmed, the patient should be physiologically prepared for surgical or endovascular intervention (*Figs. 1* and 2). Blood pressure (systolic $<$ 160 mmHg; diastolic $<$ 90 mmHg) and heart rate ($<$100 bpm) should be controlled within strict parameters to prevent rebleeding and SAH-associated cardiac abnormalities (69). An arterial line should be placed and, depending on the level of consciousness and Hunt and Hess score, consideration for a ventriculostomy and an endotracheal tube should be entertained. Central venous access may be obtained as a means to measure central venous pressure and administer hypertonic/hyperosmotic fluids (i.e., hypertonic saline, total parenteral nutrition) as needed. Nimodipine, phenytoin, and dexamethasone therapy may be considered at this time, although data concerning the mandatory use of phenytoin and dexamethasone are either scant or controversial (1, 12, 41, 43, 44, 56, 89).

Once the medical parameters have been optimized, the preference at our institution is to proceed to the endovascular operating room. Although data are accumulating concerning the diagnostic efficacy of noninvasive imaging modalities, such as magnetic resonance angiography and CT angiography, digital subtraction angiography remains the "gold standard" (36, 38, 59). Additionally, depending on the patient's age, the location and size of the aneurysm, and the overall neurological status, a diagnostic angiogram can often proceed promptly to treatment with coil embolization or stent-assisted coiling. Factors that may complicate postembolization management of a patient with a ruptured aneurysm might include a new infarct from a vessel dissection or embolus; a rerupture of the aneurysm during treatment, resulting in additional SAH; or a transient hypocoagulable state secondary to the use of heparin during the coiling. If the aneurysm morphology and/or location do not support endovascular treatment, procession to open microsurgery should occur.

Postoperative Care

The advent of the Neuroform stent (Boston Scientific/Target, Fremont, CA) has changed the approach to the endovascular treatment of aneurysms. Successful placement of a stent augments a coiling procedure by partially redirecting blood flow and subsequently buttressing the coils within a wide-necked aneurysm (5, 21). However, consideration must be given to the need for protracted antiplatelet therapy after placement of the stent. The protocol in the setting of an unruptured aneurysm consists of a preoperative load of clopidogrel (one 350-mg dose orally or via the nasogastric tube or 75 mg orally for 3 days before stent placement in a stable, unruptured patient) and up to 3 months of both aspirin and clopidogrel after stent placement. In the setting of a ruptured, wide-necked aneurysm, an attempt to gain some aneurysm dome protection should be made before initiation of antiplate-

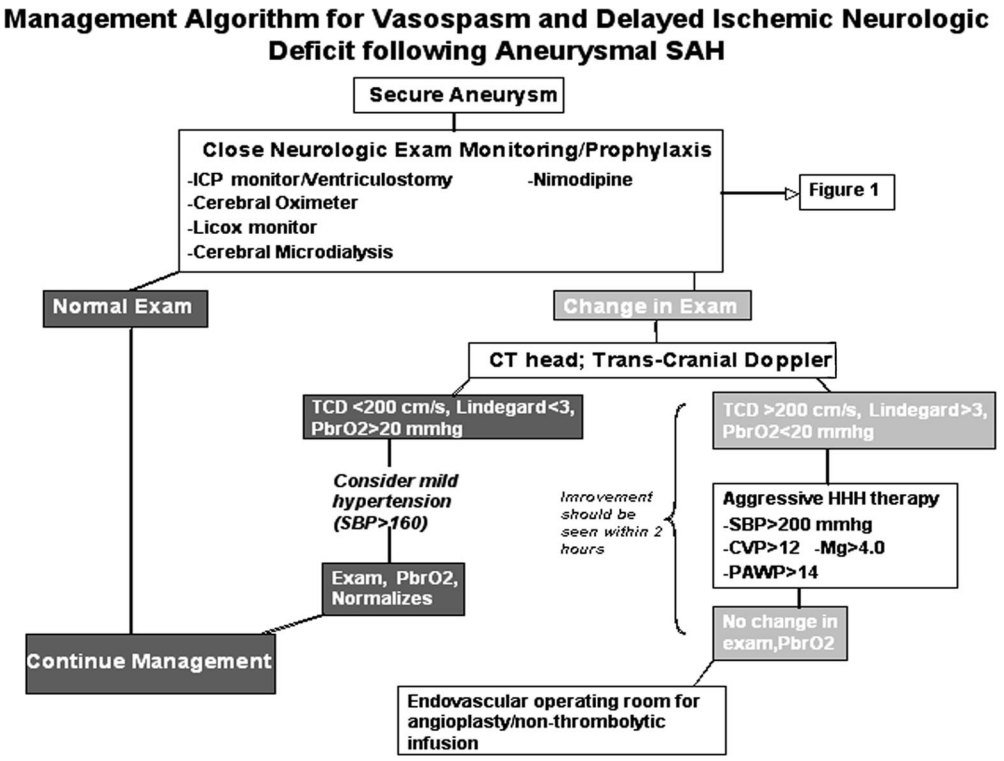

FIGURE 2. *Schematic diagram of algorithm for management of vasospasm and delayed ischemic neurological deficit after aneurysmal SAH.*

let therapy. A short course of abciximab may be required if a stent-induced thrombus is identified. The recommended dose consists of a 0.25 mg/kg bolus followed by maintenance doses of 0.125 μg/kg/min for 12 hours (3). Although the aneurysm has been secured, there is still a risk for rebleed secondary to the medical inhibition of platelet aggregation. If the risk of rerupture secondary to platelet inhibition is considered too great, balloon-assisted coiling should be considered as an alternative technique.

Once the patient is transferred back to the ICU, the femoral arterial line is typically maintained and transduced for 24 hours as the heparin-induced coagulation abnormalities resolve. This also facilitates return to the neuroendovascular operating room in case a rehemorrhage or a coil expulsion from the aneurysm occurs. Once the sheath is removed, pressure must be maintained at the groin site until an adequate arterial seal is assured. The formation of either a superficial or retroperitoneal hematoma, although initially manageable, could become hemodynamically significant if not managed appropriately. Therefore, the complaint of groin pain or low-back pain lateralized to the side of arterial entry necessitates investigation. Initiation of hypertensive, hemodilution, hypervolemic (HHH) therapy is now possible and can be tailored to the vessel velocities identified by daily transcranial Doppler (TCD) measurement. Specifically, blood pressure and central venous pressure can be augmented in response to increased blood-flow velocities.

SAH-INDUCED VASOSPASM

The risk of development of vasospasm is directly related to the amount of blood located within the subarachnoid space and correlates with eventual patient outcome (70). Measured amounts of subarachnoid blood more than 1 mm in thickness (Fisher Grade 3), as measured on a CT scan of the head, strongly correlate with the formation of this condition. Patients are at greatest risk between Days 3 and 11, but vasospasm can occur up to Day 21. It is important to remember that vasospasm can exist without neurological deficit. The incidence of vasospasm has been reported between 30 and 76%, with 30% of those experiencing an ischemic event during the course of spasm (42). This suggests that variables in addition to vasospasm may contribute to ischemic events associated with this condition.

Various noninvasive imaging modalities can augment the clinical examination in detecting vasospasm and its sequelae in the setting of aneurysmal SAH. TCD ultrasonography can be used to indirectly measure the velocity of flowing blood within the vessel. Measured velocities can then be compared with the available published vessel-specific normal velocity ranges (42, 46). With respect to the middle cerebral artery, we prefer the definitions of normal flow (60–80 cm/s), mild spasm (80–120 cm/s), moderate spasm (120–200 cm/s), and severe spasm (>200 cm/s). Increased blood-flow velocities alone may, at times, be indicative of hyperemic states rather than vasospasm. The Lindegaard ratio (ratio of the blood-flow velocity of the cervical carotid artery to the middle cerebral artery) can aid in this distinction. It is important to recognize that, because TCD ultrasonography is an operator-dependent study, it can result in false-positive or negative studies. Additional monitoring devices include cerebral oximetry, direct tissue-oxygen monitoring (see below), and metabolic analysis via microdialysis catheters. Various institutions also favor the functional measurement of cerebral blood flow by single-positron–emitted computed tomography (SPECT), Xenon-computed tomography, or computed tomographic perfusion studies (31, 42).

HHH Therapy

HHH therapy involves the artificial increase in circulatory volume, the optimization of hematocrit, and the elevation of

blood pressure to the point at which delayed ischemic neurological deficits are either reduced or resolved. There have been multiple studies since the original prospective randomized trial by Rosenwasser et al. (72) in 1983. However, the majority are either retrospective in nature or fail to demonstrate long-term therapeutic benefit (19, 60, 66, 83, 85). Multiple, institution-specific algorithms exist that correlate the degree of volume expansion and mean arterial pressure elevation with vessel velocity, cerebral blood flow, or physical exam (42). The preference at this institution is a mixture of 5% albumen and normal saline for volume expansion. If the patient is hyponatremic, 3% saline is used for both the correction of the hyponatremia and as a volume-expanding agent. Additionally, in cases in which severe hypertension (>200 mmHg) and markedly elevated central venous pressure (>12 mmHg) are required, a Swan–Ganz catheter is placed and regular pulmonary capillary wedge pressure measurements are performed to ensure adequate intravascular volume while anticipating complications, such as pulmonary hypertension (73).

Endovascular Treatment of Medically Refractory Vasospasm

Overall, each organ system can be manipulated to improve physiological outcome in the setting of vasospasm (84). If all conservative medical efforts to overcome the spasm have been maximized and the patient begins to manifest signs of delayed ischemic neurological deficits, endovascular evaluation and treatment should be strongly considered. Rosenwasser et al. (71) suggest that the timing of the intervention may be critical to eventual clinical outcome. Specifically, patients receiving angioplasty or intra-arterial (IA) papavarine within 2 hours after the onset of neurological deficit tended to fare better than those receiving intervention more than 2 hours after onset.

There are several endovascular approaches available for the treatment of medically intractable, symptomatic vasospasm. Major categories include IA nonthrombolytic infusions and angioplasty. Previously, IA papavarine was used alone or in conjunction with angioplasty. Although anecdotal evidence of individual successes with IA papavarine exist (47), recent studies by Oskouian et al. (61) and Polin et al. (63) found no long-term clinical benefit to IA papavarine, despite statistically significant improvement in both vessel diameter and blood-flow velocity. Criticism of this data includes selection bias that resulted in treatment of the most severely affected patients (84). Although not currently approved by the Food and Drug Administration (FDA) for use as an IA nonthrombolytically infused agent, nicardipine has been used successfully to treat acute symptomatic vasospasm (4). The recommended dose for direct microcatheter delivery is no more than 5 mg during a period of 30 minutes with a ventriculostomy in place. At this point, there may be a need for a prospective double-blinded placebo controlled trial evaluating the efficacy of angioplasty, IA nicardipine, and medical therapy, although such a trial would be difficult to complete.

MEDICAL COMPLICATIONS

The neurocritical care team faces numerous challenges during the course of managing patients with aneurysmal SAH. As described, the initial management focuses on patient stabilization and securing the aneurysm. Subsequent approaches focus on disease processes that result directly from degradation of the subarachnoid blood. The management of vasospasm and hydrocephalus, depending on the age of the patient, can often be as detrimental as the primary conditions. As such, a systems-based approach to neurocritical care is mandatory because secondary systemic insults can adversely affect outcome (20, 23, 27, 62, 97). The following section reviews the most common systemic abnormalities encountered during the critical care management of patients with SAH.

Cardiac

Aneurysmal SAH is directly associated with cardiac abnormalities in as many as 30% of patients who survive to reach the hospital (74). The proposed mechanism involves a catecholamine surge from the hypothalamus after stimulation by subarachnoid blood. Arrhythmias resulting in cardiac-wall motion abnormalities and ischemia are not uncommon. These disappear in a significant number of patients, but can persist and result in significant long-term effects in others. Any abnormal cardiac rhythms should be investigated, and appropriate treatment should be instituted. Because the initiation of cardiac-specific medications may be necessary, neurocritical care personnel should be familiar with advanced cardiac life-support protocols.

Pulmonary

The most common cause of non-neurological death in the cooperative aneurysm study was pulmonary dysfunction. There seems to be a direct association between pulmonary function and neurological outcome in SAH (23, 27, 67). The incidence of pneumonia, neurogenic pulmonary edema, and pulmonary embolism have all been reported in this population (23, 27). A condition frequently encountered (incidence reported as high as 19%) and difficult to treat in the setting of SAH-induced vasospasm is acute respiratory distress syndrome. Acute respiratory distress syndrome is defined by a $PaO2/FIO_2$ ratio of less than 200. This condition can be exacerbated by HHH therapy, creating a challenging treatment scenario secondary to the benefits lost if hypervolemia must be discontinued to improve oxygenation. A strategy previously maligned, although supported in a recent study, is daily prone positioning to improve oxygenation (67). Although increases in ICP and decreases in CPP were reported in this study, the partial pressure of oxygen within arterial blood and brain tissue statistically increased. This study did not, however, directly correlate the effects of prone positioning with survival, and additional review of the available Class I evidence is ambivalent on this subject (1, 24).

Ventilator adjustments may also be necessary to overcome the oxygen mismatch in acute respiratory distress syndrome. Airway pressure-release ventilation is a ventilatory mode that combines mechanical pressure variations with spontaneous breathing to improve oxygenation. The improved oxygenation seems to occur because of airway recruitment in the dependent regions of the lung. These regions also receive the greatest amount of pulmonary venous flow (14, 29, 33–35, 44, 57, 86, 94). One study advocates the combined use of prone positioning with airway pressure-release ventilation in selected patients (93). This ventilator mode is an option when obligatory mechanical ventilation modes are not sufficient. However, it must be remembered that the airway pressure-release ventilation mode cycles the patient between a high and low airway pressure, and the high pressure may exacerbate uncontrolled intracranial hypertension.

Given this information, several questions must be addressed on a daily basis. Is the patient oxygenating appropriately despite the SAH or HHH therapy? If not, is the patient in respiratory distress? Does the patient require intubation? If intubated, should a tracheostomy be considered and placed? The practice at this institution is to opt for early tracheostomy in patients with poor Hunt and Hess scores who will likely require long-term intubation. This facilitates management of all ventilatory issues in the face of persistent return to the main or endovascular operating room.

Emerging Diagnostic and Monitoring Technologies

There are several relatively new technological advancements that aid the daily management of patients with vasospasm and delayed ischemic neurological deficits. Three specific examples include direct measurement of the partial pressure of oxygen within brain tissue, catheter-based heat exchange systems to control fever, and microdialysis.

Direct tissue-oxygen monitoring may complement information provided by TCD measurements in the setting of vasospasm. The Licox monitor (Integra Neurosciences, Plainsboro, NJ) combines the tissue-oxygen monitor with a temperature sensor and intracranial pressure monitor. Recent studies in the setting of trauma suggest that partial pressures of oxygen within brain tissue can be reliably monitored (15, 30, 54, 89, 92). Other studies have shown that brain-tissue oxygen is reduced in the setting of SAH (79). This may, in part, be secondary to early increases in the cerebral metabolic rate of oxygen, potentiating the mismatch. In certain cases, there is a direct correlation between low tissue oxygen (<10 mmHg) and eventual morbidity and mortality. Extrapolating to aneurysmal SAH, direct measurement of the partial pressure of oxygen in the setting of vasospasm can alert the intensivist to possible tissue damage before the manifestation of ischemic deficits or infarct. It is specifically helpful in the intubated, sedated, or unresponsive patient. This information can be used to medically augment SaO_2 and PaO_2 by increasing the fraction of inspired oxygen (FiO_2), raising the positive end-expiratory pressure, or transfusing packed red blood cells (oxygen extraction and delivery). Although the values obtained from this monitor are accurate, they reflect only the tissue within a small radius around the probe. Global brain-tissue oxygen assessments are not currently available with existing technology.

Microdialysis systems have been used to directly sample the local cellular electrolyte environment. Predicting tissue damage before the onset of vasospasm is one specific and successful application. In this setting, trends in lactate and pyruvate can predict ischemic damage before TCD evidence of vasospasm. In some studies, ischemic changes manifested by alterations in the ratio of lactate to pyruvate are found up to 11 hours before the appearance of vasospasm with a 75 to 90% specificity (75, 76, 78).

As is well known, elevated core body temperature can increase ICP and has been shown to exacerbate injury to damaged or ischemic brain in experimental models; it can also adversely affect clinical outcomes and increase both ICU and total hospital days (13, 16, 17, 20, 41). The ICU environment affords a setting in which minute-to-minute body and brain temperature control is feasible. Efforts to maintain normal body temperature have historically focused on the use of antipyretic medications (acetaminophen) alone or in conjunction with cooling blankets. However, a recent study confirmed that cooling blankets offer no statistically significant decrease in body temperature compared with acetaminophen alone (52). Recent advances in endovascular catheter-based heat exchange systems have provided a mechanism for reproducible control of core body temperature without changing intravascular volume. This system can be used to maintain a stable body temperature and/or induce hypothermia (25, 37, 82). Specific applications of this technology in SAH, traumatic brain injury, and intracerebral hemorrhage have resulted in an average reduction in fever burden from 7.92 to 2.87 hours (17). It must be noted that an increased incidence of venous thrombosis has been seen in conjunction with the catheter systems. Therefore, cooling vests may also be used if catheter-based systems are unavailable or if the risk of venous thromboembolism is considered too great.

Emerging Therapeutic Strategies

There are currently several experimental treatment strategies aimed at reducing the severity of vasospasm so that aggressive and risky endovascular interventions may be avoided. These therapies reduce the severity and duration of vasospasm by acting on the smooth muscle or endothelial cells of the spastic blood vessels. Although some are not FDA approved and others are not commonly practiced at this time, these strategies may become available as the data accumulate.

Magnesium sulfate acts as a vasodilator by counteracting the effects of calcium within the smooth muscle of spastic blood vessels. Animal (49), in vitro (65), and human studies (6, 7, 12, 28, 48, 77, 91, 98, 99, 101) have been performed to determine the safety and efficacy of this treatment strategy. The majority of these studies provide Class III evidence both

for and against continuous magnesium infusion during vasospasm. However, two studies provide Class I evidence in support of a treatment algorithm that includes raising magnesium levels. van den Bergh et al. (91) conducted a prospective randomized trial in 283 patients with aneurysmal SAH, comparing saline infusions to daily magnesium sulfate (64 mmol/d). They concluded that the incidence of delayed cerebral ischemia was significantly reduced and that outcomes were significantly improved. Veyna et al. (97a) conducted a prospective randomized trial in 40 patients with SAH, comparing magnesium sulfate (serum level, 4.0–5.5 mg/dl) to a control solution. They concluded that there was a reduction in the incidence of vasospasm between their two treatment groups, but that outcomes were not significantly different. In general, the bulk of the currently available literature indicates that magnesium therapy is safe, is easily maintained, and may reduce the severity, duration, and sequelae of vasospasm.

The endothelin receptor class resides on the surface of endothelial cells and mitigate a potent vasoconstrictive response when activated. Their role in vasospasm is currently being elucidated (87, 95, 96). Clazosentan, an endothelin A receptor antagonist, has recently shown promise in reducing the incidence of vasospasm after aneurysmal SAH. Vajkoczy et al. (87) recently completed a prospective, randomized, double-blinded, placebo-controlled, multicenter trial evaluating the efficacy of clazosentan (0.2–0.4 mg/kg/h) in severe aneurysmal SAH. They found that clazosentan reduced the incidence and severity of angiographic vasospasm, and they also noted a trend toward a reduction in new infarcts. This medication is not currently FDA approved within the United States, but it is currently being evaluated.

REPERFUSION HEMORRHAGE AFTER ENDOVASCULAR THROMBOLYTIC THERAPY

IA medical thrombolysis can rapidly reverse thromboembolic disease if recognized within 2 to 3 hours of onset. A review of representative studies within the literature reveals good outcomes in approximately 50% of patients when the procedure was completed within 6 hours of symptom onset. Depending on the source, the rate of intracranial hemorrhage ranged from 3 to 20%, with mortality approaching 20% in one study (5, 8, 9, 13, 21, 29, 48, 62, 68, 82).

Mechanical thrombolysis can extend the window of opportunity up to 8 hours in certain patients and can be considered in patients who are ineligible for medical thrombolysis. The original Mechanical Embolus Removal in Cerebral Ischemia trial included 28 patients with a mean National Institutes of Health Stroke Scale score of 22 and a median time to treatment of 6 hours and 15 minutes. Successful recanalization and embolectomy occurred in 43% of the patients when the device was used alone. Sixty-four percent of patients demonstrated good results when tissue plasminogen activator was added. At 1 month, roughly half of the patients treated had good functional recovery. A total of 12 intracranial hemorrhages occurred (26).

Given the hazardous nature of these interventions, it is important to maintain a critical care environment when managing this disease. Initial evaluation should include a detailed neurological examination, head CT scan, and a thorough review of the patient's past medical history. Contraindications to medical thrombolysis include recent intracranial hemorrhage, history of stroke within the last 6 weeks, seizure at the time of stroke onset, suspected lacunar infarct, clinical presentation suggestive of SAH, uncontrolled hypertension, intracranial neoplasm, suspected septic embolus, known bleeding diathesis, known use of anticoagulation therapy, and not completing the entire therapy within 6 hours of onset of symptoms (80, 82a). If no contraindications are encountered, the selected patient should be transferred to the endovascular operating room for intervention. The endovascular operating room should be equipped with materials to perform an emergency ventriculostomy in case symptomatic intracranial hemorrhage occurs. Once the intervention has been performed, the patient should be transported back to the ICU for close neurological monitoring. The femoral sheath is often left in place secondary to intraoperative heparinization and can, therefore, be transduced as an arterial line. Any changes observed during neurological examination should prompt an immediate head CT scan. The formation of an intracranial hemorrhage may warrant aggressive surgical intervention. Management options include aggressive reversal of any coagulopathy, the placement of an intracranial pressure monitor, clot evacuation, and hemicraniectomy.

ICU CARE OF THE PATIENT WITH CAROTID OR INTRACRANIAL ATHEROSCLEROSIS

Craniocervical atherosclerosis is a neurosurgical disease. The North American Symptomatic Carotid Endarterectomy Trial established the role of carotid endarterectomy for patients with symptomatic carotid stenosis (57a). Although the clinical efficacy of this intervention is not disputed, the complications associated with this procedure have prompted investigation into less invasive treatment modalities. The results of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial are, therefore, profound (100). Given a patient population with symptomatic carotid artery stenosis considered too sick for endarterectomy, those same patients fared as well as or better than the ideal carotid endarterectomy patient after carotid artery stenting. In addition, recent advances in intracranial stenting for large-vessel atherosclerosis and dissection have expanded the indications for endovascular intervention (39, 45, 50, 51).

ICU management of patients who have received a cervical or intracranial stent emphasizes vigorous monitoring of the neurological examination for any signs of postoperative neurological deficits. Early postoperative complications include hyperperfusion syndromes, reperfusion hemorrhage, and new thrombus formation (53, 58). These events will likely be pre-

ceded by a change in neurological status and necessitate immediate noninvasive diagnostic imaging (head CT scan). If a hemorrhage is diagnosed, rapid correction of coagulation abnormalities is advisable, with appropriate measures to control ICP instituted. If a hyperperfusion state is suspected, TCD ultrasonography should be performed, and appropriate blood pressure control should be instituted. A nondiagnostic CT scan or one that reveals evidence of early infarct should prompt early return to the endovascular operating room. If a proximal or distal large-vessel thrombus is present, it may be possible to pass a microcatheter around the affected area and perform gentle angioplasty. A clot-retrieval device or medical thrombolytic infusion may also be required.

EMBOLIZATION OF AN AVM

This technique is particularly useful in reducing blood flow to a sizable AVM, making it amenable to either open surgical or radiosurgical intervention. Various sources also confirm the efficacy of this modality as a terminal treatment option in up to 40% of patients (68, 90). The recent FDA approval of Onyx (Micro Therapeutics, Inc., Irvine, CA) (ethylene vinyl alcohol copolymer) may increase this percentage (22). There are, however, substantial risks associated with particulate or glue embolization of a cerebral AVM. For example, occlusion of a vascular pedicle can inadvertently result in permanent or transient ischemic damage to functional brain tissue secondary to either direct arterial occlusion or edema from the treatment. Additional risks include partial or complete occlusion of venous outflow resulting in hemorrhage, systemic embolization of glue, normal perfusion pressure breakthrough, and inadvertent gluing of the microcatheter into the vessel being occluded (32, 40, 55).

Patients who receive this treatment modality are monitored in the ICU for a 24- to 48-hour period after their procedure. If Onyx is used, interventionalists may elect to keep the patient intubated for up to 24 hours after the procedure. Any change in neurological status should be investigated (refer to the algorithm for delayed ischemic neurological deficit in vasospasm) and, as with other iatrogenic causes of ischemia, aggressive medical management (volume expansion, permissive hypertension, anticoagulation) should be pursued to help prevent permanent ischemic damage. If a hemorrhage occurs, early operative intervention consisting of clot evacuation and/or resection of the AVM should be performed (40).

TRAUMATIC VASOSPASM

The management of penetrating and closed head injury can be complicated by vasospasm. Reports in the literature estimate the incidence of vasospasm in this population at 30 to 40% (43, 81, 88, 102, 103). The natural history of traumatic vasospasm has been described (81, 102), with onset occurring as early as 2 days postinjury and continuing for up to 2 weeks. There is a tendency toward less morbidity and decreased duration compared with aneurysmal SAH, although delayed ischemic neurological deficits have been described elsewhere and seen in our own population. There seems to be a positive correlation between the severity of injury and the incidence of vasospasm. In addition, observations within this institution's wartime population indicate that vasospasm can exist remote from the actual area of injury. One current hypothesis suggests that a blast pressure wave is propagated through the tissue and that this pressure wave, in addition to the associated epidural, subdural, or SAH, may be responsible for the resulting spasm (4a).

Overall, patients with traumatic vasospasm fare worse than those without. However, the trend within neurocritical care has traditionally been to observe and document the spasm rather than intervene.

Future Treatment Strategies

There is a growing trend toward the treatment of traumatic vasospasm. The preference at our institution is to perform daily TCD measurements and a diagnostic cerebral angiogram when the Lindegaard ratio is more than 3. As with aneurysmal SAH, HHH therapy is instituted when objective evidence of vasospasm and/or delayed ischemic neurological deficit is obtained. If this treatment is ineffective, early endovascular intervention is considered and implemented if the intracranial pressure is stable. We prefer the use of IA nicardipine with subsequent progression to angioplasty rather than papavarine. Although anecdotal reports of successful, intermittent papavarine injections exist (8), the persistence of this therapy has not been proven. Our experience, consistent with that reported by Badjatia et al. (4) in the setting of aneurysmal SAH, is that IA nicardipine can safely reduce blood-flow velocities within affected vessels in a manner that persists for several days.

THE NEUROSURGICAL ICU OF THE FUTURE

As we enter the digital age, information can be obtained and communicated in ways that reduce friction and increase efficiency. This concept, applied to patient care within the neuro-ICU, results in a fusion of all forms of patient information and subsequent display in a user-friendly format. All information, from minute-to-minute patient vital signs, laboratory values, and radiological imaging can be uploaded to computerized systems via wireless networks, effectively eliminating recording error from nurses and technicians. These data can then be accessed by all neurocritical care specialists anywhere in the hospital via secure handheld devices or via uplinks onto large display monitors. This type of system may reduce the time to necessary, critical interventions. In effect, time that was previously spent digging through unorganized charts can now be spent at the patient's bedside providing focused care, resident, family, and nursing education, and accurate and timely interventions with all data readily available. The overall effect—improved patient care—will hopefully translate into improved patient outcomes.

CONCLUSION

Care of the neurovascular ICU patient is a complex undertaking. At times, rapid, decisive interventions are required in response to subtle changes in neurological status. Given the need for rapid intervention and the apparent success of endovascular interventions, it is important to maintain an ICU management strategy that incorporates these treatment modalities. Thus, neurosurgeons should be intimately involved in the ICU management of their patients. In a hospital system in which a dedicated neurosurgical ICU is present, a closed unit under the supervision of neurosurgeons and neurocritical care–trained specialists is appropriate. However, the management of these patients should not be relegated to a closed-unit system in which neurocritical care from a specialist is not available. The rate of technological advancement within the field of endovascular neurosurgery exemplifies the need for direct neurosurgical supervision of these patients within the ICU.

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ANESTHESIA FOR ENDOVASCULAR NEUROSURGERY

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ENDOVASCULAR NEUROSURGICAL PROCEDURES are complex, requiring significant planning, foresight, and coordination. The neuroanesthetist is an integral part of these procedures, organizing efforts of the technicians and nurses and responding to the needs of the neurointerventionalist. The purpose of this article is to review, in detail, the role of the neuroanesthetist in the endovascular operating room. An overview of all areas either partially or completely managed by the anesthetist is provided.

KEY WORDS: Anesthesiologist, Endovascular neurosurgeon, Neuroanesthetist, Neurointerventionalist

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Evolving practice patterns, coupled with progressively advancing technologies and results from innovative trials, such as the International Subarachnoid Aneurysm Trial and the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy, have made neuroendovascular treatments increasingly more common in the treatment of neurovascular disease. Given the rapid expansion of the role of neuroendovascular procedures, it is vital for the anesthesia provider to be keenly aware of these techniques and their potential complications in order to effectively tailor the anesthetic to both the needs of the patient and the requirements of the neurointerventionalist. With anesthetized patients undergoing neuroendovascular treatments, the anesthesiologist needs to provide safe patient transport, airway protection, patient immobility, hemodynamic control, anticoagulation management, and rapid recovery from anesthesia (*Fig. 1*). Additionally, the anesthesia teams assist the neurointerventionalist in the event of cerebral catastrophes, in addition to providing safe pre- and postprocedural transports of patients and monitoring physiological changes that may indicate ischemia.

INTERVENTIONAL NEURORADIOLOGY ROOM SETUP AND TRANSPORT

The neuroendovascular surgery/interventional neuroradiology (INR) suite is a modern operating room, and adequate space for consumable equipment, ventilation gas, suction, power, and shielding for an anesthesia team are of critical importance. An adjacent workstation allows recording, reviewing, archiving, and image measurements, which are made to ensure appropriately sized implantables. The room must have a centralized entrance and exit to avoid inadvertent entrance during a procedure. An anesthesia machine should contain a universal set of consoles that allow the anesthesia team and interventionalist to monitor physiological vitals including heart rate, blood pressure, body temperature, intracranial pressure (ICP) and, when indicated, brain tissue oxygen or cerebral oximetry. As practice expands and space becomes more limited, the roles of additional rooms become an issue. Typically, a long rectangular space centered on the angiography table becomes the model for multiple rooms. At the far end, anesthesia is set up with access to a phone, oxygen, suction outlets, and power, while the near end opens into the shielded three-dimensional rotational workstation and archiving stations. A scrub sink in this space and adequate film boards allow the interventionalist to reference earlier films during the procedure. A phone in this space and adjacent to the anesthesia is vital to the management of neurovascular emergencies and routine daily business. The suites are best placed near the intensive care unit, operating room, and, ideally, with computed tomography on the same floor. The addition of flat plate technology to newer biplanar configurations has further reduced the morbidity of transport by allowing computed tomographic scanning directly on the angiography table (35). If space, cost, and support is not an issue,

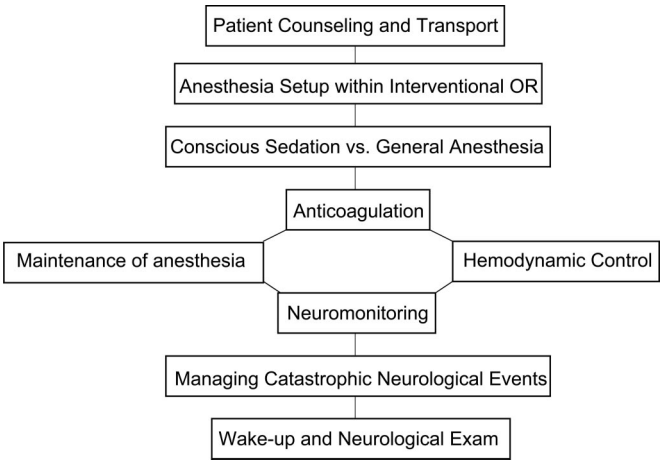

FIGURE 1. *Schematic diagram of the algorithmic approach to neuroanesthesia.* OR, *operating room.*

then the ideal operative environment would consist of a fusion of the neurosurgical operating room with a microscope, wall mounted flat panel monitors, and a biplanar floor and ceiling mount that could be centered onto a table capable of both microsurgery and radiography. The cost for such a room is difficult to justify given the low number of cases that are immediately combined with open microsurgical and neurointerventional techniques

Patient Transport

The transport of critically ill neurovascular patients within the hospital is an under-appreciated cause of morbidity and occasional mortality. Waddell (94) reported on this in 1975, noting one out of 55 deaths per month related to intrahospital transports. In evaluating a large cohort of patients transported from the neurointensive care unit, the most common reasons for transport were computed tomography (63%), angiography (12%), and the operating room (10%). In this report, 30% were unscheduled emergent transports with an average movement and study time of 1 hour with a maximum of 7 hours.

In the neurointerventional management of patients, intrahospital movement is a critical part of the patient's care. Movement of ventilated, sedated, neurocritical patients can lead to secondary insult if improperly performed. The greatest mechanism for secondary injury includes hypoxia, increased ICP, and hypotension. Referable to this review, patients are typically transported to the neurointerventional suite from the intensive care unit, emergency department, or from an outside institution. Receiving a patient directly from an outside transport team before the patient has been to the intensive care unit has an advantage of minimizing the number of transfers; however, in the majority of cases, this increases the responsibility of the anesthesia team to assess any interval changes in the patient while also establishing a baseline assessment. During the neurointerventional procedure, lines, ventriculostomy, body temperature, and endotracheal tube are all potential targets of disruption and inatrogenic injury. A ventriculostomy left open with unrestrained egress of cerebrospinal fluid (CSF) increasing the aneurysmal transmural pressure can cause aneurysm rerupture and lead to patient death. Displacement of an endotracheal tube or, more commonly, its unrecognized advancement may lead to lobar collapse and hypoxia. If patients are uncovered for prolonged periods of movement on and off the computed tomographic scanner, or to the neurointerventional suite, progressive unrecognized hypothermia may lead to difficulties throughout the procedure. Attempts to rewarm can be hampered, potentially resulting in a prolonged wake up period. Intravascular temperature regulating devices have lessened the need for surface warming or cooling techniques and may serve a larger role in the INR.

Typically, the most severely injured patients require transports as a part of their daily management, leading to the greatest potential morbidity. Contributors for such events include vasoactive drug disconnects, pulmonary artery catheter mishaps, and intravenous line infiltration. In addition, displacement of ventriculostomies, ICP monitors or femoral access lines that were not properly secured can further complicate matters. The movement of such patients on and off the neurointerventional table must take into account all of these lines and the pressure bags, intravenous pumps, and drainage chambers that accompany them. This process should resemble more of a coordinated ballet than a scramble at the scrimmage line.

CONSCIOUS SEDATION VERSUS GENERAL ANESTHESIA

When choosing an anesthetic technique, the anesthesia provider must consider the specific anesthetic needs of the patient and the impending concerns of the neuroendovascular surgeon. The absolute immobility obtained with the use of general anesthesia may not permit the necessary rapid neurological examination typically acquired with intravenous sedation. Severe patient anxiety, increased arterial carbon dioxide pressure or tension levels, and movement may complicate any sedation case and must be expected if a general anesthetic is not performed.

General patient considerations are important when selecting any anesthetic. Although most diagnostic cerebral angiograms are performed under monitored sedation, a general anesthetic approach may be appropriate for a 5′ 6″, 300 kg patient with reflux and obstructive sleep apnea. Other patient considerations include procedures on children, the patients' ability to tolerate lying supine and motionless for long periods of time, mental retardation, and gastroesophageal reflux. Headaches or burning sensations can be seen with injections of contrast dye and, due to the need for anticoagulation and the risk of problematic airway bleeding, nasal canula use is discouraged. If a monitored sedation is chosen, the selection of specific anesthetics is based on the patient, the procedure, and the anesthesiologist's personal experience. Overall, there is a trend towards a greater use of general anesthesia, especially in aneurysm and arteriovenous malformation (AVM) treatments.

However, because the neurological examination and the medical comorbidities are of paramount importance in the management of cerebral ischemic disease, the preference at most institutions is conscious sedation for carotid stent and angioplasty and thrombolysis. An effort to avoid inadvertent extubation during a rotational angiogram in which the Iso-C C-arm (Siremobil Iso-C 3D; Siemens Medical Solutions, Erlangen, Germany) rotates freely about the patient's head is required.

Fluoroscopy may be much more difficult in a non-intubated intravenous sedation case. In these cases, extension of the neck from the occiput to C2 is often needed to help keep the airway open while undergoing neuroendovascular procedures. This position is often difficult for the patient to maintain while a guide catheter and/or coaxial microcatheter are in the patient's cervical and intracranial vasculature. Movement will lead to image degradation and require repeating the contrast injection, thereby increasing the radiation dose, contrast load, and enhancing the risk of a procedurally related stroke. Attention should also be focused on ensuring that all lines, cables, and probes are cleared from the designated regions of interest and that the anesthesia team is protected from radiation with appropriate shielding.

INDUCTION AND MAINTENANCE AGENTS

Drug selection for endovascular neurosurgery should follow good general neuroanesthetic practice. Because of the considerable risk for cerebral ischemia and infarction during these procedures, the goals of agent selection should encompass analgesia, anesthesia, and cerebral protection. Those having the most stable hemodynamic profile combined with the effect of decreasing the cerebral metabolic rate are preferred. In order to quickly assess for early neurological deficits, a combination of rapid onset and rapid offset are also preferred. Agents that decrease cerebral blood flow and increase cerebral metabolic rate of oxygen can also cause systemic hypotension, thereby potentially exacerbating cerebral ischemia. Moreover, they may require prolonged periods to clear the body.

Primary Agents

All potent inhalation agents (PIAs) have adverse effects. Of primary concern is the uncoupling of the cerebral blood flow (CBF) and metabolic demand. Of these agents, N_20 and halothane are considered the worst. With respect to N_20, $CMR0_2$ is increased in addition to a disproportionate increase in CBF, which raises ICP. Halothane has the effect of reducing $CMR0_2$ by 25%, but CBF is seen as far exceeding oxygen demand by almost a 200% change. This discussion is largely academic because halothane is no longer used. As an alternative, isoflurane offers the unique feature of reducing the threshold for cerebral ischemia from 20 to 10 ml/100 g/minute. Recently, sevoflurane has gained increasing interest as a preferred agent owing to its rapid recovery when combined with nitrous oxide as compared with the standard use of propofol. In our experience, we prefer the restricted application of nitrous oxide in non-neurointerventional procedures due to the risk of air emboli expansion. In addition to the uncoupling of the cerebral blood flow and metabolic demand, a persistent postanesthestic hyperemia may remain for up to 1 hour after the use of PIA agents. Such an effect can lead to increased risk for intracranial hemorrhage, especially if the systolic blood pressure is more than 160 mmHg for two or more consecutive measurements.

Because of the unfavorable profile of most PIAs, a combination of intravenous anesthetic and neuromuscular paralysis is preferred in the neurointerventional suite. The most commonly used agents surround an amalgamation of compounds. These consist of opioids, benzodiazepines, nonopioid agents, such as propofol and etomidate, and nondepolarizing neuromuscular paralysis. The most commonly used agents for induction include a combination of etomidate (0.1–0.6 mg/kg) combined with Versed (Roche Pharmaceuticals, Nutley, NJ) (midazolam) at doses of 150–350 μg/kg. This combination allows both amnesia and anesthesia while minimizing the hemodynamic effects on mean arterial pressure, heart rate, and systemic vascular resistance (18, 36). Another induction agent, thiopental, offers a more analgesic effect, possibly blunting the sympathomimetic consequences of endotracheal intubation. Etomidate, although effective, may also increase the incidence of postoperative nausea and vomiting when compared with the use of propofol. Propofol offers a rapid onset and offset, making its use in the neurointensive care unit common (26, 44, 55, 91). Additionally, propofol, without effects on adrenocortical function, is less likely to lead to hormonal suppression when compared with etomidate.

Opioids are frequently used to supplement the main anesthetic during the maintenance phase because of their ability to provide analgesia. The rate limiting pharmokinetics of the various opioids include the mechanism for, and resulting length, of elimination. Fentanyl requires a prolonged elimination after continuous infusion when compared with sufentanil, alfentanil, and remifentanil. An example of clearance after a 4-hour infusion is typically 260, 60, 30, and 4 minutes for fentanyl, alfentanil, sufentanil and remifentanil, respectively. Typically, opioids are not used during induction due to their high dose requirements and increased skeletal muscle activity, including glottic closure, muscular rigidity of the skeletal cage, and flexion and flapping of the extremities in a seizure-like activity. Additionally, a high incidence of recall is noted with the use of opioids.

Benzodiazepines are used because of their sedative, amnestic, hypnotic, and muscle relaxant properties in the neurointensive care unit and are carried over during neurointerventional procedures in order to minimize recall and as a preinduction anxietolytic. In general, benzodiazepines reduce ICP, increase seizure threshold, and can reduce CBF at high doses. The most commonly used agents are midazolam, lorazepam, and diazepam. The rapid elimination of midazolam makes it the ideal agent for use in combination with opioids, while diazepam is reserved for pre- and postoperative anxiety secondary to its prolonged elimination time.

Additional Agents

Lidocaine is a sodium channel blocker that may also reduce ischemic cerebral injury. Lidocaine can protect neurons in the ischemic penumbra by blocking the apoptotic cell death pathways, but is not a practical agent for maintaining anesthesia (15, 52–54, 76).

Magnesium blocks both ligand and voltage-dependant calcium entry and has demonstrated to be neuroprotective against ischemia in animal models (60). Magnesium infusions in pregnant mothers seemed to neurologically protect their preterm infants (10, 80). However, the "Non-fast Magnesium" treatment trial of patients who were treated with magnesium within 12 hours of stroke has shown that magnesium is not neuroprotective and may increase mortality in some stroke patients, especially if the stroke is cortical (22, 23, 61). In addition, it does not seem to improve neurological outcome after subarachnoid hemorrhage (93).

Laboratory studies in animal models for ischemic stroke suggest that calcium channel blockers might decrease the size and severity of the ischemic cerebral infarctions (16, 47, 81). In addition, data suggested that this may also occur in humans (2). Several clinical trials suggest that calcium channel blockers nimodipine and nicardipine reduce the frequency of vasospasm subsequent to subarachnoid hemorrhage (5, 19). Radiographic vasospasm is still noted, however, and mortality is not diminished (30–32).

Dexmedetomidine, an α 2A agonist, has been observed in the laboratory to have some neuroprotective properties (56, 57). It has been shown to decrease CBF with little effect on cerebral metabolic rate, which may be due to cerebral vascular constriction (43). This vasoconstriction may not be beneficial for neuroendovascular procedures and further research is needed in this area. Dexmedetomidine can be useful in the operating room by decreasing intravenous and volatile anesthetic requirements. Dexmedetomidine can be used safely for conscious craniotomies. Upon termination of a dexmedetomidine infusion, patients remain sedated when undisturbed, but arise readily with stimulation. However, when compared with propofol in the endovascular suite, cognitive testing shows a significant diminishing of cognitive function 10 minutes after termination of infusion (7, 92). Although rapid administration of dexmedetomidine can be associated with elevated blood pressure, mild hypotension should be suspected with the use of this drug (70).

Hypothermia

It is well known that hypothermia is an efficacious technique for cerebral protection. Hypothermia reduces electrophysiological energy utilization and consumption of energy to maintain cellular integrity. Deep hypothermia used with cardio-pulmonary bypass has been associated with cerebral protection (4, 14, 34, 48, 49, 62, 63, 64, 66, 67, 95). Mild hypothermia after cardiac arrest may be mildly protective as long as patients arrive in the emergency department hypothermic. Cooling after admission to the emergency department has not been shown to improve outcome (9). In contrast to hypothermia, hyperthermia is associated with poor outcomes, therefore, increased temperatures should be avoided in patients undergoing neuroendovascular procedures (25, 29, 46, 50, 84).

The Intraoperative Hypothermia for Intracranial Aneurysm Trial compared the effect of hypothermia at 33° to a control group at 36.5° during aneurysm clipping. Results indicated that mild hypothermia was not beneficial, and the warmer patients in the hypothermia group did better than the colder patients in the hypothermia group. Postoperative mild hypothermia in head injury patients does not improve outcome and is associated with increased medical complications, especially in patients older than 45 years of age (8, 9, 58).

In general, we recommend the induction of mild hypothermia at the time of treatment of the aneurysm (coil or clip), and the duration should not exceed the timeframe associated with the occurrence of secondary neurological deficits (delayed ischemic neurological deficit secondary to vasospasm).

HEMODYNAMIC CONTROL

Tailored blood pressure control is important in the neurovascular suite. This can be complex and becomes most obvious during the embolization of an AVM, where higher blood pressure allows for distal micro-catheterization, but during the actual liquid embolic embolization for nidus penetration, lower blood pressure is required. For control of hypertension, beta-blockers, calcium channel blockers, and nitrates are often used, while adrenergic agents are administered to raise the blood pressure.

Labetalol and esmolol are the most common beta blockers used in endovascular neurosurgical procedures. Labetalol has a 7 to 1 ratio of β to α blockade. Heart rate and cardiac output are usually unchanged or only slightly depressed with a decrease in blood pressure. Labetalol preserves cerebral blood flow and autoregulation at least to a drop in mean arterial pressure by 45% (27, 69, 75, 82). Esmolol is an ultrashort acting selective B1 blocker. Rapid redistribution and an elimination half-life of 9 minutes account for its short duration of action (24). It is possible that more postoperative bradycardia is seen with labetalol when compared with esmolol. Perhaps this effect is due to labetalol's longer duration of action. Nevertheless, the preservation of CBF and autoregulation make beta-blockers ideal for first-line therapy in endovascular neurosurgical procedures.

Nicardipine may provide cerebroprotective effects by preserving cerebral autoregulation. Calcium channel blockers, in general, can also be used for blood pressure control, particularly for regulation of intraoperative hypertension during aneurysm surgery. Calcium channel blockers do not decrease local CBF or flow velocity (21, 78).

Use of hydralazine may interfere with calcium utilization and activate guanyl cyclase, causing arteriolar smooth muscle dilatation. It is also a potent cerebral vasodilator and inhibitor of CBF autoregulation. Coupled with a duration of action of 2 to 4 hours, its usefulness is limited in the endovascular suite.

Nitroglycerin and nitroprusside deliver nitric oxide to the vascular endothelial cells where guanylyl cyclase is activated and vasodilatation occurs. Nitric oxide is naturally occurring and plays an important role in regulating vascular tone and has a half-life of less than 5 seconds. Both nitroglycerin and nitroprusside dilate cerebral blood vessels and decrease the effectiveness of cerebral autoregulation. In patients with reduced intracranial compliance, if mean arterial pressure is maintained, an increase in cerebral blood volume, CBF, and ICP can be seen (13, 40, 87, 90). With the decreased autoregulation associated with nitrates, intracranial pressure and intracranial blood volume can become more pressure dependant.

α 1 agonists, such as phenylephrine, dopamine, and norepinephrine, when used to raise blood pressure, do not result in decreased CBF with an intact blood-brain barrier (68). Increased CBF has been noted with norepinephrine in an animal model, but it was also associated with an increase in cerebral metabolism due to a defective blood-brain barrier (1, 65). Dopamine probably causes a mild amount of cerebral vasodilatation without much change in cerebral metabolic rate (89). Phenylephrine is a pure α agonist that will increase blood pressure by increasing systemic vascular resistance. As with all pressors, it is important to know the patient's volume status to avoid "pressing an empty tank."

A reasonable approach for hemodyamic control during endovascular neurosurgical procedures involves the use of either a beta-blocker or calcium channel blocker where mild, slower decreases in blood pressure are desired. On the other hand, nitrates such as nitroprusside can be used for short-term and quick blood pressure reduction. If acute blood pressure elevations are required, any one of the adrenergic agonists would be appropriate.

ANTICOAGULATION

Nearly all endovascular operations are performed in conjunction with some form of anticoagulation. This section will outline medications commonly used and administered by the anesthesiologist under the direction of the endovascular neurosurgeon. To understand the drugs used for anticoagulation, a brief review of primary and secondary homeostasis is appropriate.

Review of the Coagulation Cascade

After injury to a blood vessel, exposure of the damaged endothelial surface causes platelets to change and form a platelet plug. This process of primary homeostasis is not only important in damaged blood vessels and tissue, but also when a foreign body is introduced into the cerebral circulation in the endovascular suite. The formation of a platelet plug classically follows the progression of adhesion, release of platelet granules, and aggregation. GP proteins on the platelet membranes bind the platelet to the injured tissue. GP1b then binds vWF, which causes the platelet to more firmly bind to the damaged tissue. Platelet degranulation, like that caused by collagen's interaction with phospholipase C, release numerous factors, including adenosine diphosphate (ADP), fibrinogen, vWF, and Factor V. These cause the attraction and aggregation of platelets. ADP activates GPIIb/GPIIIa, which assists in the binding of fibrinogen to activated platelets. It is here that antiplatelet drugs are most effective.

Coagulation or secondary homeostasis is responsible for the formation of a fibrin clot. The coagulation pathways are most commonly induced by tissue thromboplastin and result in strengthening of the platelet plug. Conversion of X to Xa and prothrombin to thrombin are important in secondary homeostasis. Thrombin causes the conversion of fibrinogen to fibrin. Antithrombin III, protein S, and protein C inhibit this process. Heparin works by activating antithrombin III.

A large amount of plasminogen is incorporated into a fibrin clot when it is formed. Tissue plasminogen activator causes the transformation of plasminogen to plasmin. Plasminogen is incorporated in the fibrin clot, and the change from plasminogen to plasmin causes the fibrin clot to fall apart.

Anticoagulants Associated with Endovascular Interventions

Anti-platelet Agents

Stents used in endovascular neurosurgery activate platelets through high sheer-stress stimulation of the platelet across the tines of the stent. In addition, adhesion and aggregation pathways are activated by the subendothelial matrix during angioplasty. Therefore, anti-platelet drugs are commonly used in the endovascular suite (71, 73). These include: Acuprin (aspirin; Richwood Pharmaceuticals, Florence, KY), Ticlopidine (Ticlid; Roche Pharmaceuticals, Nutley, NJ), Clopidogrel (Plavix; Bristol-Myers Squibb/Sanofi Pharmaceuticals, New York, NY), Abciximab (ReoPro; Centocor, Inc., Malvern, PA), Eptifibate (Integrilin; Cor Therapeutics, South San Francisco, CA), and Tirofiban (Aggrastat; Merck, West Point, PA). Aspirin, clopidogrel, or ticlopidine are recommended to be used 3 to 4 days before the planned endovascular procedure.

Aspirin irreversibly binds to cyclooxygenase, which results in inhibition of both thromboxane A2 and prostacyclin. Clopidogrel and Ticlopidine are thienopyridine derivatives. Unlike aspirin, thienopyridine platelet-aggregation inhibitors, such as clopidogrel and ticlopidine, do not inactivate platelet cyclooxygenase to prevent synthesis of prostaglandin, endoperoxides, and thromboxane A. Clopidogrel and Ticlopidine are both ADP-receptor antagonists. They bind selectively and noncompetitively to a low-affinity, ADP-receptor binding site on the surface of platelets, thereby inhibiting ADP binding to the receptor and subsequent activation of the platelet glycoprotein (GP IIb/IIIa) complex necessary for fibrinogen-platelet binding. Platelets exposed to clopidogrel remain affected for the remainder of their lifespan (about 7 d). Ticlopidine use is associated with rash, urticaria, and life threatening neutropenia. Clopidogrel is better tolerated with a safer side effect profile.

In endovascular neurosurgical cases in which immediate platelet plugs develop, the glycoprotein IIb/IIIa inhibitors can be given both intra-arterially and intravenously. Direct intra-arterial delivery permits delivery of the GPIIb/IIIa inhibitor directly to the site of the platelet plug that might occur during aneurysm coiling and intracranial stent deployment. Abciximab binds selectively to platelet glycoprotein (GP IIb/IIIa) receptors and inhibits platelet aggregation. Abciximab also binds to the vitronectin receptor located on platelets and vascular endothelial and smooth muscle cells. Eptifibatide and Tirofiban (Aggrastat; Merck, West Point, PA) are also selective platelet-aggregation inhibitors. In the cardiac catheter lab, Abciximab, when used with aspirin and heparin, has demonstrated efficacy in numerous studies in reducing the short- and long-term risk of ischemic complications in patients with ischemic heart disease undergoing percutaneous coronary intervention. In the Evaluation of IIb/IIIa Platelet Inhibitor for STENTing trial (Abciximab), the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy study (eptifibatide), and in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial (tirofiban) GPIIb/IIIa inhibitors showed significant decrease in incidence of death or nonfatal myocardial infarction after percutaneous coronary intervention (38, 39, 41, 45, 59, 72). In one study, Abciximab bolus given prophylactically before elective carotid artery stenting did not reduce ischemic complications (34). Severe thrombocytopenia can be seen with Abciximab and its concurrent use with dextran is highly discouraged.

The occurrence of fatal intracerebral hemorrhage associated with using a combination of antithrombotic agents, including Abciximab, in patients undergoing neurointerventional procedures has been reported. Qureshi et al. (73, 75) published reports of seven patients (average age, 60; range, 46–73 yr) who developed fatal intracerebral hemorrhages associated with neurointerventional procedures. The procedures included angioplasty and stent placement in the cervical internal carotid artery (n = 4), angioplasty of the intracranial internal carotid artery (n = 1), and angioplasty of the middle cerebral artery (n = 2). Clinical deterioration was observed within 1 hour of the procedure in five patients and 7 and 8 hours after the procedure, respectively, in the remaining two patients. All patients had received heparin and clopidogrel; six also had received aspirin (42, 74).

For reversal of life threatening bleeding of patients treated with GPIIb/IIIa inhibitors, platelet transfusions are needed. In addition, eptibatdie and triofiban are competitive inhibitors for the platelet receptor, and fresh frozen plasma transfusions or even plasmaphoresis could be required to reverse these drugs.

Anticoagulants

Unfractionated heparin is the most common anticoagulant used in the interventional suite. Heparin acts as a catalyst to markedly accelerate the rate at which antithrombin III (heparin cofactor) neutralizes thrombin and activated coagulation Factor X (Xa). Antithrombin III generally neutralizes these coagulation factors by slowly and irreversibly complexing stoichiometrically with them; however, in the presence of heparin, it neutralizes these factors almost instantaneously. Heparin apparently binds to antithrombin III and induces a conformational change in the molecule, which promotes its interaction with thrombin and Xa. In the presence of heparin, antithrombin III also neutralizes activated coagulation Factors IX, XI, XII, and plasmin. Loading doses of 75μ/kg of heparin are loaded with the goal of maintaining an activated clotting time (ACT) of about twice of the baseline. Avoiding an ACT of more than 300 is import, especially in patients on GPIIb/IIIa inhibitors undergoing endovascular neurosurgical procedures.

Acute intracranial hemorrhage can be seen in patients on heparin as an anticoagulant and immediate reversal of heparin-induced anticoagulation in these patients would be indicated (17, 28, 51, 79). Protamine is strongly basic, acts as a heparin antagonist in vitro and in vivo by complexing with strongly acidic heparin to form a stable salt. Generally, 1 mg of protamine sulfate will neutralize no less than 100 units of heparin sodium. Because blood heparin concentrations decrease rapidly after heparin is administered intravenously, the dose of protamine sulfate required to reverse also decreases rapidly as time elapses. If only a few minutes have elapsed since heparin was administered intravenously, 1 to 1.5 mg of protamine sulfate should be given for every 100 units of heparin administered. If 30 minutes have elapsed since intravenous injection of heparin, 0.5 mg of protamine sulfate should be given for every 100 units of heparin, and if 2 hours or more have elapsed since intravenous injection of heparin, 0.25 to 0.375 mg of protamine sulfate should be given for every 100 units of heparin administered. Protamine sulfate is usually administered slowly by intravenous injection during a 10-minute period. However, protamine may need to be administered quickly in the endovascular suite, as immediate reversal of heparin may be needed during acute intracranial bleeding emergencies.

Reversible thrombocytopenia has been reported with heparin. It may be a direct effect of the heparin on the platelets or secondary to a circulating antibody. It should be termed *heparin-induced platelet activation* and thrombotic complications are seen in approximately 20% of patients with heparin-induced thrombocytopenia. Thrombocytopenia, if it occurs, usually develops within 1 to 20 days and occurs more frequently with heparin prepared from bovine lung tissue. Etiologies include a direct non-immunological effect on circulating platelets or the presence of a heparin-dependent IgG platelet-aggregating antibody. Heparin should generally be discontinued if significant thrombocytopenia (platelet count less than 100,000/mm^3) occurs. Patients with heparin-induced thrombocytopenia typically display skin lesions that are painful red plaques and frank skin necrosis simulating Coumadin (DuPont Pharmaceuticals, Wilmington, DE) induced skin lesions (11, 12, 20, 86). Patients who have heparin-induced thrombocytopenia and need anticoagulation can be treated

with hirudin or Argatroban (Glaxosmithkline, Research Triangle Park, NC).

Hirudin is the polypeptide that is responsible for the anticoagulant properties of the saliva of the medicinal leech (*Hirudo medicinalis*). Bivalirudin is a synthetic 20-amino acid peptide analog of naturally occurring hirudin. These drugs are direct thrombin inhibitors that bind to circulating and clot-bound thrombin. Inhibition of thrombin prevents various steps in the coagulation process (e.g., activation of Factors V, VIII, and XIII; conversion of fibrinogen to fibrin; platelet activation and aggregation). These effects are reversed as thrombin slowly cleaves the bivalirudin-Arg3-Pro4 bond, resulting in recovery of thrombin active site function. Note that this cleavage allows for shorter acting anticoagulation reversible in 25 minutes in patients with normal renal function. The onset of anticoagulant effect is immediate following direct intravenous injection of bivalirudin. Bivalirudin has been used intra-arterially for clot lysis (24). Coagulation times return to the normal range approximately 1 to 2 hours after discontinuance of the drug.

Thrombolytics

Thrombolytics used in the neuroendovascular suite include urokinase (Abbokinase; Abbott Laboratories, Abbott Park, IL) and (Activase; Genentech, South San Francisco, CA), and alteplase recombinant tissue plasminogen activator [tPA]; Genetech, San Francisco, CA) (3, 33, 88). tPA and other plasminogen activators, such as streptokinase and urokinase (urinary-type plasminogen activator), promote thrombolysis by hydrolyzing the arginine560-valine561 peptide bond in plasminogen to form the active proteolytic enzyme plasmin. Plasmin is a relatively nonspecific serine protease that is capable of degrading fibrin, fibrinogen, and other procoagulant proteins. More than 50% of tPA is cleared from plasma within 5 minutes after discontinuance of an intravenous infusion of alteplase, and approximately 80% is cleared within 10 minutes. Recently, urokinase has returned on the market, and its availability has been improved with prepackaged vials avoiding tedious and time-consuming mixing. Urokinase is preferentially administered through an intra-arterial microcatheter injection with doses of 50k units/vial. Doses can reach up to 2 million units for venous sinus thrombosis (off-label use). tPA (recombinant type alteplase) has been used for both intravenous and intra-arterial use. The short 2- to 5-minute half-life of alteplase has necessitated the development of additional longer half-life forms of this medication. An example, Reteplase (Centocor, Inc., Malvern, PA), has a half-life of 16 to 18 minutes that limits its intracranial utility. Hemorrhagic complications are seen with doses of more than 25 mg, prolonged timing from onset of stroke symptoms, and if more than one-third of the middle cerebral artery distribution is infracted. Trials have included a divided dose with two-thirds given intravenously and one-third given intra-arterially as a bridging protocol to begin therapy as the cerebral angiogram is underway (6, 72, 77, 83, 85).

One study group examined the feasibility of combined intravenous and intra-arterial thrombolytic therapy for acute ischemic strokes with intravenous treatment followed by intra-arterial infusion (83). They used intra-arterially administered urokinase (up to 750,000 units) or intra-arterially administered recombinant tissue plasminogen activator (maximal dose, 0.3 mg/kg) to achieve recanalization. They treated 45 patients with this protocol. There was a significant improvement in National Institutes of Health Stroke Scale scores after treatment. There was also a positive correlation between abnormal perfusion-weighted imaging findings and cerebral angiographic findings (complete vessel occlusion). The incidence of symptomatic intracranial hemorrhage was 4.4% in this cohort. Seven patients died in the hospital, and the majority of survivors (77%) experienced good outcomes (83).

ANESTHESIA AND NEUROMONITORING

In the ideal setting, one would have a perfectly immobile, cooperative patient who was awake and apneic during angiography runs. During prolonged, delicate neuroendovascular procedure, this is not only unlikely, but also dangerous. Monitoring for parent vessel occlusion, distal emboli, or vessel *en passage* is performed by the neurointerventionalist. The use of electrophysiological monitoring during these procedures varies greatly between institutions and depends on the local monitoring availability. The ability to detect and intervene before irreversible injury is what makes neuromonitoring critical and a vital element in the neuroprotection mission. When neuromonitoring is required, the anesthesiologist must be cognizant of the effects of various agents on the monitoring parameters.

The scenarios in which it is vital include procedures involving the use of test balloon occlusion (posterior circulation in particular), motor strip arteriovenous malformations, and spinal cord malformations. In addition to the neuroangioarchitecture, the vessel interrogated can be selectively injected and evaluated with sodium Amytal (Eli Lilly and Co., Indianapolis, IN) or sodium thiopental. However, such evaluations are not without risks and may lead to artery dissection or vasospasm and mixed results.

MANAGING CATASTROPHIC NEUROLOGICAL EVENTS

Catastrophic neurological events should be anticipated in the neurointerventional suite (*Fig. 2*). Preparation for such events involves coordinating with neurosurgery, the operating room, and the intensive care units prior to the case and having protamine, thrombolytics, and a ventriculostomy kit readily available in the room. Appropriate anesthetic responses to such catastrophes depend on the identification of an occlusive or hemorrhagic insult. In cases in which a thromboembolic event has occurred, the interventionalist must recognize that the normal distal vessels are no longer filling. This must immediately be communicated to the anesthesia team so preparation can be made to augment the cerebral blood flow

Endovascular Catastrophes

Diagnosis	Complications
Aneurysm	Rupture Occlusion
Arterial Venous Malformation	Premature Venous Occlusion Rupture
Thrombolytic Stroke	Intracranial Hemorrhage Vessel Occlusion
Tumor	Distal Embolization
Atherosclerotic Disease - Carotid - Intracranial	Distal Embolus Cardiac Arrhythmias Intracranial Hemorrhage

FIGURE 2. *Schematic diagram of the typical endovascular diagnoses and their complications.*

and thrombolysis the clot. At this point, the decision to medically or mechanically thrombolyse depends on the status of the aneurysm and location of the clot. In cases in which the clot is significant, the interventionalist will coordinate with the anesthesiologist for the administration of the intravenous thrombolytic agent in order to balance the intra-arterial agent administered via the microcatheter. In the most common cases, the glycoprotein llb/llla inhibitor abciximab is given as a divided bolus in doses of 20% intra-arterially and 80% intravenously. In order to avoid an intracranial hemorrhage, the ACT should be less than 250, and the blood pressure should be regulated to avoid hyperperfusion post-thrombolysis.

In hemorrhagic insults resulting from an aneurysm rupture, several therapies can be implemented. The interventionalist should attempt to immediately occlude the aneurysm using a coil or balloon if remodeling is being attempted. Simultaneously, the anesthesiologist should stop any intravenous anticoagulation drips, reverse the anticoagulation with protamine, check an ACT, which should be less than 200 after reversal, call radiology for an emergency computed tomographic scan, contact the operating room, and if not already in the room, call neurosurgery. If possible, endosaccular occlusion of the aneurysm is the first priority by the interventionalist followed by or concomitant with placement of a ventriculostomy. An immediate computed tomographic scan of the head should then be performed and subsequent need for surgical intervention determined.

Delayed ischemic events postneurointerventional procedures are perhaps more common than intraprocedural rupture and can be related to multiple causes. One such cause may be retrograde thrombosis post-AVM embolization, platelet plug at a coil or stent interface, or an unrecognized dissection or plaque that can create delayed emboli. The immediate return to the neurointerventional suite after a hemorrhage is a mandatory requirement. The sooner control angiography can be performed, the more rapidly therapeutic intervention and possible reversal of any insult can be initiated. In many of these cases, if the patient is awake and alert, performing the diagnostic portion of the procedure first may identify a lesion that can be corrected while the patient can be examined. Critical parameters are maintaining cerebral perfusion pressure and close monitoring of heparin as both can lead to a reperfusion hemorrhage if poorly regulated.

In patients who present to the neurointerventional suite with aneurysmal-SAH and hydrocephalus, a ventriculostomy should be placed, confirmed to be functionally operative, and secured prior to endosaccular coiling of an aneurysm. Placement of a ventriculostomy when a patient has just been anticoagulated is highly discouraged. Symptomatic postventriculostomy hemorrhage can be prevented when performed prior to the anticoagulation. Delayed hydrocephalus can confuse the clinical picture, spiraling into progressive neurological deterioration, exacerbating the effects of subclinical vasospasm, and can result in increased permanent morbidity and death. This case is illustrated in *Figure 2*.

CONCLUSION

Coordinated anesthesia support is a critical element to the neurointerventional operating room. The six elements of such care include patient transport and setup, airway protection, hemodynamic control, anticoagulation management, neuroprotection, rapid onset and offset of anesthesia, allowing rapid patient examination at the completion of the procedure. The use of neurophysiologic monitoring combined with monitoring of cerebral oxygen either directly, via brain tissue oxygen, or indirectly, via cerebral oximetry, allows the neuroanesthetist to provide an early warning system of impending danger. Evolving neurointerventional techniques must be practiced in an environment that provides maximum patient protection.

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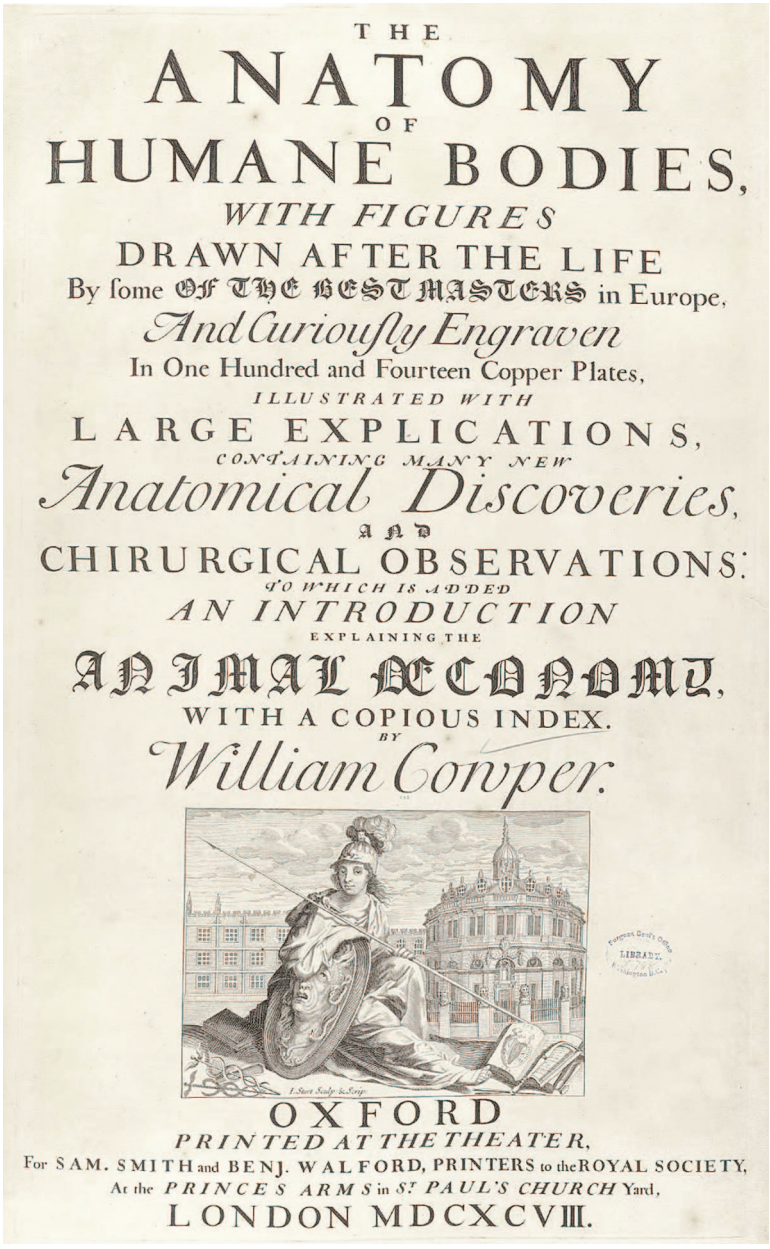
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RECENT STEPS TOWARD A RECONSTRUCTIVE ENDOVASCULAR SOLUTION FOR THE ORPHANED, COMPLEX-NECK ANEURYSM

OBJECTIVE: The purposes of this article are to summarize recent developments and concerns in endovascular aneurysm therapy leading to the adjunctive use of endoluminal devices, to review the published literature on stent-supported coil embolization of cerebral aneurysms, and to describe our experience with this technique in a limited subgroup of problematic complex aneurysms over a medium-term follow-up period.

METHODS: Between January 2003 and June 2004, 28 individuals among 157 patients with cerebral aneurysms we evaluated were identified as harboring aneurysms with exceptionally broad necks. Out of these 28 patients, 16 were treated with a combination of stents and detachable coils, preserving the parent artery. Recorded data included patient demographics, the clinical presentation, aneurysm location and characteristics, procedural details, and clinical and angiographic outcome.

RESULTS: Over an 18-month period, 16 patients with large cerebral aneurysms additionally characterized by neck sizes between 7 and 14 mm were treated, using combined coil embolization of the aneurysm with stent reconstruction of the aneurysm neck. Thirteen out of the 16 aneurysms were occluded at angiographic reevaluation between 11 and 24 months (mean angiographic follow-up, 17.5 mo). There were no treatment-related deaths or clinically evident neurological complications. Thirteen patients experienced excellent clinical outcomes, with good outcomes in two patients and a poor visual outcome in one patient (mean clinical follow-up, 29 mo). A single technical complication occurred, involving transient nonocclusive stent-associated thrombus, which was treated uneventfully with abciximab.

CONCLUSION: Stent-supported coil embolization of large, complex-neck cerebral aneurysms seems to provide superior medium-term anatomic reconstruction of the parent artery compared with historic series of aneurysms treated exclusively with endosaccular coils. In the near future, increasingly sophisticated endoluminal devices offering higher coverage of the neck defect will likely enable more definitive endovascular treatment of complex cerebral aneurysms and further expand our ability to manipulate the vascular biology of the parent artery.

KEY WORDS: Cerebral aneurysms, Endovascular treatment, Guglielmi detachable coil, Neuroform, Stents

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During the past 15 years, the endovascular treatment of cerebral aneurysms has been defined primarily by an endosaccular approach using assorted metallic coils engineered for controlled deployment and safe conformability within the aneurysmal sac. The first of these endosaccular platforms, the Guglielmi detachable coil (GDC), included a menu of preshaped aneurysm coils, each incorporating a thinly wound platinum wire affixed proximally to an insulated stainless steel mandrel through an electrolytically susceptible junction (15, 16). The GDC was distributed for clinical trial to limited centers in 1991 and received approval by the United States Food and Drug Administration for treatment of patients with surgically unmanageable aneurysms in 1995. After the publication of results from the International Subarachnoid Aneurysm Trial (41), the recommended indications were liberalized in

2003 to permit its use more broadly in select patients with ruptured cerebral aneurysms. Nevertheless, despite encouraging results from the International Subarachnoid Aneurysm Trial, which validated the usefulness of GDC in the treatment of ruptured cerebral aneurysms, and other case series supporting the effectiveness of coil embolization in unruptured aneurysms (21), the surprisingly low reported frequencies of upfront aneurysm occlusion (11, 18, 26, 43) and the prevalence of posttreatment recurrences (11, 18, 26, 37, 43, 50) among coil-treated aneurysms have surfaced as serious obstacles to the widespread acceptance of reconstructive endosaccular treatment as the definitive therapy, particularly (and paradoxically) in the large, complex aneurysms for which the treatment was initially indicated.

RECANALIZATION OF COIL-TREATED ANEURYSMS

Aneurysm recurrence after coiling has generally been thought to proceed through two mechanisms: 1) recanalization (acute or delayed) of the coiled aneurysm fundus, resulting from an underlying instability of the intra-aneurysmal coil–thrombus complex; and/or 2) progressive absolute aneurysm growth from either an unsecured niche of an incompletely coiled aneurysm or an intrinsic (initially occult) deficiency in the wall of the perianeurysmal parent artery.

The extent of the problem, first suggested in early reports (11), has received renewed scrutiny in recently published longitudinal studies. Raymond et al. (50), in a retrospective analysis of data collected from 466 patients with 501 aneurysms, observed a strong correlation between aneurysm dimensions and neck size and the prevalence of posttreatment recurrence. Among 383 patients with follow-up angiograms, recurrence defined as major by the authors was found in 20.7% of these patients (at a mean angiographic follow-up period of 17 mo). When analyzed by aneurysm morphology, recurrence (of all degrees) was observed in 50.6% of large aneurysms compared with 21.3% of small aneurysms (<10 mm) and 52.3% of wide-neck aneurysms (>4 mm) versus 23.7% of aneurysms with small neck size.

In terms of the proximate postcoiling outcome, Kole et al. (26) retrospectively analyzing results from 163 aneurysms in 160 consecutive patients treated between 1995 and 2003, found large remnants in 27% of aneurysms immediately postcoiling, suggesting an inherent technical limitation with the initial endosaccular coil treatment of certain complex aneurysm subtypes. The same authors additionally reported an increased remnant size in 19.1% out of 131 patients at a mean angiographic follow-up period of 18.2 months; 14.5% of these patients required aneurysm recoiling. This last statistic is of interest in that two deaths occurred among the 19 patients undergoing retreatment, illustrating an often-ignored source of risk to which patients with unresolved aneurysms are exposed.

Ironically, our perception of incomplete treatment or aneurysm recurrence after endosaccular coil therapy has been partly obfuscated by the rapid evolution and assimilation of new coil technologies (three-dimensional coils, polymer- and hydrogel-coated coils, and ultrasoft coils) (9, 10, 22, 44), liquid embolic agents (38, 40, 45, 51), and adjunctive techniques (balloon remodeling [28, 42, 46]), each purported to improve treatment efficacy, whether or not these new innovations actually contribute to a more secure endovascular outcome. In a provocative study examining the impact of endovascular advancements during the decade after the introduction of the GDC, Murayama et al. (43) reported results from 11 years of experience in 818 patients treated at the University of California, Los Angeles. Analyses of treatment outcomes were stratified by aneurysm morphology and date of treatment. Angiographic results from those who were treated in the first half of the decade (1990–1995) were compared with those from the second half (1996–2002), after modified specialty coils and newer adjunctive techniques had become available. The early group comprised 230 patients harboring 251 aneurysms, and the more recently treated group represented 588 patients harboring 665 aneurysms. Forty-nine percent (49.4%) of the patients presented with acute subarachnoid hemorrhage (SAH), and 41.8% had unruptured aneurysms. Angiographic follow-up ranged from 3 months to 8 years (mean, 11 mo). Ironically, despite the intervening improvements in devices and technique, recurrence rates among the larger aneurysm subgroups treated since 1996 (37.7%, large; 52.9%, giant) were not statistically different from results experienced in the first half decade (33.3%, large; 63%, giant). Furthermore, recurrences were also found in 18.2% of small wide-neck aneurysms for the years 1996 to 2002. These results, unfortunately, did not capture the effects of more recent innovations designed to improve volumetric packing of the aneurysm sac (with hydrogel-coated coils or liquid embolic agents) or to increase the effectiveness of the coil mass in promoting maturation of the intra-aneurysmal thrombus (with bioactive coatings). However, subsequently publicized, unpublished results from the Microvention-sponsored HEAL (AANS-CNS Joint Section, unpublished data) and Boston Scientific–sponsored MATRIX-ACTIVE (American Society of Neuroradiology, unpublished data) trials, in addition to early published reports of clinical experience with polyglycolic acid/lactide copolymer–coated coils (22), have been less than wholly reassuring, implicating a potential deficiency in coil-dependent endosaccular approaches to the treatment of these aneurysm subtypes, at least in terms of achieving a stable anatomic result. Additionally, early experience in the MATRIX Registry seemed to confirm the fundamental importance of the aneurysmal coil mass (the density and completeness of coil packing) and, by implication, its effect on intra-aneurysmal blood flow to the ultimate recanalization outcome, underscoring the importance of a stable hemostatic environment to enable the bioinducible potential of the polyglycolic acid/lactide copolymer–coated jacket.

CONDITIONS FAVORING SUCCESSFUL ENDOVASCULAR ANEURYSM TREATMENT

Three conditions are necessary for durable endosaccular occlusion of cerebral aneurysms with coils: 1) effective hemostasis must be established throughout the aneurysm and sus-

tained over some critical interval; 2) the thrombus formed within the aneurysm as a result of coil-induced intra-aneurysmal hemostasis must mature during this critical interval (ideally undergoing organization into a fibrointimal scar), and 3) the uniformity and stability of the coil–thrombus complex at the aneurysm base must be biomechanically sufficient to support neointimal overgrowth of the aneurysm neck defect.

Although these requirements are usually satisfied during endosaccular coiling of the idealized small-neck aneurysm (favorable neck:fundus ratio), reconstruction of the larger aneurysm neck (which, in certain dysplastic aneurysms, encompass >180 degrees of the cross-sectional vessel surface) (*Fig. 1*) is more technically challenging and frequently confounded by inadequate coiling of the aneurysm base. This has led to the adoption of adjunctive methods, such as balloon remodeling and the complementary use of endoluminal devices for more robust reconstruction of the neck defect in such aneurysms (4, 13, 27, 39, 42, 46, 58, 62, 64).

THE EMERGENCE OF ADJUNCTIVE STENT-SUPPORTED COIL EMBOLIZATION OF CEREBRAL ANEURYSMS

The rationale for adjunctive stenting in the treatment of wide-neck cerebral aneurysms relies on three effects: 1) the uncoupling of momentum exchange between the parent artery and aneurysm. This effect enhances the flow-disruptive influence of the intra-aneurysmal coil mass, diminishing intra-aneurysmal flow and increasing the mean circulation time through the aneurysm fundus (3, 8, 29, 30). The net effect is the induction of more profound hemostasis within the aneurysm, contributing hypothetically to intra-aneurysmal conditions in

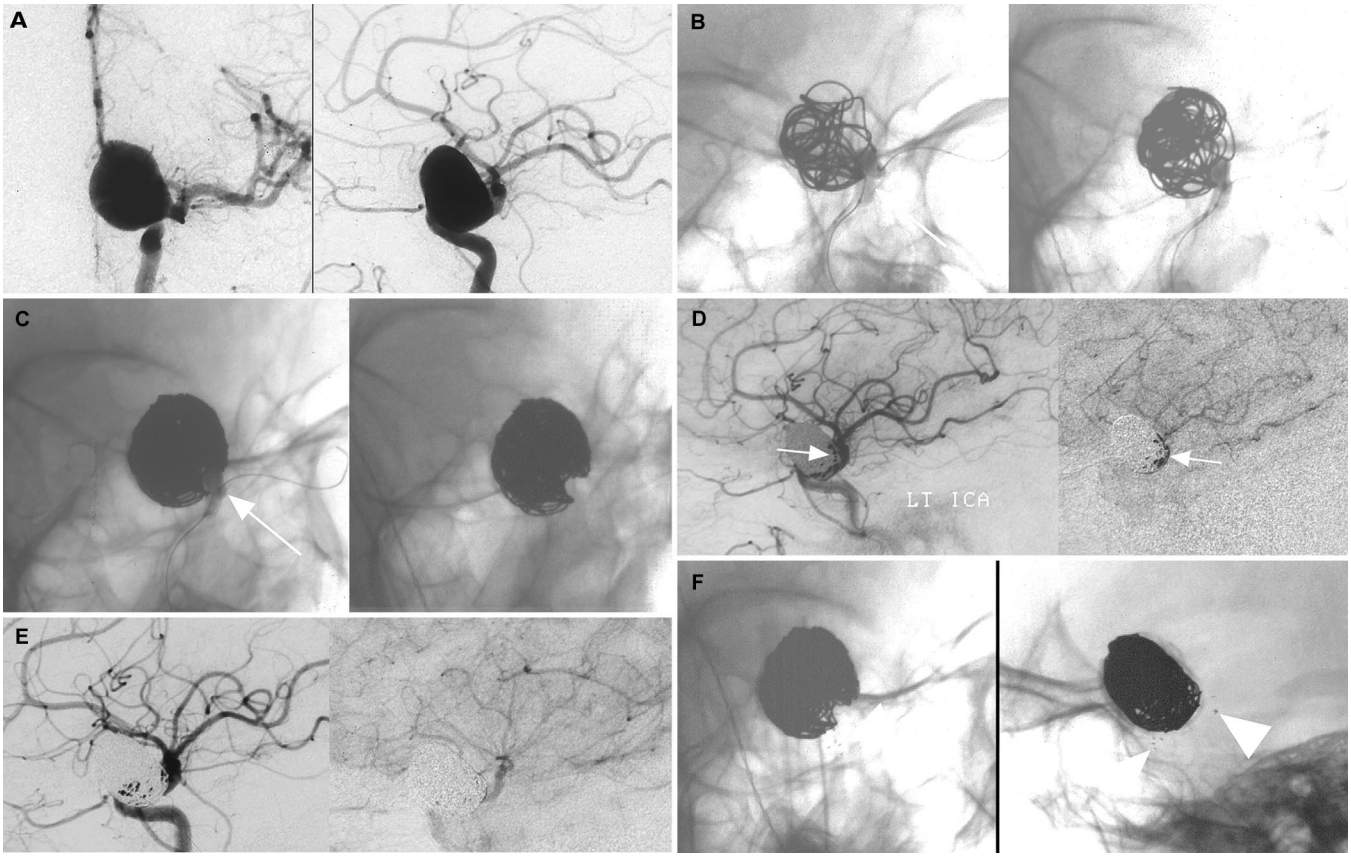

FIGURE 1. A, *frontal and lateral arterial phase images from a left–internal carotid artery (ICA) angiogram depicting a large calcified ophthalmic–segment aneurysm. The aneurysm was coiled under balloon remodeling (4 × 20 mm balloon), after which a single 4.5 × 20 mm Neuroform (Boston Scientific, Fremont, CA) stent was placed.* B *and* C, *sequential images of the inflated balloon (*large arrows*) during coil embolization demonstrates the extent of cross-sectional radial involvement of the parent artery.* D, *immediate posttreatment angiography (middle and late arterial phase images) illustrating persistent opacification through coilinterstices inter stices at the neck and posterior fundus (*small white arrows*), which is no longer evident at the time of the study, that is, 23 months posttreatment* (E). *Frontal oblique and lateral unsubtracted cranial images* (F) *suggest stable arrangement of the coil mass at the aneurysm neck and fundus despite probable persistent opacification through neck-region coil interstices that could not be distinguished from the overlapping carotid artery segment on any projection (note the rim of calcification, which defines the aneurysm margin that is particularly evident in the lateral image).* White arrowheads *identify the stent markers.*

which recanalization is less likely. 2) The subintimal incorporation of the stent into the parent vessel wall. The mural integration of the stent into the parent artery (*Fig. 2*) modifies the viscoelastic properties of the perianeurysmal vascular segment, reinforcing the parent artery at the neck margins and potentially reducing the likelihood of recurrent aneurysm growth from the neck region. 3) Neck-bridging barrier effects, which create a structural boundary across the aneurysm neck. The stent-imposed scaffolding facilitates more complete endosaccular treatment and, together with neck-region coils, provides a more organized substrate to support neointimal growth over the aneurysm neck.

Although early experience with stent-supported coil endosaccular treatment of wide-neck aneurysms has been promising (4, 13, 35), long-term angiographic evaluation of the synergy expected from such combined endovascular therapy is lacking. Examination of the existing literature on the topic reveals significant variation in the reporting of outcome milestones and imaging follow-up. Furthermore, large- (28%) and giant-size (7%) aneurysms collectively account for a minority of the wide-neck aneurysms treated with adjunctive stenting at 21 centers identified in our literature search (1, 2, 4, 6, 13, 17, 19, 20, 23, 25–27, 31, 33, 34, 36, 48, 52, 53, 60, 63).

The purposes of this communication are to review historic concerns with the direct endosaccular management of complex cerebral aneurysms that have led to the emergence of adjunctive stent-supported techniques, to review the published literature, and to report our experience with the use of stents to support endosaccular treatment of a select cohort of patients harboring larger aneurysms with exceptionally wide necks. The anatomic stability of this combined endoluminal–endosaccular approach was assessed over medium-term angiographic and clinical follow-up.

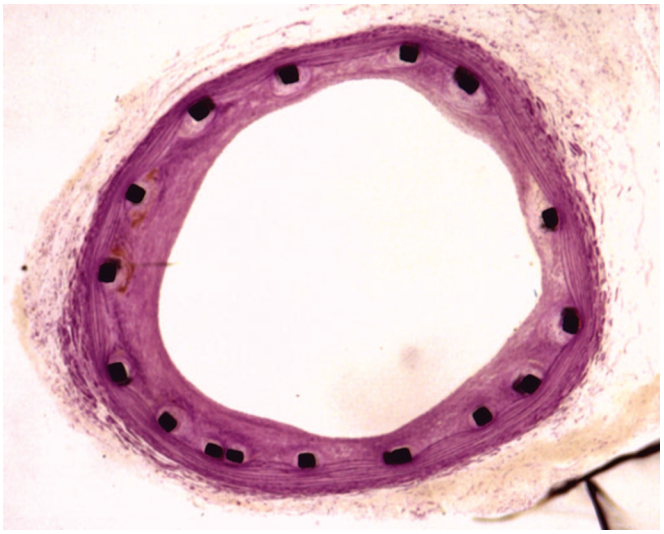

FIGURE 2. *Histological specimen demonstrating subintimal incorporation of a Neuroform stent within a rabbit subclavian artery 3 months after implantation (courtesy of SMART Therapeutics, San Leandro, CA).*

PATIENTS AND METHODS

Between January 2003 and June 2004, we evaluated 157 patients with cerebral aneurysms. Twenty-eight of these patients were found to harbor 29 aneurysms with exceptionally complex necks, which were defined as having a dimension of 7 mm or more along the length of the parent vessel. Six of these aneurysms were treated by direct microsurgical repair, six were managed deconstructively by parent vessel occlusion (three of these with combined surgical–endovascular procedures), one aneurysm was treated by stent alone, and 16 were treated with Neuroform (Boston Scientific, Fremont, CA) supported endosaccular coiling. Of the patients undergoing stent-supported coil reconstruction, six aneurysms exhibited a neck size of more than 10 mm in linear length along the parent vessel (*Figs. 1, 3,* and *4*), with the remaining nine patients harboring aneurysms with neck sizes between 7 and 10 mm. Three patients had additional small aneurysms, one with a small anterior communicating artery aneurysm, the second with a previously treated left–ophthalmic segment aneurysm, and the third patient with a small contralateral cavernous segment aneurysm. Patients comprising this cohort were entered consecutively into an internal aneurysm database and followed prospectively with respect to angiographic and clinical outcomes.

Individually, the patients referred for stent-supported endovascular treatment had been judged by our cerebrovascular working group to be suboptimal candidates for direct operative (microsurgical) or conventional endovascular management because of composite features of the aneurysm, such as size, degree of calcification, neck complexity and location, patient age, or medical condition, or because they had failed previous coiling or surgical attempts at treatment. Patients ranged in age from 31 to 78 years. Of the 16 patients undergoing Neuroform-supported coil treatment of their aneurysm, one presented with subarachnoid hemorrhage (*Fig. 3*); two with transient ischemic attacks in the vascular territory subserved by the aneurysm; one with residual brainstem symptoms (nystagmus, hemifacial paresthesias, and mild contralateral hemiparesis) (*Fig. 4*) after an episode of acute severe headache, diplopia, and transient hemiplegia three months earlier; five with diplopia ranging in duration from 1 to 12 weeks at the time of treatment; and two with monocular visual field defects related to optic nerve compression of 2 months and 1 year duration, respectively. Five were incidentally discovered during work-up of headache. Direct coil embolization had been unsuccessfully attempted in two patients (one also undergoing prior craniotomy with unsuccessful attempted surgical treatment), and coil treatment had been performed twice in two additional patients with significant recurrences observed in each after both efforts.

All therapeutic procedures were conducted under general anesthesia. Cerebral angiography was performed to evaluate morphological features of the aneurysm and parent vessel and to establish the optimal visual working projec-

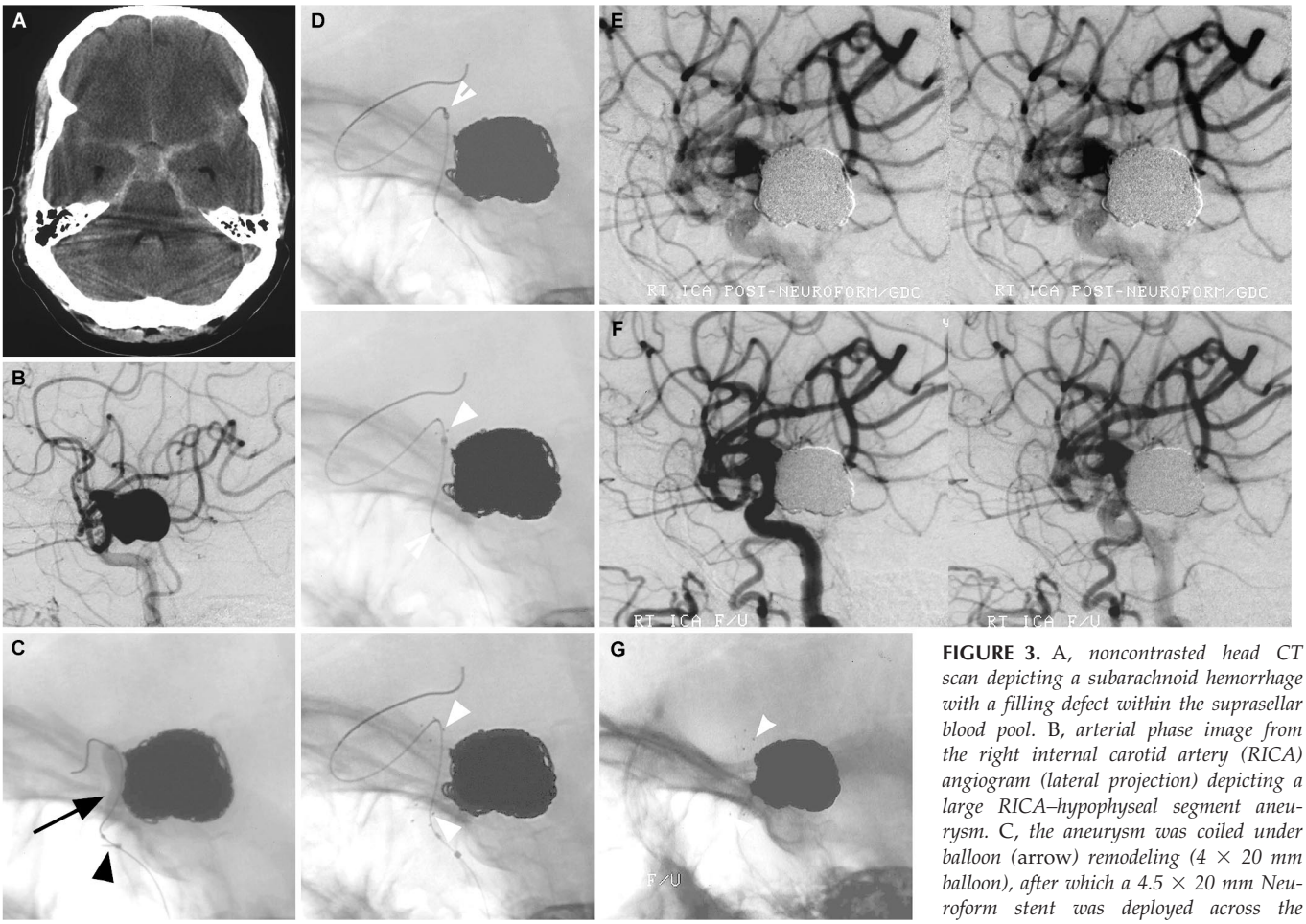

FIGURE 3. A, *noncontrasted head CT scan depicting a subarachnoid hemorrhage with a filling defect within the suprasellar blood pool.* B, *arterial phase image from the right internal carotid artery (RICA) angiogram (lateral projection) depicting a large RICA–hypophyseal segment aneurysm.* C, *the aneurysm was coiled under balloon* (arrow) *remodeling (4 × 20 mm balloon), after which a 4.5 × 20 mm Neuroform stent was deployed across the aneurysm neck.* D, *three sequential unsubtracted images during unsheathing of the loaded stent. Immediate* (E) *and 1-year* (F) *posttreatment angiographies (RICA lateral oblique working projections) confirmed stable occlusion of the aneurysm.* G, *unsubtracted image of the stent and aneurysm coils at 1-year follow-up.* Black arrowhead, *detachment marker for GDC mandrel;* white arrowheads, *deployed stent markers;* striped white arrowhead, *stent marker bands constrained within delivery microcatheter during deployment.*

tions for coil occlusion of the aneurysm. In 13 patients, one or two Neuroform stents were deployed across the aneurysm neck after the aneurysm was first coiled under balloon remodeling (12 immediately, one delayed) (*Figs. 1*, *3*, and *4*). The stent was placed before coiling in three patients, each with aneurysm neck sizes of 7 to 8 mm. Placement of a Neuroform stent alone as monotherapy was used for flow diversion in a single patient with a large aneurysm involving the midbasilar segment and further complicated by a dysplastic left anteroinferior cerebellar artery arising from the aneurysm dome (excluded from this analysis because of the absence of aneurysm coils, despite an excellent clinical outcome).

Overlapping stents (*Fig. 4*) were used in five patients to increase metallic coverage of the neck. In two patients, the aneurysm was coiled with balloon remodeling, immediately after which the balloon was deflated and removed, and two stents were then sequentially telescoped across the aneurysm neck over an indwelling 0.014 exchange-length guidewire. In Patient 12, who had a large hypophyseal segment aneurysm, difficulty was encountered crossing the proximal edge of the first stent with the second stent delivery microcatheter, and placement of the second stent was deferred for 11 weeks to allow subintimal incorporation of the first stent. Patient 14 initially underwent coiling of her aneurysm under balloon remodeling. Three weeks after treatment, she was readmitted with progressive monocular visual deterioration and underwent placement of two overlapping stents after securing access across the aneurysmal segment with a 0.014 exchange-length guidewire. In Patient 6, the initial stent delivery microcatheter was positioned across the aneurysmal segment at the beginning of the procedure, remaining adjacent to the remodeling balloon during aneurysm coiling. The stent was subsequently deployed after completion of coiling and removal of the balloon, after which the initial delivery microcatheter was

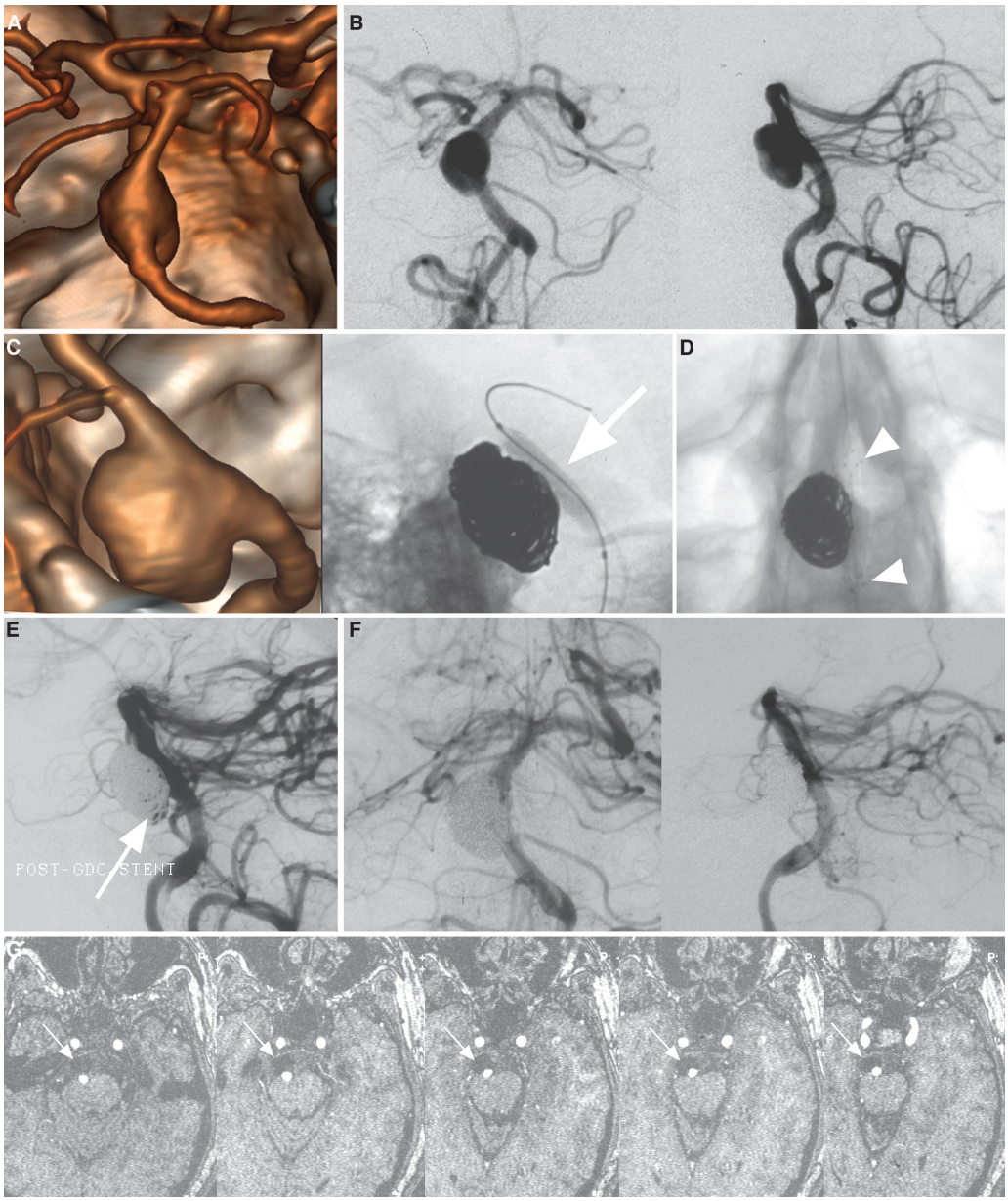

FIGURE 4. A, *images from an intracranial CT angiogram demonstrating a fusiform midbasilar artery aneurysm (Patient 1).* B, *frontal and lateral oblique angiographic images depicting the aneurysm.* C, *the aneurysm was treated with GDC under balloon remodeling conditions (4 × 20 mm balloon,* white arrow*), after which* (D) *overlapping 4.0 × 20 mm (outside) and 4.5 × 20 mm (inside) Neuroform stents* (white arrowheads*) were deployed across the aneurysm neck.* E, *immediate posttreatment angiography (lateral oblique projection) disclosed minor persistent contrast opacification throughout the intra-aneurysmal coil interstices* (white arrow*), which is not apparent on the 12-month follow-up scan.* F, *follow-up angiogram (frontal and lateral views).* G, *sequential source images through the aneurysmal segment from a magnetic resonance angiography obtained 25 months after treatment, illustrating cylindrical reconstruction of the parent basilar artery* (small white arrows, *susceptibility artifact related to the intra-aneurysmal coil mass).*

exchanged over the indwelling 0.014 exchange-length guidewire for a second stent delivery system, and the overlapping stent was deployed. In all cases, the internal stent was oversized to prevent migration of the second stent after deployment. This has the additional advantage of constraining full expansion of the internal stent and increasing the mesh coverage throughout the segment of stent overlap beyond that anticipated based on the summation of struts from overlapped, like-sized stents (*Fig. 5*). The decreased porosity of the overlapped stents further enhances the hemodynamic modification of the intra-aneurysmal circulation (4) and can be tailored to increase the mesh density of the scaffolding across the aneurysm neck while retaining low coverage densities over normal branches proximal and distal to the aneurysm.

All patients, with the exception of the individual presenting with subarachnoid hemorrhage, were premedicated with aspirin (325 mg) and Plavix (Bristol-Myers Squibb, Princeton, NJ/Sanofi-Synthelabo, New York, NY) (75 mg) orally for 3 days before the day of treatment and an additional 75 mg of Plavix the morning of the procedure. Three thousand to 5000 units of heparin, by intravenous bolus, was administered at the time of aneurysm microcatheterization, followed by institution of 500 to 800 units of heparin per hour, by intravenous infusion, for the duration of the procedure to ensure that the activated coagulation time was maintained at two to three times baseline. Treatment was followed by 12 to 24 hours of systemic anticoagulation with heparin to maintain partial thromboplastin time at 1.5 to twice the normal values, and 3 months of daily Plavix, 75 mg orally. The individual presenting with subarachnoid hemorrhage first underwent balloon-assisted coiling of her aneurysm under systemic heparinization. During coiling of the aneurysm, she received an additional 300 mg of Plavix by nasogastric tube and 650 mg of aspirin rectally, 2 hours in advance of stent deployment.

Aneurysm occlusion was graded as complete, near complete, or subtotal, as previously described (46). Angiographic follow-up was available for all patients between 11 and 24 months after stent treatment (mean angiographic follow-up, 17.5 mo). Clinical outcome was graded periodically according to the Barthel index and a modified Rankin scale score (mean clinical follow-up, 29 mo).

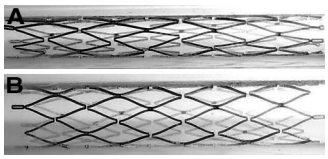

FIGURE 5. *Images depicting in vitro deployment of a 4.5-mm-diameter Neuroform stent within 3 mm (*A*) and 4 mm (*B*) diameter glass tubing (image provided courtesy of John Ortiz, Boston Scientific, Fremont, CA). Note the increasing intrastrut area with progressive stent expansion. By constraining the internal stent of an overlapped pair, it is possible to decrease porosity of the construct.*

REVIEW OF THE LITERATURE

A Medline search was performed to identify relevant articles published between January 1999 and May 2006 using search strings of "Neuroform," "intracranial stent," "aneurysm coiling," "aneurysm coiling rupture," "aneurysm coiling thrombosis," and "cerebral stent." Additional sources were identified through the bibliographies of existing articles. The articles selected for analysis were required to contain information on:

1) The total number of subjects in the series
2) The total number of aneurysms treated
3) The fraction of subjects presenting with SAH
4) The periprocedural anticoagulation regimen
5) The total number of periprocedural thrombotic complications (TC), with indication of event outcome as classified into:
   A. Deceased
   B. Symptomatic: temporary as well as permanent symptoms. Wide range of outcomes was chosen because of heterogeneity in outcome reporting
   C. Asymptomatic: in the majority of cases, this implies no change in clinical status after emergence from anesthesia

Additional information was collected, where available, on other aspects of stenting, including the incidence of technical stent complications (misdeployment, malpositioning, migration, or fracture), vessel dissection and perforation, aneurysm rupture, technical complications with coiling (coil prolapse/stretch/fracture), clinical outcome, and angiographic follow-up.

In some instances, publications from an individual center or centers contained duplicate patient data. A single publication providing the most comprehensive data set was then selected for analysis.

RESULTS

Sixteen patients with large and giant cerebral aneurysms additionally characterized by exceptionally wide necks were treated with stent-supported endovascular coiling of their cerebral aneurysms (*Table 1*). The cohort included one giant aneurysm (>25 mm in diameter) and 15 large aneurysms (ranging in size from 11 to 22 mm in fundus diameter). All aneurysms exhibited neck sizes of at least 7 mm in linear dimension along the parent vessel (range, 7–14 mm). There were no treatment-related deaths or clinically evident neurological complications. A single technical complication occurred involving transient nonocclusive stent-associated thrombus in Patient 9, which resolved without clinical sequelae after the administration of abciximab (10 mg intravenously) and 6 mg of slow intraarterially via microcatheter.

Fourteen patients underwent angiographic follow-up between 11 and 24 months posttreatment. One patient received a follow-up angiographic exam 3 months posttreatment and a second study 9 months later (12 mo posttreatment). An additional patient underwent follow-up angiographic exams at 6 and 13 months posttreatment.

With the exception of Patients 11, 14, and 16, all treated aneurysms were occluded at angiographic reevaluation. In Patient 11 (a 78-year-old female initially presenting with a 4-week history of sudden left ophthalmoplegia secondary to a giant cavernous segment aneurysm, and who failed balloon test occlusion of her left internal carotid artery), postembolization control angiography was notable for subtotal occlusion, which evolved during the subsequent 11 months into frank recanalization of the aneurysm fundus with coil compaction and recurrence of her earlier resolved symptoms. During her exam at 11 months, she was retreated with additional coils placed into the recurrent fundus. Follow-up angiography completed 20 months after her initial treatment (9 mo postretreatment) documented persistent occlusion of the recoiled fundus with persistent filling and coil compaction at the aneurysm neck. Although she has experienced resolution of her recurrent left ptosis, she remains symptomatic from residual partial III and VI nerve palsies, requiring an eye patch for treatment of diplopia. She has declined bypass-supported carotid occlusion. Patient 14 had overlapping Neuroform stents placed for treatment of an acutely worsened ipsilateral monocular visual deficit 3 weeks after near-complete coiling of her aneurysm under balloon remodeling. At follow-up angiography 1 year after stent placement, there was diminished yet persistent opacification of a small 1-mm neck remnant without interval coil compaction, which was graded as stable near-complete aneurysm occlusion. Clinically, within 2 weeks after stent treatment, her visual field had recovered significantly, with a minor residual fixed peripheral deficit at the follow-up perimetry exams at 3 and 12 months. Patient 16, who harbored a complex ophthalmic segment aneurysm (*Fig. 1*), exhibited persistent opacification through neck-region coils without coil mass compaction at follow-up angiography and was likewise graded as stable near-complete aneurysm occlusion.

Clinical follow-up averaged 29 months for the cohort. All patients had excellent clinical outcomes, with the exceptions of Patient 11, who experienced recurrent III and VI nerve palsies after earlier posttreatment resolution of her presenting symptoms; Patient 7, who presented with a Grade 3 subarachnoid hemorrhage and recovered to Rankin

TABLE 1. Patient demographics and treatment outcomes[a]

Patient no.	Age (yr)/sex	Patient history	Aneurysm size/neck	Occlusion grade		Complications	Barthel		Rankin (1 yr)
				Initial	Follow-up		1 mo	1 yr	
1	50/M	Brainstem stroke/mass effect (hemiparesis, diplopia)	Midbasilar fusiform 18 mm/14 mm	NC	C	None	90	100	0: hemiparesis and double vision fully resolved
2	62/M	IDA	L ophth 15 mm/7 mm	C	C	None	100	100	0
3	51/M	III nerve palsy	L pcom 20 mm/8 mm	C	C	None	100	100	0: cranial neuropathy resolved at 1 mo
4[b]	54/F	IDA	R ophth 14 mm/8 mm	C	C	None	100	100	0: suicidal death at 22 mo
5[b]	77/F	IDA	L pcom 22 mm/9 mm	C	C	None	100	100	0
6	50/F	R III, VI nerve palsies	R cavernous segment 20 mm/12 mm	NC	C	None	100	100	0: cranial neuropathy resolved at 1 mo
7	49/F	SAH (Grade 3)	R hyp 20 mm/13 mm	C	C	None	95	100	2: nonfocal neuro-exam, neurocognitive deficit preventing return to work
8	75/F	R III, VI nerve palsies; remote preexisting right hemiparesis related to stroke sustained during earlier clipping of a left ophth segment aneurysm	R cavernous segment 18 mm/10 mm	NC	C	None	85	85	3: cranial neuropathies resolved at 6 wk
9	52/M	Incidentally discovered aneurysm	Basilar apex 11 mm/8 mm	C	C	Stent associated thrombus; treated with abciximab	100	100	0
10	31/F	TIA	R ophth 12 mm/7 mm	C	C	None	100	100	0
11	78/F	L III, IV, VI nerve palsies	L cavernous segment 25 mm/12 mm	S	S (11 mo)/S (20 mo)	Technical: loss of microcatheter position, resulting in undercoiling	100	100	1: recurrent cranial neuropathy; persistent partial III and VI nerve palsies at 22 mo
12	72/F	IDA	R hyp 20 mm/13 mm	C	C	None	100	100	0
13	48/M	TIA	L hyp 16 mm/8 mm	C	C	None	100	100	0
14[c]	57/F	Monocular visual deficit (worsened after coil treatment)	L ophth 16 mm/9 mm	NC	NC	None (related to stenting procedure)	100	100	1: nearly completely resolved visual deficit
15	62/F	III, IV, VI nerve palsy	L cavernous segment 20 mm/14 mm	NC	C	None	100	100	1: near-complete resolution of cranial neuropathy: prism glasses initially followed by corrective surgery at 10 mo
16	74/F	Monocular visual deficit	L ophth 22 mm/12 mm	NC	NC	None	100	100	1: stabilized monocular visual deficit

[a] IDA, incidentally diagnosed aneurysm; L, left; R, right; SAH, subarachnoid hemorrhage; Ophth, ophthalmic segment (including paraclinoid and dural ring ICA aneurysms); pcom, posterior communicating segment; hyp, superior hypophyseal segment; C, occlusion; NC, near-complete occlusion (coils throughout aneurysm with minimal interstitial opacification); S, subtotal treatment (portion of the aneurysm without coils); TIA, transient ischemic attack.
[b] Recurrent aneurysms following previous coil treatment.
[c] Visual field cut worsened 3 weeks after balloon-assisted primary coiling of the aneurysm.

TABLE 2. Published articles reporting results on stent-supported aneurysm coiling (1999–2006) meeting inclusion criteria[a]

Series (ref. no.)	Baseline data		
	No. of patients with stent deployed (no. stenting attempted)	Stent type(s)	No. of aneurysms stented (no. of aneurysms stented and coiled)
Lanzino et al., 1999 (27)	10 (NR)	GFX, INR, Microstent II	10 (8)
Luo et al., 2003 (34)	9 (9)	Balloon mounted	9 (8)
Han et al., 2003 (17)	10 (13)	Balloon mounted	10 (10)
Perez-Arjona and Fessler, 2004 (48)	3 (3)	Neuroform	3 (3)
Alfke et al., 2004 (2)	6 (9)	Neuroform	6 (6)
Liu et al., 2004 (31)	18 (NR)	S670, BX Velocity	18 (18)
Benitez et al., 2004 (4)	48 (56)	Neuroform	49 (41)
Higashida et al., 2005 (19)	5 (NR)	Enterprise	5 (5)
Brisman et al., 2005 (6)	7 (7)	Neuroform	7 (7)
Thorell et al., 2005 (60)	7 (NR)	Neuroform	7 (7)
Sani and Lopes, 2005 (52)	10 (10)	Neuroform Treo	10 (10)
Santos Souza et al., 2005 (53)	16 (17)	Neuroform	16 (16)
Lee et al. , 2005	18 (18)	Neuroform	19 (18)
Wanke et al., 2005 (63)	25 (NR)	Neuroform	26 (25)
Akpek et al., 2005 (1)	31 (32)	Neuroform	34 (30)
Lylyk et al., 2005 (36)	46 (50)	Neuroform	48 (34)
Fiorella et al., 2005 (13)	64 (NR)	Neuroform	74 (61)
Horowitz et al., 2006 (20)	8 (NR)	Neuroform	8 (8)
Lubicz et al., 2006 (33)	11 (11)	Leo	11 (11)
Kis et al., 2006 (25)	20 (21)	Leo	24 (23)
Katsaridis et al., 2006 (23)	44 (45)	Neuroform 2	53 (52)

[a] SAH, subarachnoid hemorrhage; TC, thrombotic complications; F/U, follow-up; NR, not reported.

Grade 2 and minor residual short-term memory deficit preventing full-time return to work; and Patient 16, whose monocular visual deficit remained unchanged. Patient 11 was retreated at her angiographic follow-up at 11 months; however, she has experienced negligible resolution of her diplopia through the subsequent 12 months. Patient 8, admitted for treatment of a large cavernous segment right–internal carotid artery aneurysm, had a baseline preexisting right hemiparesis related to a stroke sustained during earlier clipping of a left–ophthalmic segment aneurysm. There was one suicide-related death 22 months after treatment.

REPORTED RESULTS FROM THE LITERATURE

A total of 21 articles (416 patients, 449 aneurysms) satisfying our inclusion criteria were identified (1, 2, 4, 6, 13, 17, 19, 20, 23, 25–27, 31, 33, 34, 36, 48, 52, 53, 60, 63) (*Tables 2* and *3*). The majority of data reflect use of the Neuroform stent (14 articles, with 361 patients). Thirty-five percent of aneurysms were treated after SAH. Approximately 28% of the described aneurysms were large (usually at least 10 mm in diameter). Approximately 7% were giant (uniformly more than 25 mm).

In approximately 7.3% of the cases, stent delivery was unsuccessful. Most of the articles excluded these patients from subsequent analyses. Stent malpositioning occurred approximately 6.1% of the time overall and in 4.2% of Neuroform cases. No specific malposition was reported with Neuroform 2 (Boston Scientific) or Neuroform Treo (Boston Scientific) stents.

Complications

The collective prevalence of TC was found to be 10.3%. Of these events, 7% resulted in death, 53% were symptomatic, and 40% were asymptomatic. Parent vessel dissection (without vessel rupture) occurred in five (1.4%) cases and was asymptomatic in four cases. The prevalence of technical complications with the coiling component of treatment (such as prolapse or stretching) was 2.2%. All coil complications were reportedly asymptomatic. Aneurysm perforation was seen in five cases (1.4%), resulting in one death and one permanent neurological impairment. Causes included two guidewire-

TABLE 2. Continued

Baseline data		Complications			
No. of aneurysms with SAH	No. of large (giant) aneurysms	Total no. of TC	No. of nonlethal symptomatic TC (no. of deaths attributable to TC)	Intraprocedural aneurysm rupture and cause	No. of nonlethal symptomatic perforations (no. of perforation-related deaths)
0	NR (NR)	2	1 (0)	0	0 (0)
4	NR (NR)	2	2 (0)	0	0 (0)
3	5 (5)	2	1 (1)	0	0 (0)
0	2 (0)	0	0 (0)	0	0 (0)
1	NR (NR)	0	0 (0)	0	0 (0)
15	NR (NR)	0	0 (0)	0	0 (0)
16	NR (NR)	4	3 (1)	NR	NR (NR)
3	1 (0)	0	0 (0)	0	0 (0)
2	5 (0)	2	1 (0)	0	0 (0)
0	NR (NR)	2	2 (0)	0	0 (0)
3	0 (0)	0	0 (0)	0	0 (0)
8	8 (0)	3	1 (0)	0	0 (0)
6	4 (0)	0	0 (0)	0	0 (0)
7	3 (2)	2	2 (0)	1 microcath, 1 coil	2 (0)
4	11 (0)	9	2 (0)	1 guidewire, 1coil	2 (0)
23	11 (6)	6	3 (0)	1 microwire	0 (1)
16	22 (4)	6	5 (1)	0	0 (0)
7	2 (0)	0	0 (0)	0	0 (0)
0	2 (2)	0	0 (0)	0	0 (0)
4	6 (2)	2	0 (0)	NR	NR (NR)
33	NR (NR)	2	0 (0)	0	0 (0)

induced perforations, two coil-mediated perforations, and one microcatheter perforation.

Initial Degree of Occlusion

Although the descriptive classifications of posttreatment angiographic results were variable, the intended categories could generally be characterized as complete, almost (near) complete, or subtotal. Approximately 57% of aneurysms were felt to be completely occluded on immediate postprocedure angiography, and 22% were reported to be almost completely occluded.

Angiographic Follow-up

Angiographic follow-ups were reportedly performed in 201 patients (14 articles), with outcome results actually described for 172 patients in 13 articles. The mean time to follow-up angiography was 6.3 (± 2.5) months, with a range of 1 to 18 months.

Among those articles with follow-up outcome in which a distinction could be made between occlusion and residual filling (11 articles), 69% (n = 83) of aneurysms were found at follow-up to be occluded. Thirteen articles reported recanalization data indicating 4.3% of aneurysms occluded on the initial posttreatment angiogram to have recanalized, and 14.1% of incompletely occluded aneurysms to have progressive degrees of occlusion. Among the 201 patients with angiographic follow-up, 16 underwent repeat coiling.

In-stent stenosis was observed in nine cases (4.5% of patients with follow-up angiograms) at an average duration (reported for four patients) of 4 months posttreatment. At least three out of the nine stenoses were symptomatic. One was seen in a case of noncompliance, with poststenting anticoagulation.

DISCUSSION

Since the introduction of GDC for treatment of cerebral aneurysms in 1991, numerous reports have been published that attest to the safety of the device and its efficacy, particularly in treating saccular aneurysms with small neck size. Unfortunately, for those aneurysms with large neck size or unfavorable neck-to-fundus ratio, durable aneurysm occlusion has been more elusive, partly because of difficulty in resolving the vessel to neck interface of large, complex-shaped aneurysms under real-time, two-dimensional fluoroscopy to a degree sufficient to enable confident reconstruction of the aneurysm neck. This contributes to operator uncertainty in positioning coils at the aneurysm base,

TABLE 2. Continued

Complications		Follow-up							
Suboptimal stent position (migration/ early deployment/ fracture)	No. of parent vessel dissections	No. of initial complete or "near-complete" occlusions	No. of patients with f/u angiograms	F/U angio: complete occlusion	F/U angio: residual filling	F/U angio: demonstrating progressive thrombosis/occlusion	F/U angio: no. of recanalizations in aneurysms initially occluded	F/U angio: number of in-stent stenoses	No. of patients retreated
2	1	8	6	3	3	0	0	1	0
2	1	NR	NR	NR	NR	NR	NR	NR	NR
0	1	8	5	2	3	2 (occluded)	1	0	2
0	0	NR	2	2	0	0	0	0	0
0	0	6	NR	NR	NR	NR	NR	NR	NR
4	0	16	18	13	5	0	0	0	0
1	0	35	5	NR	NR	NR	NR	0	NR
0	0	NR	NR	NR	NR	NR	NR	NR	NR
2	0	NR	NR	NR	NR	NR	NR	NR	NR
1	0	7	6	4	2	0	0	0	1
0	0	9	10	9	1	0	0	0	1
1	1	11	1	0	1	0	0	0	0
0	0	21	NR	NR	NR	NR	NR	NR	NR
NR	0	26	26	16	10	4 (occluded)	1	1	0
0	0	21	12	6	6	4 (occluded)	0	0	1
9	1	32	29	NR	NR	NR	0	0	0
1	NR	28	46	NR	NR	25 (progressive thrombosis-degree of occlusion not specified)	11	3	8
0	0	NR	NR	NR	NR	NR	NR	NR	NR
0	0	11	NR	NR	NR	NR	NR	NR	NR
3	0	17	17	10	7	0	3	1	3
0	0	52	18	18	0	0	0	0	0

frequently leading to undercoiling of the aneurysm neck. In this regard, experience from the MATRIX registry is instructive. Among 100 aneurysms enrolled after undergoing MATRIX coil treatment, 54% were initially judged to be angiographically occluded at the time of immediate posttreatment angiography. However, a later retrospective review by an independent core lab found the prevalence of immediate posttreatment occlusion to be only 15%, suggesting an important bias in operator adjudication of anatomic treatment outcome and illustrating the potential role of inadequate endosaccular control of the aneurysm neck in postcoil recanalizations.

The long-term consequences of subtotal aneurysm coiling have not been studied scientifically, but they can be inferred from several single-center (50) and multicenter (41, 61) series that suggest incomplete coiling of the aneurysm neck increases the likelihood of recurrence and may be a factor in delayed (54) posttreatment rehemorrhage, which is estimated to range between 0.2 and 0.3% per year for previously ruptured aneurysms treated with coils.

Theoretically, the collective factors responsible for recurrence (24, 55, 56, 59) can be divided into factors operational in incompletely occluded aneurysms and factors responsible for recanalization of aneurysms initially occluded at the time of coil treatment. For complex-neck, large and giant aneurysms, recanalizations frequently result from unintentional or deliberate undercoiling of the neck region and involve a sequence of events leading to lysis and remodeling of incompletely organized intra-aneurysmal thrombus and coil compaction, with or without true continued growth of the aneurysm. Once formed, the fate of the intra-aneurysmal coil–thrombus complex depends on a number of factors, including the coagulative disposition of the specific patient, the coil composition (i.e., surface texture, coatings, and charge density), the completeness of aneurysm packing, and, importantly, the degree of sustained aneurysmal hemostasis. Although coil packing density has been correlated anecdotally to stable aneurysm occlusion, with bare metallic or polymer-coated coils, coil packing densities of treated aneurysms usually are significantly less than 40% by volume, even in ideally packed aneurysms (9). Therefore, it is likely that the effectiveness of coils in treating aneurysms is largely dependent on the degree by which intra-aneurysmal flow is reduced and, correspondingly, on the inherent stability of the intra-aneurysmal coil–thrombus complex.

TABLE 3. Summarized data from articles reporting results with stent-supported aneurysm coiling (1999–2006)[a]

Parameter	Value	No. of articles providing these data out of 21
Total no. of patients with stent deployment	416	21
Total no. of aneurysms treated	447	21
Total no. of aneurysms treated with Neuroform 1, 2, and Treo stents	360	14
Total no. of aneurysms stented but *not* coiled for various reasons	44	20
Percent of aneurysms treated following subarachnoid hemorrhage	35%	21
Percent of large aneurysms (>10 mm in most studies)	28%	14
Percent of giant aneurysms (>25 mm in all studies)	7%	14
Stent delivery failure		
Percent of patients in whom stent delivery had failed and was aborted	7.3%	14
Stent migration/premature deployment/fracture, etc.		
Percent (no.) of cases with suboptimal stent position as a fraction of treated aneurysms	6.1% (26)	20
Percent (no.) of cases with Neuroform 1, 2, and Treo delivery complications	4.2% (15)	13
No. of patients with second generation Neuroform or Treo delivery complications	0	13
Thromboembolic complications (TEC)		
No. of patients with thrombotic complications	43	21
Percent ± SD of patients with thrombotic complications	10.3 ± 10.8%	21
Percent (no.) of patient deaths as a result of TEC (as fraction of all treated patients)	0.7% (3)	21
Percent of patient deaths as a result of TEC (as fraction of patients with TEC)	7%	21
Percent (no.) of nonlethal symptomatic patients as a result of TEC (as fraction of all patients treated)	5.5% (23)	21
Percent of nonlethal symptomatic events caused by TEC (as fraction of all patients with TEC)	53%	21
Coil complications		
Percent (no.) of patients with coil complications	2.2% (9)	21
No. of patients dead or symptomatic as a result of coil complications	0	21
Dissection		
Percent (no.) of parent vessel dissections	1.4% (5)	20
No. of "asymptomatic" dissections	4	20
Aneurysm perforation		
Percent (no.) of intraprocedural aneurysm perforations	1.4% (5)	19
No. of deaths as a result of perforation	1	19
Aneurysm occlusion		
Percent (no.) of aneurysms completely occluded on initial post-Rx angiogram	57% (196)	14
Percent (no.) of aneurysms nearly completely occluded on initial post-Rx angiogram	22% (77)	14
Percent (no.) of aneurysms completely or nearly completely occluded on initial post-Rx angiogram	73% (308)	16
Angiographic follow-up		
Total no. of patients with angiographic follow-up	201	14
Average ± standard deviation of angiographic follow-up (mo)	6.3 ± 2.5	14
Range of angiographic follow-up	1–18 mo	14
Angiographic follow-up results		
No. of patients with angiographic follow-up *and* reported appearance of aneurysm	172	13
Percent (no.) of aneurysms with complete occlusion as a fraction of the total number of follow-up angiograms	69% (83)	11
Percent (no.) of recanalizations in initially completely occluded aneurysms	4.3% (16)	11
Percent (no.) of incompletely occluded aneurysms that were completely occluded on follow-up	14.1% (10)	10
Percent (no.) of patients retreated after follow-up angiogram	8.2% (16)	13
In-stent stenosis		
Percent (no.) of in-stent stenoses as a fraction of total number of follow-up angiograms	4.5% (9)	14
Average duration of follow-up (mo) at the time of in-stent stenosis (data from four out of nine patients only)	4.0	3

[a] SD, standard deviation; post-Rx, posttreatment.

One might anticipate, therefore, that any strategy that further diminishes residual intra-aneurysmal flow and increases the stability of the endosaccular construct would likely contribute to a more effective endovascular outcome. From the perspective of this hypothesis, the results of this study are encouraging. Among the 16 patients treated by combined Neuroform endoluminal and coil endosaccular approach, during a mean follow-up interval of 17.5 months, only one patient (Patient 11) experienced angiographically evident aneurysm recurrence. Two additional patients (Patients 14 and 16) (*Fig. 1*) were found to have small stable neck remnants at angiographic follow-up at 12 and 16 months, respectively. In each of these two cases, follow-up angiography remained unchanged from the immediate poststent study with no further increase in neck remnant size or coil compaction, suggesting a stent-related effect to arrest progression of aneurysm growth and progressive coil compaction.

The coils used in these treatments varied, with nine out of the 16 patients treated with blends of bare platinum and Matrix-coated GDC and seven patients with platinum coils alone. It is therefore not possible to comment on any potential role that coil selection and composition may have had in determining outcome.

Although comparable published long-term follow-up evaluation of Neuroform-supported coiling of complex aneurysms is lacking, our immediate posttreatment results (56.3% complete occlusion and 37.5% near-complete occlusion) are similar to preliminary outcomes reported among the articles surveyed (mean, 57% completely occluded and 22% nearly completely occluded). Those results and these reported here are particularly encouraging compared with the immediate occlusion rate of 40.4% for large aneurysms reported by Murayama et al. (43) and are in line with initial occlusion rates reported for balloon remodeling techniques in other series of broad-neck aneurysms (42, 46). Caution must be exercised, however, in the interpretation of data pooled from the surveyed articles, particularly considering the variability in outcome definitions and technical approaches to aneurysm treatment used by individual investigators. For instance, our posttreatment results differ from the immediate and follow-up outcomes with Neuroform-supported aneurysm coiling reported by Fiorella et al. (13). In their 20-month prospective study of 61 aneurysms undergoing stent-supported coiling with Neuroform, combined complete or near-complete aneurysm occlusion was observed in only 28 (45.9%) of the aneurysms, with partial (analogous to subtotal) occlusion in 54% of patients. Follow-up angiography (in 43 patients) or magnetic resonance angiography (in five patients) was available at a median reevaluation period of 4 months (mean, 4.6 mo). However, the grade of aneurysm occlusion for each patient was not specified; instead, it had been reported in terms of progressive thrombosis (25 patients), recanalization (11 patients, eight of whom were retreated), and no change (12 patients). In part, the differences in immediate angiographic occlusion between their experience and ours may be attributed to variations in aneurysm characteristics and differing therapeutic strategies for stent use. The Barrow series (13) included a higher percentage of smaller aneurysms with small necks, but unfavorable neck/fundus ratios and a larger number of ruptured aneurysms (16 aneurysms), for which they advocate a conservative, staged approach in which the aneurysm is deliberately undercoiled during the initial therapeutic setting to reduce the likelihood of acute complications. Our cohort of aneurysms reflected, on average, a larger volume and neck size, necessitating use of balloon remodeling in coiling the aneurysm before placement of the stent, which may have accounted for better coil coverage of the neck region.

The adjunctive use of balloon remodeling before stent placement differs from the pattern of Neuroform use reported in other case series in which the stent has been primarily employed to provide protection from coil herniation into the parent artery and developed as a strategy to address the positional instability of early-generation stents when used to cover dysplastic necks larger than 12 mm in size. In this setting, the 20-mm stent length (the longest available at the time) did not provide sufficient proximal and distal anchoring within the parent vessel to prevent displacement or folding (jackknifing) of the stent into the aneurysm (7) when deployed across an empty aneurysm fundus. Since the enrollment of these patients, Neuroform has become available in 30-mm stent lengths and as a Treo variant with three interconnects between internal contiguous crowns, enhancing its architectural stability. Nevertheless, for complex aneurysms in which the parent vessel–aneurysm interface cannot be sufficiently resolved by two-dimensional fluoroscopy or angiography, approaches using balloon remodeling to coil the aneurysm before stent placement may provide more confidence in coiling compartments of the neck that overlap the parent vessel, particularly when small finishing coils would ideally be used to achieve more complete volumetric packing of the aneurysm base, which may have accounted for better coil packing (particularly at the neck) among aneurysms in our series. Furthermore, as suggested by the treatment regimen employed with our one case of subarachnoid hemorrhage (Patient 7) (*Fig. 3*), balloon remodeling may remain useful in facilitating more complete initial occlusion in complex ruptured aneurysms, permitting later staged stent placement once conditions allowing the safe institution of antiplatelet coverage evolve.

Overlapping stents were deployed in five patients in this series to increase metallic coverage over the aneurysm–parent vessel interface (*Fig. 4*). The additional stent coverage increases the mesh density across the aneurysm neck and enhances the hemodynamic modification of the intra-aneurysmal circulation (4), an effect also seen with the use of single lower-porosity balloon expandable and self-expanding stents.

COMPLICATIONS OF STENT-SUPPORTED COIL TREATMENT OF CEREBRAL ANEURYSMS

Thrombotic Complication

The prevalence of TC in coil-treated aneurysms has been estimated to range from 2.5 to 61%, depending on the individual case series cited and the method of surveillance em-

ployed, with permanent deficits ranging from 2.5 to 5.5% (47, 49, 57).

A transient TC was observed in this series. Patient 9, who harbored a large basilar apex aneurysm, developed nonocclusive in-stent thrombus within the left P1 segment during treatment, despite what was felt to be adequate antiplatelet coverage. This mirrors what has been reported in the literature for stent-supported aneurysm treatment: 10.3% collective incidence among articles surveyed in this review (*Table 2*). Four stent-related TCs (two clinically consequential) were reported by Fiorella et al. (14) in their series of 21 Neuroform-treated aneurysms in 19 patients. Importantly, three out of the four events occurred during treatment of acutely ruptured aneurysms without antiplatelet pretreatment, further emphasizing the inherent thrombogenic hazard of primary stenting in the absence of adequate antiaggregant coverage.

The likelihood of TC and the implied remedies potentially limit the use of stents in the treatment of ruptured aneurysms (as in Patient 7), in which the consequences of rescue thrombolytic therapy could lead to iatrogenic aneurysm rerupture. In this context, a staged approach to Patient 7 may have proven more rational. This could have involved coiling the aneurysm as completely as possible with balloon assist in the acute setting, followed by stent placement 2 to 4 weeks later to reduce the likelihood of recanalization, once the potential requirements for an intraventricular drain or subsequent angioplasty for treatment of SAH-associated vasospasm could be assessed and antiplatelet drugs more safely administered.

In-stent Stenosis

Additional concerns regarding the placement of stents within the intracranial circulation include the potential for perforator occlusion (32) and delayed in-stent stenosis (12). Among our patients, there were no incidents of clinically apparent perforator vessel occlusion or delayed in-stent stenosis (defined in this series as interval luminal narrowing >25%). Among the articles reviewed that provided this information, stent-related stenosis (usually not quantitatively defined) was observed in approximately 4.5% of the aneurysms with angiographic follow-up. Assessing in-stent stenosis in the setting of aneurysm therapy requires circumspection in deciding what degree of asymptomatic vessel narrowing will be viewed as abnormal, especially considering the initial degree of cross-sectional compromise inherent in deploying an endoluminal device and the vascular response implicit to the implantation of the stent and its normal progressive subintimal incorporation into the vessel wall. Since the original preparation of this article, D. Fiorella (Congress of Neurological Surgeons 2005 Annual Meeting, Boston, MA, October 8–13, 2005) and H. Woo (World Federation of Interventional and Therapeutic Neuroradiology, WFITN 2005 Annual Meeting, Venice, Italy, October 19–22, 2005) have reported, from combined experiences at the Barrow Neurological Institute and Cleveland Clinic, several isolated cases of Neuroform-associated delayed in-stent stenosis found on further follow-up angiography to have resolved spontaneously. These findings are of importance in that they implicate a dynamic series of self-limited local histovascular events set in motion by stent implantation (some of which may be important in mediating aneurysm healing).

Controlled Stent Deployment

As suggested by the prevalence (6.1%) of stent misdeployment *(Tables 2* and *3*), precise control of stent placement is paramount in the effective and safe use of these devices. Toward this end, refinements made to the microdelivery system in Neuroform 2 and 3 have dramatically improved the likelihood of successful stent delivery and the accuracy of deployment compared with early experiences with Neuroform 1 and early-generation balloon-mounted coronary stents. Longer-length stents (Neuroform 30 mm) and stents characterized by a less open architecture, such as Neuroform Treo and Enterprise (Cordis Neurovascular, Miami, FL), further contribute to more secure deployments across wider-neck aneurysms, decreasing the frequency and degree of stent encroachment or prolapse into the aneurysm fundus (5). Deployment is further aided by the use of an indwelling microguidewire to stabilize the stent deployment microcatheter, particularly when deploying stents around severe vessel curvatures such as those frequently encountered in the carotid siphon.

Considering the number and sizes of guide catheters and groin sheaths, an increased likelihood of groin complication, particularly when employing a combination regimen of heparin anticoagulation with antiplatelet medication, is not unexpected; however, in this series, such complications were not observed despite indwelling groin sheaths being left in place for 10 to 16 hours after aneurysm treatment.

CONCLUSION

Early experience with stent-supported coil embolization of cerebral aneurysms has engendered significant interest in an endoluminal solution for cerebral aneurysms. To date, available devices have primarily been used within the context of increasing the effectiveness of existing coil-based endosaccular strategies. Although the effectiveness of this complementary therapeutic approach is supported by the data presented here, and combined stent-supported coil embolization will undoubtedly evolve, future innovation in the area of low-porosity endoluminal devices may ultimately offer the possibility of stand-alone therapy for some subset of aneurysms, enabling a more complete anatomic reconstruction of the aneurysm–parent vessel interface and potentially providing a definitive endovascular treatment of the complex cerebral aneurysm.

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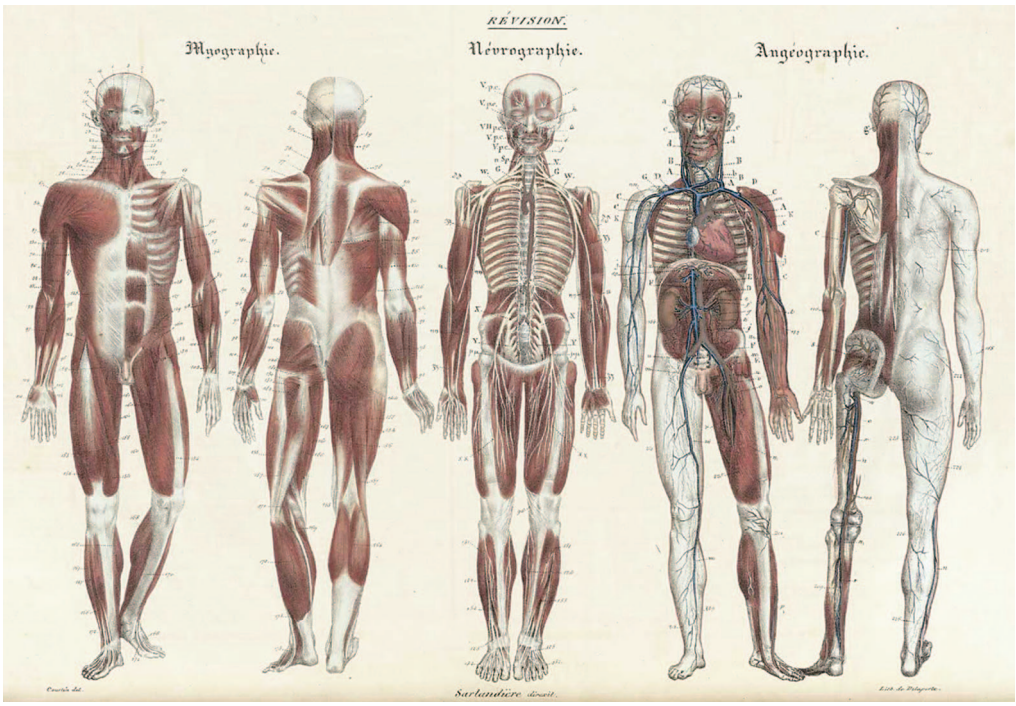

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ENDOVASCULAR MANAGEMENT OF INTRACRANIAL ANEURYSMS: CURRENT EXPERIENCE AND FUTURE ADVANCES

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OBJECTIVE: The past 15 years have seen a revolution in the treatment of intracranial aneurysms. Endovascular technology has evolved rapidly since the Food and Drug Administration approval of Guglielmi detachable coils in 1995, which now allows successful treatment of most aneurysms. The authors provide a review of their 11-year experience at Jefferson Hospital for Neuroscience with endovascular embolization of intracranial aneurysms and discuss clinical trial outcomes and future directions of this treatment method.

METHODS: The authors reviewed the clinical and angiographic outcomes for 1307 patients undergoing endovascular treatment of intracranial aneurysms. Their analysis focuses on posterior circulation and middle cerebral artery aneurysms, as well as cases of stent-assisted coil embolization. They review their procedural protocol and patient selection criteria for endovascular management.

RESULTS: Several large clinical trials have demonstrated the safety and efficacy of endovascular treatment of intracranial aneurysms. The International Subarachnoid Aneurysm Trial provides Level I evidence demonstrating a significant reduction in disability or death with endovascular treatment compared with surgical clipping. The most common procedural complications include intraprocedural rupture and thromboembolic events; avoidance strategies are also discussed. Vasospasm after subarachnoid hemorrhage causes neurological morbidity and mortality and can be successfully managed by early recognition and interventional treatment with angioplasty, pharmacologic agents, or both.

CONCLUSION: Long-term studies evaluating experience with aneurysm coil embolization during the past decade indicate that this is a safe and durable treatment method. The introduction of stent-assist techniques has improved the management of wide-neck aneurysms. Future technology developments will likely improve the durability of endovascular treatment further by delivering bioactive agents that promote aneurysm thrombosis beyond the coil mass alone. It is clear that endovascular therapy of both ruptured and unruptured aneurysms is becoming a mainstay of practice in this patient population. Although not replacing open surgery, the continued improvements have allowed aneurysms that previously were amenable only to open clip ligation to be treated safely with durable long-term outcomes.

KEY WORDS: Aneurysm, Endovascular, Subarachnoid hemorrhage

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The past 15 years have seen a revolution in the treatment of intracranial aneurysms. The development of the Guglielmi detachable coil, and its Food and Drug Administration approval in 1995, introduced a potential alternative treatment for 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. The past several years have produced a wealth of new technology that has allowed treatment of aneurysms that were not amenable to endovascular

therapy. We review a single-institution 11-year experience emphasizing technique, patient selection, and outcomes focusing on clinical trial results, complication management and avoidance, and future directions of endovascular aneurysm technology and treatment strategies.

THE JEFFERSON HOSPITAL FOR NEUROSCIENCE EXPERIENCE

Patient Selection

From July 1994 through December 2004, 2721 patients were treated for intracranial aneurysms at Thomas Jefferson University Hospital and Jefferson Hospital for Neuroscience. The age range was 9 to 89 years; women made up 72% of the cohort and 18% of patients had multiple aneurysms. The clinical presentation on treatment included 599 (22%) patients with unruptured aneurysms and 2122 (78%) patients with acute subarachnoid hemorrhage (SAH). Most patients treated were either Grade III or Grade IV. Hunt and Hess grade was as follows: Grade I, 8%; Grade II, 20%; Grade III, 62%; Grade IV, 10% (*Table 1*). No patients who remained a Grade V after ventricular drainage and aggressive critical care support underwent diagnostic angiography.

Among our cohort of patients with intracranial aneurysms, 1414 patients (52%) underwent transcranial surgery and 1307 patients (48%) underwent endovascular treatment. Aneurysm location for endovascular treatment involved 66% anterior circulation and 34% posterior circulation. *Table 2* outlines our criteria for selecting coil embolization versus craniotomy for clip ligation. The patients were individualized based on physiological age and surgical, medical, and anesthetic risk factors using American Society of Anesthesiologists classification and Goldman classification for cardiovascular risk factors as well as neurological grade (*Fig. 1*). In general, patients with poor neurological grade, regardless of age, were selected to undergo an endovascular procedure. Those with a large intraparenchymal hematoma, regardless of the aforementioned, underwent transcranial surgery for relief of intracranial pressure and treatment of the aneurysm at the same time. More recently, several patients underwent a combined treatment of endosaccular aneurysm occlusion followed by immediate surgery for transcranial removal of the hematoma. Small hematomas either in the temporal lobe or frontal lobe were not contraindications to endosaccular treatment and heparinization. Patients whose aneurysms were in difficult or high-risk anatomic locations, such as posterior circulation aneurysms, including low-lying or posteriorly pointing basilar aneurysms, were selected for an endovascular approach as well (*Fig. 2*). Endovascular treatment usually was excluded for giant aneurysms, aneurysms with thrombus, fusiform lesions, and unfavorable aneurysm fundus-to-neck ratio. Indications have expanded with balloon remodeling techniques and more recently with the Neuroform (Boston Scientific/Target, Fremont, CA) stent-assisted coiling procedure. Newer complex

TABLE 1. Hunt and Hess grade for 2122 subarachnoid hemorrhage patients treated at Jefferson Hospital for Neuroscience between July 1994 and December 2004

Hunt and Hess Grade	No. patients (%)
I	169 (8)
II	425 (20)
III	1316 (62)
IV	212 (10)
V	Not treated if remained Grade V after ventricular drainage; patients given aggressive critical care support

TABLE 2. Selection criteria for endovascular treatment

Inclusion factors
Elderly (physiologic age)
High surgical risk (medical and anesthetic risk)
Poor neurological grade
No intraparenchymal hematoma (negotiable)
Difficult or high risk (anatomical location: proximal internal carotid artery, posterior circulation)
Inability to occlude surgically
Relative exclusion factors (no longer absolute with stent/balloon-assisted techniques)
Giant aneurysm with or without thrombus
Fusiform lesion
Unfavorable fundus-to-neck ratio

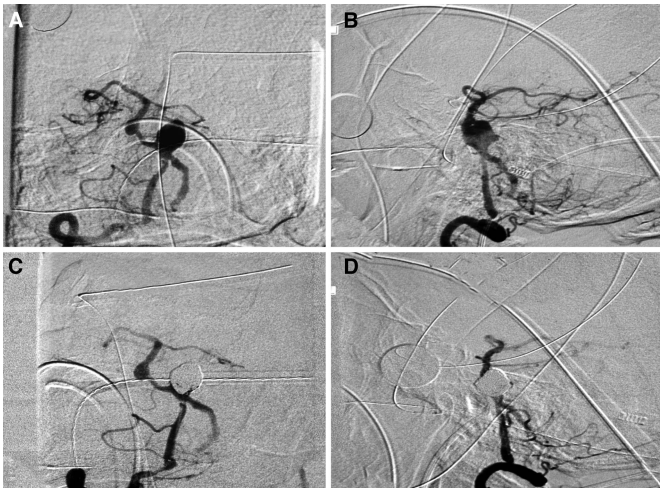

FIGURE 1. *Angiograms obtained from an ideal endovascular candidate.* A *and* B, *oblique anteroposterior and lateral views demonstrating a ruptured vertebrobasilar junction aneurysm with a favorable fundus-to-neck ratio in an 87-year-old woman with heart failure and an ejection fraction of 20%.* C *and* D, *postembolization views demonstrating near complete obliteration.*

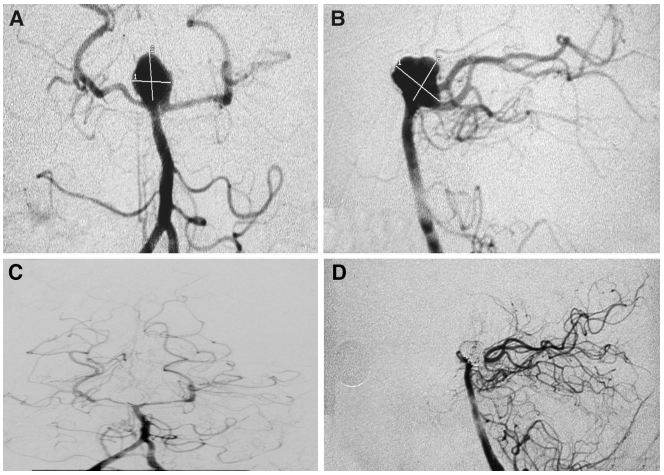

FIGURE 2. *Angiograms demonstrating the role of anatomic location and neurological grade in treatment selection.* A *and* B, *anteroposterior and lateral views demonstrating a posteriorly pointing basilar apex aneurysm in a 38-year-old man with a Hunt and Hess Grade III SAH.* C *and* D, *postembolization views demonstrating complete obliteration.*

coils that retain shape have allowed safer treatment of aneurysms with unfavorable morphological features. Giant aneurysms and those with thrombus are difficult to treat endovascularly because of a high recurrence rate and increased thromboembolic risk. Coil embolization has been a useful multimethod component combined with surgical clipping and/or vessel deconstruction for these lesions. *Figure 3* illustrates the evolution in treatment method selection during the past 5 years as new coil technologies have allowed a greater percentage of aneurysms to be treated successfully by endovascular means.

Endovascular Protocol

All SAH patients underwent preoperative placement of an arterial line and central venous line. For patients with Hunt and Hess Grade III or IV aneurysms, a Swan-Ganz catheter and ventriculostomy were also placed. All patients were treated under general anesthesia with neurophysiologic monitoring to include brainstem auditory evoked responses, somatosensory evoked potentials, and electroencephalography. The mean arterial pressure was often lowered 15 to 20% during coil deployment, particularly in the acute hemorrhagic lesion. As soon as the dome was secured, mean arterial pressure was elevated. As soon as the dome or excrescence, if present, was controlled, heparin was administered at a dose of 2000 units, and then activated clotting time of 2 to 2.5 times baseline was maintained throughout the procedure and for 24 hours after endosaccular occlusion. The placement of a ventriculostomy in an acute fashion did not limit the heparinization (*Table 3*).

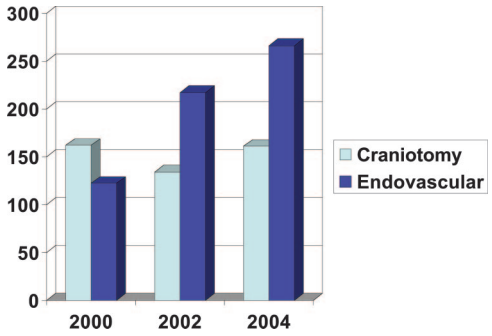

FIGURE 3. *Bar graph demonstrating the evolving practice paradigm toward endovascular treatment.* y *axis, units represent number of aneurysms treated.*

The goal involved no filling of the aneurysm under full anticoagulation with rotational views obtaining at least six different views of the aneurysm and, more recently, with a rotational technique with three-dimensional reconstruction. After occlusion of the aneurysm, the mean arterial pressure was increased to a minimum of 100 mmHg and, with the exception of heparin infusion for 24 hours, patients were treated identically to any transcranial surgery patient, with prophylactic volume expansion and all the critical care protocols for an aneurysm treated with transcranial microsurgical repair. When portions of the coil mass extended beyond the aneurysm neck, antiplatelet agents were administered after surgery for at least 6 weeks. Elective stent placement was preceded by antiplatelet therapy (aspirin and IIb/IIIa inhibitors) for at least 3 days. For patients with SAH requiring stent placement because of coil prolapse, an intraoperative loading dose of antiplatelet therapy was given. All patients receiving a stent received at least 6 weeks of postoperative antiplatelet

TABLE 3. Jefferson Hospital for Neuroscience endovascular treatment protocol[a]

Placement of arterial line, central venous line, and ventriculostomy for Hunt and Hess Grades III and IV in all patients with SAH
General anesthesia
Neurophysiological monitoring: BAERs (for posterior circulation and posterior communicating aneurysms), SSEP, EEG
MAP lowered 15–20% during coil deployment
Heparin 2000 units after dome secured; ACT 2.0–2.5 times baseline; fresh ventriculostomy does not limit heparinization
Goal: no filling of aneurysm under full anticoagulation; rotation in multiple views
MAP increased to 100 mmHg after coiling completed to increase cerebral perfusion
Heparin infusion 24 h with goal of ACT twice that of baseline followed by 24 h dextran; antiplatelets agents when necessary
Follow-up angiography and MRA at 6 mo

[a] SAH, subarachnoid hemorrhage; BAERs, brainstem auditory evoked responses; SSEP, somatosensory evoked potential; EEG, electroencephalography; MAP, mean arterial pressure; ACT, activated clotting time; MRA, magnetic resonance angiography.

therapy. All elective patients must be hospitalized overnight, with the average length of stay being 48 to 72 hours at our institution. This is because of the use of postembolization anticoagulation and the need for frequent nursing neurological assessments for delayed thromboembolic and/or femoral access site complications.

A 6-month follow-up angiogram is obtained with a concurrent gadolinium-enhanced magnetic resonance angiography (MRA). Thereafter, the patients are followed up at 6-month intervals with MRA for 18 months. If there are no changes from the initial MRA examination, the patients are then followed up annually with MRA unless there is an indication of regrowth. Such patients then undergo cerebral angiography (*Fig. 4*). Exclusions to the above protocol are made for elderly patients or those with incomplete obliteration on initial therapy.

Clinical Results

We recently reviewed our outcomes with endovascular management of posterior circulation aneurysms. The breakdown of aneurysm location was as follows: 60% basilar apex, 20% posteroinferior cerebellar artery, 12% posterior cerebral artery, 5% superior cerebellar artery, and 4% anteroinferior cerebellar artery, with eight technical failures treated with microsurgery. Angiographic outcomes were 80% complete obliteration and 20% partial neck remnant. Clinical outcomes based on Glasgow Outcome Scale scores were 90% excellent or good, 5% fair, 2.5% poor, and 2.5% mortality. Procedural complications occurred in 6% of patients, mostly involving transient morbidity from thromboembolic events. We also analyzed outcomes of coil embolization of 46 ruptured middle cerebral artery aneurysms resulting in an independent outcome (mRs 0–2) for 85% of patients with Hunt and Hess Grades I to III and a complete or near complete obliteration rate of 93% for all patients. Our overall experience both demonstrates a learning curve and reflects the growth of technology that has reduced the technical failure rate of 16% noted within the first 6 years to 8% for the last 5 years. To date, 7.2% of patients have required retreatment because of recurrence; longer follow-up demonstrates that this number is increasing. Beginning in December 2003, Neuroform stent-assisted coiling was used for patients who could not be treated without this technique because of a fundus-to-neck ratio of less than two. A total of 172 patients underwent 165 deployments. Initial angiographic outcomes show a complete occlusion rate of 95%. Initially, with the first generation delivery system, there were seven failures to deploy. All patients underwent attempted coil embolization without stent placement. There were two strokes, primarily related to stent placement within the M1 segment with perforator and lenticulostriate occlusion. We have had five patients experience transient ischemic attacks with no angiographic cause. There has been a higher complication rate with stent-assisted coil embolization for middle cerebral artery aneurysms and for recurrent aneurysms previously embolized. *Table 4* summarizes the clinical outcomes analyzed at our institution.

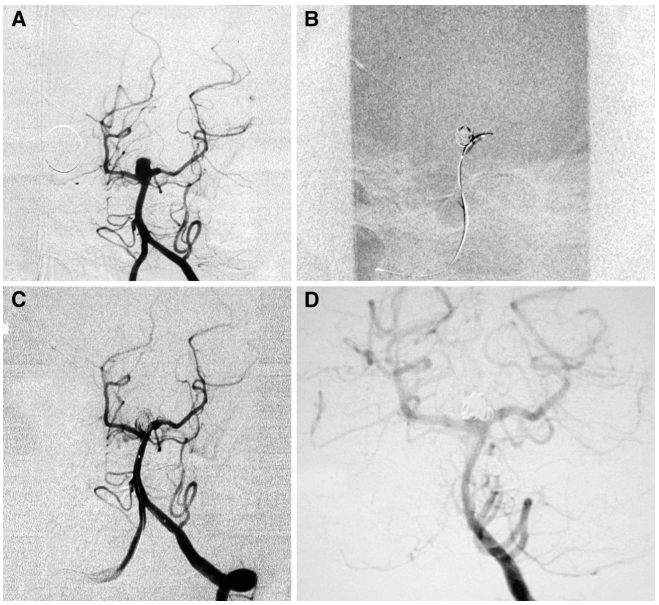

FIGURE 4. *Angiograms demonstrating the role of balloon-assisted coil embolization and long-term follow-up in endovascular treatment.* A, *anteroposterior view demonstrating a wide-necked basilar–P1 junction aneurysm in a 49-year-old patient with Hunt and Hess Grade IV SAH.* B, *intraoperative view demonstrating an inflated balloon maintaining the microcatheter and coils within the aneurysm neck during embolization.* C, *immediate postembolization view while fully anticoagulated demonstrating a small residual neck filling that was obliterated completely at the 60-month follow-up.* D, *60-month follow-up view demonstrating complete obliteration despite a suggestion of recurrence on MRA.*

CLINICAL TRIAL OUTCOMES

One of the earliest prospective studies published on Guglielmi detachable coil aneurysm treatment involved 403 patients treated at eight centers in a Food and Drug Administration trial leading to approval in 1995 (91). Patients were selected for coil embolization because of surgical exclusion risk factors including difficult size or location in 69%, failed surgical exploration in 13%, poor neurological status in 12%, and poor medical status in 5%. Aneurysm dome morphological features were characterized as small (4–10 mm) in 61%;

TABLE 4. Summary of clinical outcomes[a]

Hunt and Hess Grade	No. of patients (%)
I	454 (46)
II	385 (39)
III	79 (8)
IV	29 (3)
V	39 (4)

[a] There were 986 patients available for 6-month follow-up.

large (10–24 mm) in 35%; and giant in 4%, with a small neck size (<4 mm) in 54%, a wide neck size in 36%, and fusiform in 6%. Aneurysm location was in the posterior circulation in 57%, with the three most common sites involving basilar bifurcation (31%), anterior communicating (13%), and posterior communicating (13%). Angiographic outcomes were dependent on aneurysm morphological features, with 71% achieving complete occlusion rate in small aneurysms with a small neck versus 31% achieving complete occlusion in small aneurysms with a wide neck. The overall morbidity and mortality rates were 8.9% and 6.2%, respectively, with intraprocedural rupture in 2.7%, thromboembolic events in 2.5%, and unintentional parent vessel occlusion in 3% with a rebleed rate of 2.2%. Although these preliminary data led to Food and Drug Administration approval, the long-term efficacy remained unknown.

Murayama et al. (61) provided a more recent review of an 11-year experience with 916 aneurysms at a single institution. They divided treatment groups into an early cohort treated from 1990 to 1995, and a latter cohort treated from 1995 to 2002. The overall rate of complete occlusion improved from 50 to 57% with fewer partial or incomplete treatments in the latter group. The recanalization rate was 21%, with a reduction from 26 to 17% between the initial and more recent groups. The technical complication rate was 8.4% and was comprised mostly of thromboembolic events and intraprocedural rupture. The overall rate of delayed aneurysm rupture was 1.6% but was only 0.5% in the more recently treated cohort, predominately involving large or giant aneurysms. This study demonstrated better results with the evolution of newer coil techniques and technology; however, recanalization and rate of delayed rebleeding remained a concern requiring close follow-up imaging studies. Byrne et al. (13) reviewed a 5-year experience in England with 313 patients embolized after SAH. They achieved complete occlusion in 64%, small remnant in 34%, and incomplete treatment in 2%. Follow-up angiography at 6 to 12 months after embolization demonstrated a stable occlusion in 85% and recurrence in 15%, whereas there was progressive thrombosis in 8.5% of patients. Annual rebleeding rates were 0.8% in the first year, 0.6% in the second year, and 2.4% in the third year, with no rebleeds in those followed up beyond 3 years. Rebleeding occurred in three (7.9%) out of 38 aneurysms with an unstable occlusion, and one (0.4%) out of 221 aneurysms with a stable occlusion observed on 6-month follow-up angiography. Raymond et al. (76) demonstrated that recurrent aneurysms have a low incidence of rebleeding in a retrospective review of 501 aneurysms with a recurrence rate of 33.6% over an average of 12 months demonstrated on angiographic follow-up, but a hemorrhage rate of only 0.8% over a mean clinical follow-up period of 31 months.

The success documented in several retrospective and prospective series on endovascular treatment led to a need for Level I evidence (25, 38, 88). Koivisto et al. (48) carried out a small prospective, randomized trial comparing endovascular and surgical clipping outcomes of ruptured aneurysms in 109 patients. They found no difference in Glasgow Outcome Scale scores and neuropsychological testing at 12 months after treatment between the two groups. Angiographic obliteration rates were better in the surgical clipping arm (86% versus 77% complete) with no delayed rehemorrhages at 1 year in either group. The most comprehensive study to date is the International Subarachnoid Aneurysm Trial (59). This study identified 9559 patients with ruptured aneurysms and randomized the 2143 patients deemed by both the open surgical and endovascular teams to be amenable to either treatment. The primary outcome assessment was a modified Rankin score of 3 to 6 (dependent or dead) at 1 year of clinical follow-up. 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 it was slightly more frequent in the endovascular group (0.15% versus 0.07%). 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 (World Federation of Neurosurgical Societies Grades 1–3, 88%), and certain aneurysm morphological features and location (size <10 mm, 93%; anterior circulation, 97%), and the lack of significant outcome difference in all mRs groups other than 3 to 6 (40). Clearly, many questions surround this study, but it remains the only Level I evidence comparing endovascular with open surgical treatment of ruptured aneurysms.

COMPLICATION MANAGEMENT AND AVOIDANCE

Thromboembolic Events

In our experience, the two most important coil placements related to complication avoidance are the first and last coil. Reported rates of thromboembolic complications occurring during Guglielmi detachable coil embolization vary widely, with estimates ranging from 2.5 to 28% (6, 18, 21, 28, 70, 75, 91). The incidence of clinically silent infarcts, or those causing transient ischemic attacks demonstrated on diffusion-weighted magnetic resonance imaging is as high as 60 to 80%, frequently occurring in vessels proximal to the treated aneurysms as a result of catheter manipulation and with an increased risk associated with those undergoing balloon assisted procedures for wide-neck aneurysms (79, 83, 84). The first coil should be placed with few, if any, attempts to reposition it within the aneurysm dome to minimize the risk of disrupting any fresh thrombus within the aneurysm or on the coil itself. The final coil placed should be the one that provides optimal aneurysm occlusion without forcing coil into the parent vessel, because this provides a thrombogenic surface for delayed thromboembolic events. We have learned that attempts to obtain the ideal angiographic result by overpacking the aneurysm until coils begin to move or herniate at the neck provides

minimal improvement in long-term aneurysm obliteration at a significant cost of ischemic events and hemorrhagic complications associated with longer-term administration of antiplatelets, anticoagulation, or both. Close follow-up of aneurysms left with a small neck remnant to avoid a complication demonstrates a 7% rate of recurrence requiring retreatment associated with low morbidity and no delayed hemorrhages. Thromboembolic events can be avoided before coil embolization begins by verifying patient response to heparin administration with an activated clotting time, as well as platelet aggregometry to determine the percentage of inactive platelets with use of selective platelet inhibitors. When a coil loop is present in a stable position within the parent vessel, we routinely use 48 to 72 hours of heparinization and 24 to 48 hours of dextran in conjunction with a minimum of 6 weeks of aspirin and clopidogrel. When coil loops are moving within the parent vessel, we attempt to place a stent to wedge the coil loop into the aneurysm or against the vessel wall, allowing an endothelial layer to grow over the coil. When a thromboembolic event is recognized during embolization, we quickly complete aneurysm occlusion to reduce the risk of hemorrhage from an unsecured aneurysm because intra-arterial antiplatelet or fibrinolytics may be needed. A variety of agents along with mechanical thrombolysis have been effective for intra-arterial or intravenous treatment of thromboembolic events, including tissue plasminogen activator (47, 74), urokinase (19), and/or abciximab (31); however, there is a risk of hemorrhage with this procedure. The use of IIb/IIIa inhibitors may be a safer and more effective option, because they were shown in one study to provide complete or partial resolution of thrombus in 13 out of 13 patients with no hemorrhagic complications (31).

Intraoperative Rupture

The rate of rupture during coil embolization is cited in most studies to be between 2 and 8%, causing morbidity or mortality in up to 50% of patients (22, 50, 57, 61, 69, 77). We have experienced a rupture rate of 1.4% occurring at multiple steps in the procedure, noting dye extravasation during contrast injection proximal to the aneurysm prior to aneurysm catheterization, during introduction of the guidewire or microcatheter into the aneurysm, and during coil placement. Raymond et al. (76) demonstrated a learning curve in both technique and technology improvements, reducing the incidence of intraprocedural rupture as it occurred in five out of the first 25 patients treated acutely, one out of the next 25 patients, and none of the last 25 patients during a 3-year period. Risk factors for intraprocedural rupture include small aneurysm size, recent rupture, and presence of daughter sac. To avoid intraprocedural rupture, as mentioned above, one must remember that the most important coil placements are the first and last coils. Before placing the first coil, selection of a soft hydrophilic guidewire and microcatheter is crucial to minimize force and tension that may build up in the system during aneurysm catheterization. To avoid the microcatheter jumping into the aneurysm, the guidewire should precede the catheter into the aneurysm followed by removing any forward tension on the microcatheter before entering the aneurysm, then slowly removing the guidewire under close fluoroscopic observation. The microcatheter should be positioned to allow the coil loops to break without excessive stress on the aneurysm wall. The size of the first coil is undersized, 1 to 2 mm smaller than the maximal fundus diameter. When perforation occurs during catheterization, anticoagulation is reversed immediately and coils are deposited into the subarachnoid space and pulled back against the outer wall of the aneurysm to occlude the perforation site. Completing coil embolization within the aneurysm follows as the microcatheter is pulled back into the dome. Our experience has led us to avoid packing an aneurysm with additional coils that displace the coil mass and aneurysm dome under tension. This increases the danger of the final coil causing rupture with little additional improvement in long-term angiographic outcome and protection from hemorrhage. We also have been aggressive in ventriculostomy placement in most patients with SAH, which has prevented permanent severe neurological deterioration in all cases of intraprocedural rupture.

Management of SAH-related Vasospasm

Vasospasm affects 60 to 70% of patients after SAH, resulting in symptomatic ischemia in approximately half of those patients. It reaches maximal severity in the second week after SAH, typically resolving spontaneously in the third or fourth weeks. Vasospasm causes death or serious disability from infarction in up to one-third of patients with SAH. Although the pathogenesis is not clearly known, the risk is related to the amount of subarachnoid blood (33, 35, 85). Transcranial Doppler (TCD) ultrasound of the circle of Willis is a useful noninvasive screening tool with a high sensitivity and specificity for vasospasm, but requires technical expertise and experience (73). Vasospasm prophylaxis includes pharmacologic therapy, judicious hydration and volume, and blood pressure support in vulnerable patients. van den Bergh et al. (90) recently demonstrated a 34% reduction in delayed cerebral ischemic events and better outcomes using a continuous infusion of magnesium after SAH in a randomized trial. Hypervolemia and induced hypertension are instituted in cases of TCD velocities indicating severe vasospasm or if there is any hint of neurological deterioration attributed to vasospasm (7). When vasospasm becomes severe, a Swan-Ganz catheter is used to optimize volume resuscitation. Pressors are used to induce hypertension, titrated in proportion to TCD velocities, or to reverse ischemic neurological deficits. Typically, volume status is aimed at central venous pressure of more than 8 to 10 mmHg, pulmonary wedge pressure of more than 14 to 16 mmHg, and mean arterial blood pressure of more than 110 to 120 mmHg. Alternated crystalloids and colloids are used for volume resuscitation, and dopamine or Neo-Synephrine drips are used for induced hypertension, after withholding all antihypertensive agents (92). If patients fail to respond to maximal

medical therapy, early diagnostic angiography with a plan for intervention is warranted (9, 24, 41, 66, 80, 82). Angiography may be used to confirm vasospasm when the cause of delayed neurological deterioration is not clear, when TCD ratios increase suddenly, or when endovascular therapy for vasospasm is necessary. Endovascular treatment of spasm traditionally has consisted of balloon angioplasty, mostly for large vessel spasm, and/or intra-arterial papaverine infusions for more distal branch vasospasm. Angioplasty is associated with greater risk of arterial rupture or dissection, especially if applied to more distal vessels, but its effect is more durable than intra-arterial pharmacologic infusions (23, 44, 51, 66). For patients with delayed SAH who have severe vasospasm proximal to the aneurysm site, a combined endovascular treatment with angioplasty and endovascular aneurysm coiling is safer than surgical clipping (12, 62). Recently, a variety of calcium channel antagonists and other vasodilators have been studied via intrathecal and intra-arterial delivery. Intrathecal nitroprusside has been proven safe, but efficacy is still controversial (81, 86, 87). The use of intra-arterial calcium channel blockers such as nicardipine, verapamil, or nimodipine has been shown to significantly reduce TCD velocities, to provide clinical improvement in up to 72% of patients, and to increase vessel caliber by 44% (8, 11, 26). The application of nicardipine prolonged-release implants in the basal cistern of Fisher Grade III SAH patients has shown promising results (45). Future therapies for vasospasm will be aimed at improved delivery systems and developing biological agents that target the numerous cellular substrates responsible for vasospasm. Many animal research studies are being carried out on intrathecal immunotherapy, which is also a vast field to explore (14, 34, 72).

FUTURE DIRECTIONS

Management of Wide-Neck Aneurysms: Evolution of Coil Technology and Stent-Assisted Techniques

With the use of early endovascular coil technology, the rate of angiographic obliteration was significantly lower for aneurysms with a fundus-to-neck ratio of less than 2 (21, 27, 91). This led to development of balloon-assisted coil embolization techniques that were successful in swine aneurysm models as early as 1994 (89). Moret et al. (60) first described the clinical use of this technique in humans and described their results on 52 aneurysm in 50 patients, achieving complete occlusion in 77%, subtotal occlusion in 17%, and incomplete occlusion in 6%, with a 1% morbidity rate and no mortalities. Several other centers have achieved excellent obliteration rates for wide-neck aneurysms with balloon-assisted coil embolization (4, 5, 49, 53). However, this technique is associated with an increased risk of thromboembolic events as high as 18% (65). Also, there may be a higher risk of hemorrhagic complications because of increased pressure at the aneurysm neck with balloon inflation (4). Although balloon-assisted coil embolization techniques remain a valuable tool, the use of stent-assisted techniques have become a more preferred alternative for wide-neck aneurysms. Early reports of intracranial stent-assisted coil embolization for a fusiform vertebro-basilar-junction aneurysms (42) and for a dissecting pseudoaneurysm of the petrous carotid artery (58) first demonstrated the application of these techniques. The development of a self-expanding flexible stent designed to navigate the tortuous intracranial vasculature has revolutionized endovascular management of wide neck aneurysm. The Neuroform stent is a nitinol stent delivered over the guidewire enclosed within a microcatheter that expands with limited radial force on the vessel. Benitez et al. (10) and Rosenwasser et al. (82) published the largest series of preliminary data with the first-generation Neuroform stent demonstrating complete occlusion in 73% of patients with a complication rate of 10.7%, mainly involving thromboembolic events. Other centers have demonstrated similar results with improved technical success of stent, delivery with a newer design, whereas procedural morbidity and mortality remains at 11% (30, 52). Newer coil designs include complex-shaped three-dimensional coils (Boston Scientific) or spherical coils (Micrus) that provide a basket-like frame to reconstruct a wide neck from within the aneurysm (17, 39, 54, 71). Although the use of stent-assisted technology has expanded rapidly, the risk of thromboembolic events is not benign and the potential for long-term development of in-stent stenosis (29) requires using a serious effort to use complex coils alone when possible.

Role of Bioactive Coils

Although the annual risk of rebleeding from partially embolized or recurrent aneurysms is not well known, the rate of recanalization after endovascular aneurysm management remains a concern for treatment durability. Several modifications of bare platinum coils exist to increase the formation of thrombus within the aneurysm, thus reducing risk of recanalization. The Matrix coil (Boston Scientific) involves a platinum coil with an outer coating of a bioabsorbable polymeric material (polyglycolic acid/lactide) that has been shown in swine aneurysm models to accelerate aneurysm fibrosis and neointima formation with increased neck tissue thickness but no parent artery stenosis (63, 64). The Cerecyte coil (Micrus, San Jose, CA) uses a similar polyglycolic acid material, but as an inner coating of a platinum coil. A different bioactive coil technology, the Hydrogel coil (Microvention, Aliso Viejo, CA), consists of a platinum coil coated with a polymer that swells on contact with blood, increasing coil volume by threefold to ninefold. Early data involving the Hydrogel coil and the Matrix coil suggest equivalent or inferior periprocedural outcomes and recanalization rates, respectively (15, 16, 32, 67). Long-term clinical efficacy of Cerecyte coils remains to be seen. 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 (36, 37). The future of bioactive endovascular technology likely will involve

delivery of growth factors (vascular endothelial growth factor, transforming growth factor β, fibroblast growth factor), gene therapies, or cellular substrates within the aneurysm that will regenerate an endothelial wall layer across the aneurysm neck (1–3, 20, 43, 46, 55, 56, 68).

CONCLUSION

It is clear that endovascular therapy of both ruptured and unruptured aneurysms is becoming a mainstay of practice in this patient population. Although endovascular therapy is not replacing open surgery, the continued improvements have allowed aneurysms that were previously amenable only to open clip ligation to be treated safely with durable long-term outcomes. This is reflected not only in larger centers, but also at most centers treating cerebrovascular disease across the country. The training of resident neurosurgeons also has reflected this fact. The great majority of residents completing fellowships for cerebrovascular neurosurgery also will be trained, if not exposed to in greater detail, in endovascular surgery to allow added armaments for cerebrovascular disease.

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FUTURE MEETINGS—CONGRESS OF NEUROLOGICAL SURGEONS

The following are the planned sites and dates for future annual meetings of the Congress of Neurological Surgeons:

2006	Chicago, IL	October 7–12
2007	San Diego, CA	September 15–20
2008	Orlando, FL	September 20–25
2009	New Orleans, LA	October 24–29

FUTURE MEETINGS—AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS

The following are the planned sites and dates for future annual meetings of the American Association of Neurological Surgeons:

2007	Washington, DC	April 14–19
2008	Chicago, IL	March 29–April 3
2009	San Diego, CA	May 2–7
2010	Philadelphia, PA	May 1–6

GIANT INTRACRANIAL ANEURYSMS: ENDOVASCULAR CHALLENGES

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THE TREATMENT OF giant aneurysms remains a formidable challenge for endovascular and surgical strategies. The use of endovascular techniques in a deconstructive (e.g., parent vessel occlusion) and reconstructive (e.g., stent coiling) methodology is reviewed. The results of endovascular coiling as a primary therapy for giant aneurysm occlusion have been disappointing. Hunterian strategies have had more success in published series, but recent developments in coil, glue, and stent technology show great promise in allowing parent vessel reconstruction as a primary endovascular target, with acceptable morbidity, mortality, and durability. A literature review of giant aneurysm endovascular treatment strategies was undertaken after 1994, when Guglielmi detachable coils were approved by the Food and Drug Administration. Where possible, follow-up, durability, and occlusion rates are also reviewed.

KEY WORDS: Coil, Endovascular, Giant aneurysm, Onyx, Review, Stent

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A giant aneurysm is defined arbitrarily as an intracranial aneurysm with a fundus diameter of 25 mm or more (35, 44, 50). Giant aneurysms are relatively rare entities, comprising approximately 5% of intracranial aneurysms in most published series (8, 28). They seem to show a predilection for regions of higher velocity blood flow, such as the cavernous and supraclinoid carotid, vertebrobasilar region, and basilar apex (7, 24, 31).

Giant aneurysms are not a homogeneous entity; three major types are those with demonstrable necks (saccular), a fusiform dilatation of the vessel wall (fusiform), and a large dilatation with distal normal vessel (serpentine) (8, 11, 33, 37). All are thought to be the result of constant aberrant vascular remodeling caused by abnormal hemodynamic flow and secondary healing responses to constant vessel injury by hemodynamic stresses. This theory seems to be supported by pathological observation (43, 57). Abnormal vessel healing from a dissection may also explain the formation of giant aneurysms, as has been suggested from study of a middle cerebral artery giant aneurysm cohort (12).

Saccular aneurysms are thought to develop from smaller saccular aneurysms caused by this aberrant flow-remodeling response (8). Layers of thrombus and scar tissue formation are, thus, often observed in the aneurysm wall (57). Similar to smaller aneurysms, giant aneurysms are often seen at points of maximal hemodynamic stress, such as flow vector points and vessel bifurcations. Damage to the endothelium induces mural thrombus formation and a secondary inflammatory response, including fibroblast invasion, collagen deposition, neovascularization of the vessel wall, and progressive weakening of the vessel wall to further hemodynamic stress. This cycle will then continue to repeat itself. As the diameter of the aneurysm grows progressively larger, the transmural pressure will rise according to the law of Laplace, which favors further expansion (8). In addition, the relatively slower flow in the aneurysm outflow zone that is seen in larger or giant aneurysms may contribute to thrombus formation (8, 43). The neovascularization of the vessel wall may also play a role in the tendency of these aneurysms to rupture (8).

Fusiform aneurysms are thought to arise from atherosclerotic degeneration of the vessel wall, leading to dilatation of the entire vessel. They often involve entire segments of a first or second order intracranial artery, incorporating branches and perforators into the lumen of the aneurysm. They are more commonly found in patients with collagenopathies such as Ehlers-Danlos

syndrome and pseudoxanthoma elasticum (25). These aneurysms are usually not amenable to surgical reconstruction and treatment often requires a Hunterian strategy with or without a revascularization procedure (6, 8, 33).

Serpentine aneurysms have a luminal dilatation similar to a fusiform aneurysm, but seem to have an irregular channel that is caused by thrombus deposition. There are instances of fusiform aneurysms that evolved into a serpentine appearance. Their treatment is usually similar (8, 40, 46) to fusiform aneurysms.

NATURAL HISTORY

As stated above, giant saccular aneurysms seem to have a predilection for locations that are subjected to higher hemodynamic stress. It also seems that sites in which significant flow redirection occurs are predisposed to the generation of giant aneurysms (16). High-risk locations include the cavernous and supraclinoid carotid arteries, the vertebral arteries and vertebrobasilar junction, which are relatively proximal to the intracranial circulation (8). The basilar apex is another common site because of the often straight flow vector directed at the basilar bifurcation (33). Aneurysms in other vessel locations are more likely to be fusiform or serpentine (2). Approximately 5% of all intracranial aneurysms are giant, and most present in the fifth to seventh decades (1). Approximately 5 to 10% present in the pediatric population. These lesions are slightly more common in females. Approximately two-thirds are in the anterior and one-third in the posterior circulation (35).

The natural history of a giant aneurysm, once it is diagnosed, is very unfavorable. Drake (13), in a landmark study, observed a group of 31 patients with what he determined to be untreatable giant aneurysms. He found a mortality rate of 66% at 2 years and over 80% at 5 years. The proportion of patients who present with rupture varies between 20 and 70%, with rebleeding rates similar to those seen in smaller aneurysms that present with subarachnoid hemorrhage (SAH) (13, 28, 50). Other methods of presentation are with mass effect and ischemic syndromes. Ischemic syndromes are seen in fewer than 10% of giant aneurysms (8, 50).

SURGICAL TREATMENTS OF GIANT INTRACRANIAL ANEURYSMS

The surgical treatment of giant aneurysms has a primary and a secondary aim. The primary aim is the permanent exclusion of the aneurysm from the circulation with possible preservation of adequate distal blood flow, and the secondary aim is the relief of mass effect caused by the aneurysm. These aims can be achieved by a variety of methods including direct clipping of the aneurysm neck, aneurysmorrhaphy (reconstruction of the vessel using redundant aneurysm sac or graft material), proximal (Hunterian) ligation, and trapping of the aneurysmal segment with or without bypass (36, 48, 55).

Clipping of the aneurysm neck is generally seen as the best treatment strategy if it is feasible. In giant aneurysm surgery, this usually involves the use of tandem clips to reinforce the wide aneurysm neck and often also involves reconstruction of the vessel branch points incorporated in the aneurysm fundus or neck. This also allows resolution of the mass effect by removal of the contents of the aneurysm fundus. A variety of clips and strategies to use them have evolved, as well as improvements in anesthetic and intensive care management, cranial base approaches, cerebral protection and monitoring, hypothermia and cardiac bypass, and operative instrumentation and technology (including microscopes). These developments have allowed primary aneurysm repair to now be performed with acceptable morbidity and mortality rates in experienced centers (3, 8).

Some aneurysms, especially fusiform or serpentine, are not amenable to direct clip reconstruction, and an alternative strategy must be used. Factors that may preclude direct repair of a giant fusiform or serpentine aneurysm include involvement of a long vessel segment, incorporation of perforators or branch vessels, calcification of the aneurysm, proximity to eloquent brain, deep location, a long or indefinable neck, and difficult or dangerous surgical access. For these lesions, alternative strategies include proximal ligation and trapping with or without bypass. Proximal ligation has been used for many years to treat these lesions, with an acceptable success rate (2). Trapping of the affected segment is only possible if the aneurysm does not incorporate critical perforators or branch vessels. The advent of minimally invasive trial balloon occlusion has allowed selection of patients appropriate for bypass procedures and increased the safety of permanent occlusion and trapping of the aneurysmal segment (2).

The early reports of Drake (13) and the more modern surgical series of Lawton et al. (32), Samson et al. (52), and Batjer et al. (5) have shown improvement in the morbidity and mortality in surgically treating these lesions. The results of these series and others in a meta-analysis by Raaymakers et al. (50), which examined the outcome of surgical treatment in unruptured aneurysms, showed posterior circulation aneurysms to have a 9.6% mortality, 37.9% morbidity, and, in the anterior circulation, 7.4% mortality and 26.9% morbidity. A recent series from the Mayo Clinic of 109 surgically treated giant aneurysms had an overall mortality of 21% and a surgical mortality of 8.6%, although this series studied exclusively aneurysms that had ruptured (49).

The experienced neurosurgeon, thus, has a large body of published experience, as well as the application of modern techniques, with which to tackle a giant aneurysm surgically. The results of these surgical techniques must always be the "gold standard" with which endovascular therapies are compared.

ENDOVASCULAR THERAPEUTIC OPTIONS

The explosion of technology that has transformed the endovascular treatment of intracranial aneurysms has led to many exciting developments in the treatment of giant aneurysms. Giant aneurysms, the "final frontier" of the neurovas-

cular specialist, have always been the most difficult lesions to treat because of their physical size, incorporation of parent vessels and perforators, and often poor tissue characteristics (e.g., thrombus, calcification, and thin tissue).

The current results of definitive surgical and endovascular treatments in the best centers remain relatively poor compared with the improvements made in the results of treatment of smaller aneurysms. Most surgical series have an operative mortality of at least 6% and a major morbidity of at least 20%. On the endovascular side, there is a significant incidence of rebleeding after coil occlusion and a relatively high incidence of recanalization and coil compaction.

Much discussion has taken place on the relative importance of surgery and endovascular strategies and their relative merits on the "big four" tenets of treatment: safety, efficacy, ease of use, and durability. The place of combined endovascular and surgical strategies also still has to be determined. There is little doubt, however, that Drake's observation that every giant aneurysm is a unique entity and must be treated as such still holds true in the current clinical environment.

The uses of endovascular techniques can generally be divided into the following categories:

1. Adjuncts to definitive therapies, such as trial balloon occlusion, Wada testing, operative suction decompression, operative balloon occlusion, and intraoperative angiography.
2. Deconstructive strategies: these aim to permanently divert flow from the aneurysm and exclude it and its parent vessel from the circulation. Techniques to achieve this include coil occlusion, detachable balloon trapping, and *n*-butylcyanoacrylate glue embolization. These techniques have commonly been performed in combination with a revascularization procedure such as an extracranial-intracranial (EC-IC) bypass if there is poor collateral flow or clinical sensitivity to a trial balloon occlusion demonstrated.
3. Reconstructive strategies: these aim to restore flow through the parent vessel while excluding the aneurysm from exposure to pulsatile blood flow. Techniques to achieve this include primary coiling with or without balloon remodeling, stenting with or without coiling, and the newer experimental technique of polymer embolization with or without stenting.

Recent advances in coil technology, including three-dimensional, bioactive, and hydrophilic coils, have made packing of the fundus and exclusion of the aneurysm neck a much more feasible goal of primary coiling. Similarly, recent advances in stent design, metallurgy, size, and delivery systems have allowed both self-expanding and balloon expandable stents to be delivered distally, accurately, and safely. These stents have allowed coiling in broad-necked aneurysms to produce far better packing and neck occlusion than previously possible. The Neuroform stent (Boston Scientific, Fremont, CA) is the first stent to receive Food and Drug Administration (FDA) approval for intracranial use; in the near future, there will be others. Another exciting development in stent technology is the use of covered stents to occlude the aneurysm neck without the need for coils (30). This has the theoretical advantage of reduction of mass effect, as well as reconstruction of the parent vessel. The use of a liquid polymer (Onyx) and its recent use in a multicenter trial, the Cerebral Aneurysm Multicenter European Onyx (CAMEO) trial, is another exciting development which shows great promise.

INDICATIONS FOR ENDOVASCULAR TREATMENT

The evaluation of a patient (and an aneurysm) for endovascular treatment is different than a surgical evaluation. Access and exposure are rarely issues that cause a major problem. The aneurysm geometry is a far more important issue for the endovascular surgeon because the dome-to-neck ratio and the neck width will determine the stability of coils placed in the aneurysm and the likelihood of both primary neck occlusion and later recanalization. The geometry will also dictate the need for adjunctive strategies, such as stenting or balloon remodeling, to retain and stabilize the endovascular repair. It will also indicate whether or not a reconstructive or deconstructive strategy should be used.

The indications for endovascular coiling treatment of giant aneurysms (with the aim of sparing the parent vessel) currently are anticipated surgical difficulty, comorbidities precluding craniotomy, poor-grade SAH, and favorable morphological features. Currently, the most common factor is anticipated surgical morbidity. A staged approach may be taken in patients with high-grade SAH, occluding the bleeding point and then planning definitive treatment once the patient has recovered.

Parent artery endovascular occlusion is usually reserved for aneurysms that cannot be treated by any other means. These lesions are usually more distally located or fusiform/serpentine, without a definable neck. The occlusion can be achieved by either detachable/pushable coils, detachable balloons, or liquid embolic material. These approaches may or may not need a bypass on the basis of test occlusion results (47, 56).

Combined surgical and endovascular treatments planned on a collaborative basis have been reported by Lawton et al. (32) and others (2, 3, 22, 41, 59). The treatments were planned on an individual basis, so it is difficult to draw any conclusions about the relative merits of each treatment for comparison.

RESULTS OF ENDOVASCULAR TREATMENT

A literature review was undertaken to assess the results of treatment of different endovascular strategies in the treatment of giant aneurysms. A PubMed literature search with the search terms "giant," "aneurysm," and "endovascular" was entered, as well as "aneurysm" and "endovascular." Series re-

TABLE 1. Results of treatment by endovascular modality[a]

Series (ref. no.)	No. of cases	No. of SAH	Anterior circulation	Posterior circulation	Method	Percent complete	Neurological morbidity (%)	Mortality (%)
Arat et al., 2002 (2)	8	0	0	8	PVO with coils	100	12.5	0
Ciceri et al., 2001 (9)	5	0	0	5	PVO with coils	100	20	0
Cognard et al., 1997 (10)	4	0	3	1	Coil	75	0	0
Eskridge et al., 1998 (14)	14	4	0	14	Coil	NS	NS	21
Ewald et al., 2000 (15)	8	0	4	4	PVO with coils + bypass	100	37.5	0
Fiorella et al., 2004 (16)	2	0	1	1	Stent + coil	0	0	0
Gobin et al., 1996 (19)	9	4	4	5	7 PVO coils + TBO, 1 coil (90%)	87.5	0	0
Gruber et al., 1999 (20)	12	5	9	3	Coil	42	33	33
Gurian et al., 1996 (21)	2	NS	2		Coil	0	NS	0
Han et al., 2003 (23)	4	0	3	1	Stent + coil	0	50	25
Hayakawa et al., 2000 (25)	10	NS	NS	NS	Coil	10	NS	NS
Islak et al., 2002 (27)	2	2	1	1	Bare stent-graft	100	0	0
Klein et al., 1997 (29)	2	2	0	2	Coil	100	50	0
Lubicz et al., 2003 (37)	18	3	18	0	PVO Coil + TBO	72	NS	11
Lubicz et al., 2004 (38)	13	4	0	13	PVO Coil + 6 selected TBOs	7.6	7.6	7.6
Mawad and Klucznik, 1995 (40)	7	NS	4	3	PVO (NBCA, coil, balloon) + TBO	100	29	0
Mawad et al., 2002 (39)	11	0	11	0	Stent + Onyx	81	9	18
Molyneux et al., 2004 (CAMEO) (42)	19	NS	NS	NS	Balloon + Onyx	47	16	0
Murayama et al., 2003 (Group A) (45)	33	NS	NS	NS	Coil	12		
Murayama et al., 2003 (Group B) (45)	40	NS	NS	NS	Coil	37.5	NS	NS
Otsuka et al., 2001 (46)	2	0	1	1	PVO Coil	100	0	0
Ross et al., 2000 (51)	27	7	21	6	8 coils, 1 NBCA, 9 PVO + TBO, 2 bypasses	37	NS	10
Sluzewski et al., 2001 (53)	6	1	0	6	PVO bilateral VA balloon occlusion, 2 bypasses	66	0	50
Sluzewski et al., 2003 (54)	31	19	17	14	Coil	52	13	10
Tateshima et al., 2000 (58)	10	NS	0	10	Coil	0	NS	NS
Uda et al., 2001 (60)	6	1	0	6	Coil, 1 bilateral VA occlusion (PVO)	0	NS	NS
Weill et al., 1998 (62)	2	0	2	0	PVO coil + EC-IC bypass	100	50	0
Wanke et al., 2002 (61)	6	0	5	1	Coil	100	NS	0
Wenderoth et al., 2003 (63)	3	2	0	3	PVO BA trunk occlusion	66	0	0
Total	316	54	106	108	Mean	56.87857143	17.2421053	7.733333333

TABLE 1. Continued

Clinical follow-up time, mean (range)	Imaging follow-up time, mean (range)	Percent recanalized	No. rebleed	Treatment failure	Comments
8 mo (6–12 mo)	8 mo (6–12 mo)	0			
8 mo (NS)	8 mo (NS)	0			
11 mo (4–17 mo)	11 mo (4–17 mo)	50			
NS (0–43 mo)	NS (0–43 mo)	N/A	1		FDA GDC trial
1d, 36 mo	1 day, 36 mo	0			
None	None	N/A		1	
7.8 mo (3–12 mo)	7.8 mo (3–12 mo)	12.5		2	
24.3 mo (1–65 mo)	24.3 mo (1–65 mo)	37.5			
NS	NS	50			
NS	15 mo	N/A		1	
NS	NS	90			All had residual necks, natural history
4.5 mo (3–6 mo)	4.5 mo (3–6 mo)	0			First covered stent experience
NS	27.5 mo (25–30 mo)	NS			
30 mo (6–80 mo)	30 mo (6–80 mo)	NS		1	
28 mo (12–48 mo)	28 mo (12–48 mo)	7.6			Postcirculation PVO
NS	NS	NS			Giant serpentine aneurysms
6 mo	5 mo (3–6 mo)	0			Onyx
12 mo	12 mo	NS			Onyx CAMEO trial
NS	NS	63		1	
12 mo	NS	52.9			UCLA experience
1.87 mo (3 wk–3 mo)	6 mo (4–8 mo)	0			Giant serpentine aneurysms
41 mo (3–96 mo)	NS	47	1	8	
15.3 mo (6–22 mo)	9.5 mo (1–15 mo)	NS	1		Bilateral balloon for VB aneurysms
41 mo (13–64 mo)	14.6 mo (1–46 mo)	45			
NS	6 mo (NS)	50	1	1	Basilar apex aneurysm series
15 mo (6–55 mo)	10.6 mo (6–14 mo)	33		1	Basilar trunk aneurysm series
1 mo	8.5 mo (6–11 mo)	0			MCA GA trap + bypass
NS	NS	NS			
NS	NS	0			Trunk occlusion with good PComAs
17.6	12.4	26.925			

[a] SAH, subarachnoid hemorrhage; PVO, parent vessel occlusion; NS; not significant; TBO, trial balloon occlusion; NBCA, *n*-butylcyanoacrylate; CAMEO, Cerebral Aneurysm Multicenter European Onyx trial; VA, vertebral artery; BA, basilar artery; EC-IC, extracranial-intracranial; N/A, not available; FDA, Food and Drug Administration; GDC, Guglielmi detachable coil; UCLA, University of California, Los Angeles; VB, vertebrobasilar; MCA, middle cerebral artery; GA, giant aneurysm; PComA, posterior communicating artery.

ported before 1994 were not included because Guglielmi detachable coils did not receive FDA approval before this time and, thus, were not widely used. The articles included had at least two giant intracranial aneurysms treated by a single endovascular method, were published in refereed journals, and the patients presented had undergone endovascular treatment as a primary and potentially curative strategy. There was a single prospective multicenter nonrandomized trial (the CAMEO trial evaluating Onyx aneurysm cement).

The results of treatment by any endovascular modality (coiling, parent vessel occlusion, Onyx, stenting with or without coil/Onyx) are presented in *Table 1*. Overall, there were 316 patients treated in the period examined. Approximately 19% had presented with SAH. A mean complete occlusion rate or cure was achieved in 57% of the cases, with 7.7% mortality and 17.2% major neurological morbidity. The mean clinical follow-up time was 17.6 months, the mean imaging follow-up time was 12.4 months, and the recanalization rate noted at this follow-up was 27% of 238 giant aneurysms for which this information was available. It should be noted that only general trends can be examined because of the poor quality of imaging and clinical follow-up and the lack of a standardized system of angiographic measurement of outcome.

Tables 2 to *5* examine the literature pertaining to specific modalities of endovascular treatment. *Table 2* is a summary of the articles that used detachable coils with the intent of parent vessel preservation as a primary strategy. The figures are worse than overall (as seen in *Table 1*): an approximately 43% complete occlusion rate, with 9% mortality and 24% major neurological morbidity. The morbidity and mortality figures are comparable with published surgical series, but the occlusion rates are much worse. Comparison of morbidity and mortality with surgery and endovascular strategies is also difficult because of variability in patient selection and poor documentation of selection criteria. It is possible that at least a proportion of these patients were unsuitable for surgical management and, thus, are not directly comparable with surgical outcomes because surgery had been judged too dangerous or the patient had other comorbidities that precluded surgery. In 164 giant aneurysms, the recanalization rate was approximately 55% where this information was avail-

TABLE 2. Summary of studies that used detachable coils with intent of parent vessel preservation as primary strategy[a]

Series (ref. no.)	No. of cases	Percent recanalized	Anterior circulation	Posterior circulation	Method	Percent complete	Neurological morbidity (%)	Mortality (%)
Cognard et al., 1997 (10)	4	50	3	1	Coil	75	0	0
Eskridge et al., 1998 (14)	14	N/A	0	14	Coil	NS	NS	21
Gruber et al., 1999 (20)	12	37.5	9	3	Coil	42	33	33
Gurian et al., 1996 (21)	2	50	2		Coil	0	NS	0
Hayakawa et al., 2000 (25)	10	90	NS	NS	Coil	10	NS	NS
Klein et al., 1997 (29)	2	NS	0	2	Coil	100	50	0
Murayama et al. (Group A), 2003 (45)	33	63	NS	NS	Coil	12		
Murayama et al. (Group B), 2003 (45)	40	52.9	NS	NS	Coil	37.5	NS	NS
Sluzewski et al., 2003 (54)	31	45	17	14	Coil	52	13	10
Tateshima et al., 2000 (58)	10	50	0	10	Coil	0	NS	NS
Wanke et al., 2002 (61)	6	NS	5	1	Coil	100	NS	0
Total	164	54.8	36	45	Mean	42.85	24	9.142857143

Clinical follow-up time, mean (range)	Imaging follow-up time, mean (range)	Percent follow-up angiography	Percent recanalized	No. of rebleed	Treatment failure	Comments
11 mo (4–17 mo)	11 mo (4–17 mo)	75	50			
NS (0–43 mo)	NS (0–43 mo)	NS	N/A	1		FDA GDC trial
24.3 mo (1–65 mo)	24.3 mo (1–65 mo)	100	37.5			
NS	NS	50	50			
NS	NS	100	90			All had residual necks, natural history
NS	27.5 mo (25–30 mo)	100	NS			
NS	NS	NS	63		1	
12 mo	NS	NS	52.9			UCLA experience
41 mo (13–64 mo)	14.6 mo (1–46 mo)	100	45			
NS	6 mo (NS)	NS	50	1	1	Basilar apex aneurysm series
NS	NS	NS	NS			
			54.8			

[a] NS; not significant; N/A, not available; FDA, Food and Drug Administration; GDC, Guglielmi detachable coil; UCLA, University of California, Los Angeles.

TABLE 3. Current literature available on Onyx liquid aneurysm filling technique[a]

Series (ref. no.)	No. of cases	No. of SAH	Anterior circulation	Posterior circulation	Method	Percent complete	Neurological morbidity (%)	Mortality (%)
Mawad et al., 2002 (39)	11	0	11	0	Stent + Onyx	81	9	18
Molyneux et al. (CAMEO), 2004 (42)	19	NS	NS	NS	Balloon + Onyx	47	16	0
Total	30	0	11	0	Mean	64	12.5	9

Clinical follow-up time, mean (range)	Imaging follow-up time, mean (range)	Percent recanalized	No. of rebleeds	Treatment failure	Comments
6 mo	5 mo (3-6 mo)	0			Onyx
12 mo	12 mo	NS			Onyx CAMEO trial
		0			

[a] SAH, subarachnoid hemorrhage; CAMEO, Cerebral Aneurysm Multicenter European Onyx trial; NS, not significant.

TABLE 4. Studies that have used stenting with or without coils or Onyx[a]

Series (ref. no.)	No. of cases	No. of SAH	Anterior circulation	Posterior circulation	Method	Percent complete	Neurological morbidity (%)	Mortality (%)
Fiorella et al., 2004 (16)	2	0	1	1	Stent + coil	0	0	0
Mawad et al., 2002 (39)	11	0	11	0	Stent + Onyx	81	9	18
Han et al., 2003 (23)	4	0	3	1	Stent + coil	0	50	25
Islak et al., 2002 (27)	2	2	1	1	Bare stent-graft	100	0	0
Total	19	2	16	3	Mean	45.25	14.75	10.75

Clinical follow-up time, mean (range)	Imaging follow-up time, mean (range)	Percent follow-up angiography	Percent recanalized	No. of rebleeds	Treatment failure	Comments
None	None	0	N/A		1	
6 mo	5 mo (3–6 mo)	100	0			Onyx
NS	15 mo	25	N/A		1	
4.5 mo (3–6 mo)	4.5 mo (3–6 mo)	100	0			First covered stent experience
			0			

[a] SAH, subarachnoid hemorrhage; N/A, not available; NS, not significant.

able and noted, with extremely variable follow-up times. It would seem that primary coiling is not a robust strategy for the majority of giant aneurysms. This may be because of the tendency of a giant aneurysm to rapidly recanalize, the large coil mass to compact, and the difficulty of occluding a broad aneurysm neck with currently available coil technology.

Table 3 illustrates the current literature available on the Onyx liquid aneurysm filling technique and its use in giant aneurysms. The seminal report by Mawad et al. (39) and the multicenter European trial (CAMEO) (42) describe the use of Onyx as a primary curative strategy. Mawad et al. examined the use of Onyx with a stent crossing the aneurysm lumen in 11 patients. The CAMEO trial studied 19 patients with a balloon remodeling technique used to help deliver the polymer. A mean complete occlusion rate of 64% was achieved, and there were no recanalizations noted in the short mean follow-up period (< 1 yr). Mortality and major morbidity were comparable with surgical series (9 and 12.5%, respectively). Recanalization and subsequent rupture of Onyx treated aneurysms have been reported (42). The polymer is not adhesive, and, therefore, a channel may open between the polymer and the aneurysm internal lumen (42).

Table 4 illustrates the studies that have used stenting with or without coils or Onyx. The article by Islak et al. (27) is the only one to examine the use of a bare stent within a stent to occlude a giant aneurysm neck. Islak et al. used a covered stent inside a bare porous stent to achieve this and gained angiographic occlusion in the two cases in which it was performed. The results of coiling with stenting, however, are disappointing. There were no angiographically complete occlusions in the six patients examined. The question of selection bias must again be asked. Clinical follow-up was again extremely short (< 6 mo). It is difficult to draw any other conclusions from this small patient population.

Table 5 shows the results of parent vessel occlusion with or without bypass to achieve aneurysm occlusion. Most occlusions were performed with detachable coils. Detachable balloons were used in earlier series, but have recently become unavailable

TABLE 5. Results of parent vessel occlusion with or without bypass to achieve aneurysm occlusion[a]

Series (ref. no.)	No. of cases	No. of SAH	Anterior circulation	Posterior circulation	Method	Percent complete	Neurological morbidity (%)	Mortality (%)
Wenderoth et al., 2003 (63)	3	2	0	3	PVO BA trunk occlusion	66	0	0
Otsuka et al., 2001(46)	2	0	1	1	PVO Coil	100	0	0
Weill et al., 1998 (62)	2	0	2	0	PVO coil + EC-IC bypass	100	50	0
Lubicz et al., 2004 (38)	13	4	0	13	PVO Coil + 6 selected TBOs	7.6	7.6	7.6
Lubicz et al., 2003 (37)	18	3	18	0	PVO Coil + TBO	72	NS	11
Arat et al., 2002 (2)	8	0	0	8	PVO with coils	100	12.5	0
Ciceri et al., 2001(9)	5	0	0	5	PVO with coils	100	20	0
Ewald et al., 2000 (15)	8	0	4	4	PVO with coils + bypass	100	37.5	0
Mawad and Klucznik, 1995 (40)	7	NS	4	3	PVO (NBCA, coil, balloon) + TBO	100	29	0
Sluzewski et al., 2001 (53)	6	1	0	6	PVO bilateral VA balloon occlusion, 2 bypasses	66	0	50
	72	10	29	43	Mean	81.16	17.4	6.86

Clinical follow-up time, mean (range)	Imaging follow-up time, mean (range)	Percent follow-up angiography	Percent recanalized	No. of rebleeds	Treatment failure	Comments
NS	NS	100	0			Trunk occlusion with good PComAs
1.87 mo (3 wk–3 mo)	6 mo (4–8 mo)	0	0			Giant serpentine aneurysms
1 mo	8.5 mo (6–11 mo)	100	0			MCA GA trap + bypass
28 mo (12–48 mo)	28 mo (12–48 mo)	NS	7.6			Posterior circulation PVO
30 mo (6–80 mo)	30 mo (6–80 mo)	100	NS		1	
8 mo (6–12 mo)	8 mo (6–12 mo)	87.5	0			
8 mo (NS)	8 mo (NS)	0	0			
1 d–36 mo	1 d–36 mo	100	0			
NS	NS	NS	NS			Giant serpentine aneurysms
15.3 mo (6–22 mo)	9.5 mo (1–15 mo)	0	NS	1		Bilateral balloon for VB aneurysms
13.16	14		1.085714286			

[a] SAH, subarachnoid hemorrhage; PVO, parent vessel occlusion; BA, basilar artery; EC-IC, extracranial-intracranial; TBO, trial balloon occlusion; NS, not significant; NBCA, *n*-butylcyanoacrylate; VA, vertebral artery; PComA, posterior communicating artery; MCA, middle cerebral artery; GA, giant aneurysm; VB, vertebrobasilar.

because of manufacturing restrictions. The results with this treatment method seem to be encouraging: of 72 cases, an 81% initial occlusion rate was achieved, with an extremely low recanalization rate (1%). Mortality was 7%, morbidity 17%, and the mean follow-up period with imaging was 14 months.

CURRENT TREATMENT PARADIGMS FOR GIANT ANEURYSMS

The results of this nonstatistical analysis must be interpreted with caution. However, it seems likely that the initial morbidity and mortality related to endovascular treatment of giant intracranial aneurysms are comparable with surgery. It is also likely that the results of parent vessel sacrifice, where possible, seem to be the superior endovascular treatment in terms of durability and success in initial treatment. The short follow-up time in the majority of these reports precludes any other conclusions, as does the variability in follow-up imaging. Only one study (the CAMEO trial) (42) used an independent referee to judge the results of follow-up imaging. In addition, there is currently no standardization of the results of endovascular treatment. A system of reporting similar to that used in the North American Symptomatic Carotid Endarterectomy Trial (4) needs to be proposed.

CURRENT RESEARCH

There is currently great interest in the development of covered or partially covered stents to occlude the neck of an aneurysm. Currently, these stents have significant in-stent stenosis, stiffness, intracranial delivery problems, and thromboembolism. An elegant summary of the current theories of aneurysm flow redirection by a stent, and the influence of stent porosity on aneurysm filling, has been provided by Lieber and Gounis (34) and also demonstrated in a model of a human basilar artery by Imbesi and Kerber (26). The reduction in stent porosity from 85 to 76% had a significant impact on the stagnation of flow inside an aneurysm. As the authors surmise, an optimal stent may be devised that combines the properties of flow stagnation in an aneurysm with a low neointimal reaction and minimal in-stent

stenosis. The use of coated stents in the coronary literature, especially heparinoid and sirolimus coated stents, such as the Hepacoat and the Cypher stents (Cordis Corp, Miami Lakes, FL), respectively, has been associated with a significantly reduced incidence of restenosis.

There has been little in the literature on the use of bioactive coils (coated hydrophilic or pro-inflammatory coils such as HydroCoil and Matrix coils, respectively) in the treatment of giant aneurysms. It is hoped that these treatments, with or without adjunctive treatments such as stenting, will lead to an improvement in the initial occlusion rate for giant aneurysm treatment where parent vessel preservation is a desirable goal. The incidence of aseptic meningitis in these bioactive coils is, however, cause for some concern (41). Recent research into growth factor markers and histological changes associated with aneurysm rupture, including inflammation and remodeling, and increased vascular endothelial growth factor/transforming growth factor-β/fibroblast growth factor expression, may provide an avenue for modification of aneurysm healing after endovascular repair. This is a very exciting avenue for further study (17, 18).

CONCLUSION

The current results for the endovascular treatment of giant aneurysms with parent vessel preservation are not encouraging with current technology. The endovascular application of a Hunterian strategy seems to result in a durable treatment of these lesions. It is hoped that future developments, coupled with carefully designed studies and rigorous follow-up, will yield significant improvement in occlusion rates, durability, and reduction in complications for these formidable aneurysms.

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CHALLENGES IN THE ENDOVASCULAR TREATMENT OF GIANT INTRACRANIAL ANEURYSMS

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OBJECTIVE: Giant intracranial aneurysms present unique therapeutic intricacies. The purpose of this study was to evaluate the anatomic and hemodynamic characteristics of these lesions and the current endovascular and combined surgical and endovascular techniques available for their treatment.

METHODS: A review of the literature and the personal experiences of the authors with endovascular treatment of giant aneurysms are presented. This review included anatomic and hemodynamic features and analysis of the diverse endovascular techniques that have been reported for the management of these aneurysms.

RESULTS: Anatomic features that create particular challenges in the therapeutic approach of giant aneurysms include size, shape (saccular, fusiform, serpentine), neck dimensions, branch involvement, intraluminal thrombosis, and location. Hemodynamic characteristics that affect endovascular treatment are lateral or terminal aneurysm type of flow and embolic material placement (inflow versus outflow aneurysmal region). The current endovascular therapeutic approaches include parent artery occlusion, trapping, endosaccular embolization with or without adjunctive techniques such as balloon-assisted or stent placement, and combined surgical and endovascular approaches, mainly with surgical revascularization and endovascular occlusion.

CONCLUSION: Although there are a wide variety of endovascular therapeutic options for the treatment of giant intracranial aneurysms, none of the current techniques is completely successful and free of complications in the management of these complex lesions. A detailed and individualized analysis of each case in conjunction with sufficient understanding of the anatomy and hemodynamics of a particular aneurysm should guide the therapeutic decision. Further research advances will assist in elucidating the factors predisposing to genesis, progression, and aggressive clinical manifestations of these giant lesions.

KEY WORDS: Bypass, Coil embolization, Endovascular, Giant intracranial aneurysms, Parent artery occlusion, Trapping

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Giant intracranial aneurysms often pose difficult and unique problems in their surgical or endovascular treatment. Although they comprise approximately 5% of all intracranial aneurysms in most clinical series (23, 58, 80, 98, 100), they represent an increasing proportion of lesions seen at referral centers (91). Giant aneurysms have been defined as those whose maximum diameter exceeds 2.5 cm (14, 79). Even though the limit of 2.5 cm was selected in an arbitrary fashion, the early studies conducted by Locksley (79) on the natural history of intracranial aneurysms grouped the lesions above this maximum value because of increased rate of associated morbidity and mortality. What makes an aneurysm giant is, by definition, its size, but this implies high morbidity, mortality, and particular difficulties in its management.

The natural history of these lesions is deceptive because they are associated with high morbidity and mortality rates. Mortality rates for untreated giant aneurysms have been reported to be between 65 and 100% after 2 years of follow-up (68, 87, 96). In a prospective study, Drake et al. (25) reported that 15 out of 18 patients with untreated giant aneurysms

died or experienced severe morbidities as a direct result of complications caused by the aneurysm. The mainstream of treatment for intracranial aneurysms has been surgical clipping since Dandy (19) introduced the technique in 1937. However, the peculiar characteristics of giant aneurysms sometimes demand more complex objectives in the treatment than the simple isolation of the aneurysm lumen while preserving the parent artery patency. These objectives may include prevention of hemorrhage, treatment and control of thromboembolic complications, and relief of mass effect. Therefore, techniques that go from the isolation of the aneurysm with surgical clipping to sacrifice of the parent artery have been part of the surgical armamentarium available for the treatment of these lesions. Despite the significant advances in the microsurgical techniques, giant aneurysms have surgical morbidity and mortality rates that are relatively high. Endovascular therapy has evolved as a safe and effective treatment option for selected intracranial aneurysms; however, similar to the surgical approach, the endovascular treatment of giant aneurysms is difficult and is often associated with a high rate of complications and failures.

In this article, we discuss the specific peculiarities of giant aneurysms that affect the endovascular approaches and techniques and the available endovascular and combined surgical and endovascular therapeutic strategies, providing an overview of the rationale, advantages, and disadvantages of each method.

ANATOMICAL PECULIARITIES

Aneurysms that reach a size larger than 2.5 cm present unique anatomical characteristics with relevant therapeutic implications. Aneurysms of this size have a body and fundus that exceed the size of the parent artery incorporating almost invariably a significant proportion of the parent vessel either in a saccular aneurysm with wide neck or in a fusiform dilatation. Also, the disproportion between the size of the aneurysm and the parent artery may include several branches of the parent artery either in the fundus or neck of the aneurysm. These peculiarities have significant impact in both the surgical and endovascular treatment.

Saccular aneurysms are more common and arise from gradual enlargement of a small aneurysm with a neck (113). In a series of 335 giant aneurysms in the anterior circulation, Drake et al. (25) found that 15% were fusiform. Similarly, Steinberg et al. (114), on reviewing 201 unclippable aneurysms of the posterior circulation treated by Hunterian ligation, of which 87% were giant, found 17% fusiform aneurysms.

In both types of giant aneurysms, there is a defect in the arterial wall involving the elastic lamina and muscular layers (4, 41, 77, 92, 118). The specific mechanism generating the development of saccular aneurysms is not completely understood. Both congenital and acquired causes have been suggested. The congenital theory states that medial gaps that are identifiable during fetal development represent weakness of the wall where aneurysms would tend to form (28).

An alternative theory states that aneurysms are the result of degenerative changes in the arterial wall that appear with age and hypertension (1, 17, 18, 51, 113). Atherosclerotic changes and calcifications of aneurysm necks support this view.

Recent studies by Frösen et al. (31) have been dedicated to better understanding the mechanisms that produce aneurysm rupture. They have identified four histological wall types that represent consecutive stages of wall degeneration proceeding to rupture. These types include: Type A, endothelialized wall with organized smooth muscle cells; Type B, thickened wall with disorganized smooth muscle cells; Type C, hypocellular wall with myointimal hyperplasia or organizing thrombosis; and Type D, extremely thin hypocellular wall lined with thrombus. They also have shown that transforming growth factor β receptor 2 and vascular endothelial growth factor receptor 1 were associated with rupture, and that transforming growth factor β receptor 3 and vascular endothelial growth factor receptor 1 were associated with wall remodeling (32). In their report, the giant aneurysms that were included were unruptured, with a maximum diameter of 34 mm. These studies suggest that saccular aneurysms are continuously undergoing a process of remodeling that includes constructive phases to enlarge their size, with addition of smooth muscle cells and endothelium, as well as a destructive activity, mediated by proteolysis to allow this change. In this regard, a predominant de-endothelialization, fresh and organizing luminal thrombosis, proliferation ratio in myointimal hyperplasia/organizing thrombosis areas, apoptosis ratio outside these areas, and leukocyte infiltration were seen in the walls of ruptured aneurysms. Based on these findings, giant aneurysms should have an evolution characterized by a successful adaptation for a prolonged time to wall tension and other hemodynamic factors without rupture, but also have a formation of wall that is not strong enough to prevent distension, allowing the lesion to expand until reaching giant size.

Fusiform aneurysms have several causes. Atherosclerosis may be present but is not the rule (97). Diseases such as von Recklinghausen's disease, fibromuscular dysplasia, systemic lupus erythematosus, and various collagen vascular diseases have been associated with abnormalities of the arterial wall as described above (30, 61) and have been found in fusiform aneurysms. Congenital and acquired segmental abnormalities of the arterial wall have been implicated in fusiform aneurysms in children (60, 108). Other causes associated with fusiform aneurysms are mycotic origin, dissecting aneurysms, and arteriovenous malformation association (38).

Size, the typical characteristic that defines giant intracranial aneurysms, is the anatomical feature that produces the most challenges in their treatment. From a surgical perspective, the amount of brain retraction, dissection of surrounding structures, and the deformity of perianeurysmal vessels create obvious difficulties. From the endovascular perspective, size may limit the efficacy of the endoluminal occlusion in controlling symptoms commonly associated with aneurysm, such as mass effect. Giant aneurysms may require vast quantities of embolic material, such as platinum coils, which actually may

exacerbate symptoms secondary to mass effect (46). However, even more important in the endovascular treatment of these lesions is the presence of wide necks. In a review of 102 giant intracranial aneurysms treated with endovascular techniques in our institution (unpublished data), only two had a relatively small neck (sac-to-neck ratio more than two), and none was smaller than 4 mm. The presence of a wide neck has been associated with incomplete occlusions and higher recanalization rates after endosaccular obliteration with embolic materials (40, 91). The neck size of the aneurysm also may interfere significantly with the surgical success, requiring complex arrangements of surgical clips to obtain adequate aneurysm isolation.

The large size of giant aneurysms is responsible for the development of thrombosis inside of their lumen (*Fig. 1*). According to the classic studies by German and Black (34, 35), when the ratio of the intra-aneurysmal volume to the area of the orifice exceeds 25:1, thrombosis is more likely to occur. The presence of thrombus inside of the aneurysm has a negative impact on the efficacy of the endosaccular obliteration being associated with higher recanalization rates secondary to migration and compaction of the embolic material (most commonly coils) into the wall thrombus (67) and with inadvertent embolic events during endoluminal catheterization and coil deposition.

In fusiform aneurysms, there is involvement of the entire artery with a circumferential arterial dilatation (112), there is a higher chance of incorporating branches arising from the aneurysm, and they do not tend to occur in arterial bifurcations (41, 77, 109). Surgical clipping of a small fusiform aneurysm may be possible using special clips, such as the angled fenestrated type (117), but this is extremely difficult in giant fusiform aneurysms (102). Endovascular coil bracing has been used as temporary wall reinforcement (3, 94). However, this technique is insufficient to protect the aneurysm.

The anatomic results of coil embolization in saccular aneurysms depend on the size of the neck. Fusiform aneurysms are the most challenging for this technique because they have no neck, limiting the possibility of an endovascular approach if the preservation of the parent artery is required. New tools such as the Neuroform stents (Boston Scientific Inc., Freemont, CA) may play a role in reconstructing the arterial lumen in a fusiform aneurysm. However, the stent requires adequate support in both proximal and distal terminus to be held in place and to prevent stent displacement into the aneurysmal pouch. Finding this support may be difficult, if not impossible, in giant fusiform aneurysms.

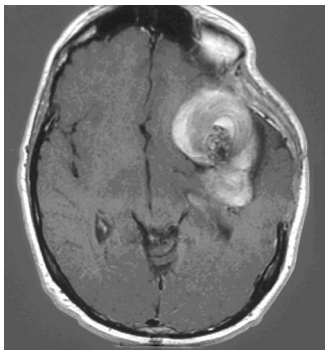

FIGURE 1. *Axial T1-weighted magnetic resonance imaging scan of a patient with a giant fusiform partially thrombosed aneurysm of the left middle cerebral artery. The lumen of the artery (central flow void) is surrounded with layers of clot in a laminar fashion. The tendency of giant aneurysms to thrombose is a major difficulty in the stability of endovascular embolization of these lesions with high incidence of coil compaction into the wall thrombus.*

The specific anatomical location of a giant aneurysm within the intracranial circulation is a fundamental consideration for endovascular and surgical treatment. For example, giant aneurysms of the anterior communicating artery with the dome pointing posteriorly in relation to the plane of the pericallosal arteries are more difficult for surgical approach (99) and have a significantly higher risk of incomplete occlusion and higher recanalization after endovascular embolization (39).

Finally, the involvement of branches into the aneurysm sac limit the possibilities of endovascular embolization, thereby increasing the risk of thrombosis of the origin of these arteries, the risk of embolization of these branches from thrombus induced by the embolic material, and the need to leave residual portions of the aneurysm unembolized to preserve the origin of these vessels.

HEMODYNAMIC PECULIARITIES

Hemodynamic analysis of intracranial aneurysms have provided valuable insight in understanding the pathological mechanisms involved in the behavior of giant aneurysms (9, 11, 33, 99, 104). Multiple hemodynamic characteristics of intracranial aneurysms are shared among small and giant lesions. However, the main difference between small and giant aneurysms is the relative tendency of the latter to grow and to demonstrate a higher incidence of intra-aneurysmal thrombosis (63, 101).

There are two major types of giant saccular aneurysms: lateral and terminal. In hemodynamic models of lateral aneurysms, three distinct flow zones have been identified (42): the inflow zone at the distal neck, the outflow zone at the proximal neck, and the central area of a slow flow. Flow velocities and shear stress are higher in the inflow zone. Pathological, radiological, and computer modeling studies have shown that saccular aneurysms grow from this region (17, 111). This observation has enormous relevance in the surgical and endovascular treatment of intracranial aneurysms; specifically, posttreatment residual necks involving the inflow zone are more likely to produce recanalization of the aneurysm (11, 15).

Terminal aneurysms have a more complex and variable hemodynamic behavior, with variable inflow zones and higher central velocities that reduce the chances of spontaneous thrombosis. The inflow zone of this type of aneurysms depends on the geometry of the lesion and the size of the parent and daughter arteries. The flow enters from the distal portion of the neck adjacent to the dominant outflow branch and exits near the nondominant outflow branch or from the central portion if the outflow is relatively symmetrical (11). These intricate features adversely affect the technical success of endovascular approaches for terminal giant aneurysms, generating increased rates of coil compaction and redistribution and coil dislodgement (9, 44, 55).

The higher presence of intraluminal thrombosis in giant aneurysms has been attributed to two main reasons. First, and possibly the most relevant, is the relation between the diameter of the fundus and the entry orifice as discussed above. The second feature is the presence of a slow flow zone toward the center of lateral aneurysms, which may facilitate stagnation and thrombus formation. This latter hemodynamic effect theoretically would be beneficial from the endovascular perspective in facilitating thrombosis after coil embolization of these lesions; however, the presence of laminated thrombus can adversely affect endovascular embolization by increasing the risk of compaction of the coil and distal emboli. Also, histopathological studies have revealed the presence of neovascularization in the thrombus of giant aneurysms, which may play a role in the development of intramural bleedings and the growth of these lesions. Histological analysis of aneurysms treated with coils have shown the same finding, although its pathological significance in allowing regrowth or recanalization has not been completely established.

The more complex hemodynamics, specifically the higher velocities in the central zone and higher intensity mechanical vibrations in terminal giant aneurysms, reduce the effectiveness of endovascular obliteration by increasing the compaction rates and reducing the thrombosis of embolized aneurysms.

THERAPEUTIC OBJECTIVES

Giant intracranial aneurysms represent a particular group of vascular lesions that may manifest in a wide variety of clinical presentations, ranging from incidental findings to serious thromboembolic events or significant mass effect. Their location, morphological features, size, and type of associated symptoms may dictate different strategies for their appropriate treatment. An understanding of these variables is fundamental in selecting the most adequate approach and achieving some success in the treatment of these lesions. The objectives of giant intracranial aneurysm treatment can be summarized as: 1) protection from bleeding, 2) reduction of size for mass effect relief, and 3) prevention of thromboembolic complications.

Subarachnoid hemorrhage (SAH) may occur in 25 to 70% of giant intracranial aneurysms (14, 23, 80, 90, 119). The 5-year cumulative rupture rates for patients with no history of subarachnoid hemorrhage with giant aneurysms are 40% for aneurysms in the anterior circulation and 50% for giant aneurysms of the posterior circulation and posterior communicating arteries (125). No significant anatomic differences have been found between giant aneurysms that bleed and those that are discovered incidentally or because of mass effect (8).

When a giant intracranial aneurysm presents with SAH, the cumulative frequency of rebleeding at 14 days has been reported to be 18.4% (66), which is comparable with that of smaller aneurysms (14.1–26.5%) (62). The distribution of rebleeding, however, may differ from the well-known pattern for a smaller aneurysm that present with SAH, where the peak interval for rebleeding is during the first 24 hours after the initial ictus (62, 122). In giant aneurysms, the incidence of rebleeding reaches its highest point by Day 5 and maintains a plateau of this point at approximately 15% (66). In the study by Khurana et al. (66), 30% of patients who had some degree of intraluminal thrombosis experienced rebleeding and, even with extensive intraluminal thrombus, did not preclude rehemorrhage.

Prevention of hemorrhage is a significant objective to be achieved with any type of treatment for giant intracranial aneurysms that extend into the intradural space, and early protection should be advocated for those lesions that present with SAH. Parent artery occlusion significantly reduces the flow into a giant aneurysm and may produce thrombosis and involution in several cases (5, 20, 24, 29, 36, 76, 95, 23). Obviously, this type of treatment can be performed only when there is adequate collateral flow in the territory supply by branches of the parent artery and when there are no significant collateral branches between the occlusion side and the giant aneurysm, in which case the parent artery occlusion would not provide lasting protection from rebleeding (23, 55, 69, 116).

The most reliable endovascular treatment to prevent bleeding in a giant intracranial aneurysm would be the complete isolation from the circulation, which may be achieved with aneurysm trapping, in which case the collateral flow for the territory supplied by the parent artery should be sufficient by natural collaterals or should be improved by the creation of a surgical bypass. The endosaccular occlusion with embolic materials is a second option that has proven to be less durable, and therefore the long-term protection from rebleeding is questionable.

The most common presentation of giant aneurysm is mass effect on adjacent structures. The incidence of symptoms attributed to mass effect range from 39 to 75% of cases (10, 14, 119). Drake (23) reported improvement of symptoms secondary to brainstem compression after deliberate occlusion of the basilar artery with no other decompressive procedures. A reduction in the pulsation of the aneurysmal mass was considered the reason for this improvement. Similarly, isolation of the aneurysm from the circulation with endovascular parent occlusion, trapping, or endosaccular obliteration may improve mass effect symptoms in some patients. In non-giant aneurysms, improvement of symptoms secondary to mass effect have been reported in 53% of cases (82). Shrinkage of approximately 30% of the initial volume after 12 months of parent vessel occlusion and reductions of 57% of volume after 18 months of endosaccular coiling also have been reported (123). In contrast, aggravation of mass effect symptoms has been published in a case of Guglielmi detachable coiling (GDC) embolization of a giant aneurysm (75). In a recent study by Gruber et al. (43), 45.5% of patients with symptoms of neural compression improved after endosaccular embolization, whereas 27.2% had worsening symptoms after embolization and therefore required additional treatment (trapping and surgical decompression).

Thromboembolic complications associated with giant intracranial aneurysms are infrequent (2, 86, 10) and present a therapeutic challenge from different perspectives. Antiplatelet and systemic anticoagulation have been used in cases of thromboembolic events associated with giant aneurysms (16), and they may be the only option in cases where any additional treatment of the aneurysm carries unacceptable risks (23, 95). However, failure to exclude giant aneurysm from the circulation has increased risk of rupture, as mentioned above, and use of anticoagulation, theoretically, can increase the risk of hemorrhagic complications and recanalization of partially thrombosed giant aneurysms (93). The impact of anticoagulation therapy on the odds of recanalization of giant aneurysms treated with endosaccular coiling embolization has not been well established; however, these measures may be necessary when associated thrombosis of the sac may produce extension into the lumen of the parent artery and distal embolism. After recent experiences using Neuroform stents (Boston Scientific/Target, Fremont, CA), it seems necessary and relatively safe to use anticoagulation routinely in patients undergoing placement of endovascular stents, given their thrombogenicity. Fiorella et al. (27) reported, in a series of 22 aneurysms (only two of them giant), four cases of thromboembolic complications, two clinically manifest and two subclinically found in follow-up magnetic resonance imaging scans. In one patient, subsequent fatal intracranial hemorrhage occurred after an intraarterial thrombolysis was performed in an effort to recanalize the occluded middle cerebral artery branches. The two patients with no clinical symptoms had SAH and were not pretreated with double antiplatelet agents. Future studies should elucidate the adequacy of double antiplatelet therapy in the setting of endovascular stent use as well as the most appropriate length for these medications to be used and their impact in recanalization rates.

Isolation of the aneurysm from the intracranial circulation is the primary option to prevent thromboembolic complications. However, the endovascular procedures that achieve this goal carry the risk of generating an embolic complication either by the occlusion of the parent artery or by dislodging clots from a partially thrombosed aneurysmal lumen in the case of intrasaccular embolization (81). One usual finding after parent artery occlusion is the development of retrograde thrombosis of the occluded artery to the next proximal large branch vessel (38). This may produce occlusion of small perforating branches or even larger branch vessels, and therefore it is considered that systemic anticoagulation is required during the embolization procedure. There is no agreement regarding the postprocedural need for anticoagulation, either with heparin or antiplatelet therapy, after parent artery occlusion. However, caution should be taken, especially if the aneurysm is not completely isolated from the circulation.

In the case of endosaccular occlusion, full heparinization during the procedure is usually performed, and careful deployment of the coils and repeated angiographic inspection are keys in preventing clot dislodgement and detecting early possible embolic events.

ENDOVASCULAR TECHNIQUES FOR THE MANAGEMENT OF GIANT ANEURYSMS

The currently available techniques for the endovascular management of giant aneurysms can be grouped in two categories: deconstructive or reconstructive techniques (16, 44, 95). The main difference between them is the sacrifice of the parent artery in the deconstructive techniques, whereas the reconstructive techniques attempt to isolate the aneurysmal lumen from the intracranial circulation.

Deconstructive Techniques

These methods include parent artery occlusion (PAO) and aneurysm trapping. PAO is one of the oldest endovascular techniques used for the management of intracranial aneurysms. Serbinenko (105), Serbinenko et al. (106), and Debrun et al. (21, 22) were pioneers in using this technique. Since the introduction of the procedure, multiple reports have shown that PAO is an effective treatment in cases of unclippable giant aneurysm, facilitating aneurysm thrombosis and clinical improvement (20, 29, 54, 6, 114, 38, 110, 74, 81). *Table 1* summarizes these studies. The clinical experience with PAO techniques demonstrates that this is a safe and effective technique, with most of the patients exhibiting good or excellent outcome and aneurysm size decrease in the long term. The endovascular technique is advantageous compared with surgical PAO, not only because of sparing patients the potential of morbidity and discomfort inherent in the surgical procedure, but also because the endovascular approach allows a closer occlusion to the aneurysm, reducing the chances of leaving significant collateral flow between the occlusion site and the aneurysm that may increase the risk of persistent aneurysm filling, growth, and rupture. Also, the angiographic procedure permits assessment of the adequacy of collateral flow and evaluation of any residual flow after permanent artery occlusion has been performed (74).

Although PAO is a safe treatment, patient outcome depends mainly on the tolerance to occlusion. There is no protocol that predicts with complete accuracy delayed ischemic events after balloon test occlusion of the parent artery. Anatomical criteria may be enough in selected cases, particularly when good filling of the vessel distal to the aneurysm is observed (38). In numerous cases, however, a balloon occlusion test is required before complete occlusion. This may be performed with only angiographical and clinical examination while the patient is awake (29, 110) or with adjunctive measures including xenon 133 computed tomography (6), single-photon emission computed tomography (88), transcranial Doppler (37), and electroencephalographic monitoring (78). In our institution, we routinely use neurophysiological monitoring during balloon test occlusions and Amytal tests. We also make an effort to maintain controlled hypotension during the procedure to mimic a physiological condition after definitive embolization. The correlations between changes in cerebral blood flow and electric brain activity have been well established in the surgi-

TABLE 1. Parent artery occlusion treatment of intracranial aneurysms[a]

Series (ref. no.)	No. of aneurysms	Technique	Anatomical results	Follow-up	Complications
Debrun et al., 1981 (20)	9	Balloon PAO			2 (22%) transient blindness; 1 (11%) permanent blindness
Fox et al., 1987 (29)	68	65 balloon PAOs	51 complete (78%; only 10 out of 21 in the supraclinoid ICA and 3 out of 6 basilar trunk)	NI	8 (12%) transient ischemic events; 1 (1.5%) stroke
Higashida et al., 1991 (54)	215	Balloon PAO		2–43 mo	21 (9.8%) deaths; 16 (7.4%) strokes
Aymard et al., 1991 (6)	21	Balloon PAO	13 complete (62%); 6 incomplete (29%)	6 mo–6 yr	1 (5%) transient ischemia; 2 (10%) deaths
Steinberg et al., 1993 (114)	201	8 balloon PAO	157 complete (78%); 43 incomplete (21%)	1–23 yr	26 (13%) strokes; 48 (24%) deaths
Gobin et al., 1996 (38)	9	6 coil aneurysm and PAO	5 complete (83%); 2 recanalizations (33%)	2 mo–2 yr	No permanent complications
Sluzewski et al., 2001 (110)	6	5 balloon PAO; 1 coil PAO	4 complete (67%); 1 incomplete (17%)	1 wk–9.5 mo	1 (17%) stroke; 2 (33%) deaths
Leibowitz et al., 2003 (74)	13	3 balloon PAO; 9 coil PAO; 1 combined	13 complete; 1 recanalization (8%)	1–76 mo	Group I (n = 6), 2 transient ischemic events (15%); Group II (n = 7), 4 deaths (31%)
Lubicz et al., 2004 (81)	13	4 coil PAO	3 complete (75%); 1 recanalization (25%)	12–48 mo	1 (8%) brainstem stroke

[a] PAO, parent artery occlusion; NI, no information published; ICA, internal carotid artery. Group I, PAO to obtain thrombosis of aneurysm; Group II, PAO to palliate when complete occlusion was not desirable.

cal literature (48, 49, 107). This technique has some advantages compared with imaging examinations that require transportation of the patient to obtain the scans and blind inflation of the balloon while the images are performed. Electroencephalography has been reported to alter treatment decision in endovascular procedures in approximately 14% of cases in which it is used. However, electroencephalographic monitoring does not substitute a careful analysis of the vascular anatomy and the clinical examination of the patient while the test is performed, but it complements them (78).

Even after successful balloon occlusion test, delayed ischemic complications may appear, and they have been reported to occur in between 4 and 15% of cases (16). The procedure itself carries some risks, including arterial dissection, pseudoaneurysms, and transient or permanent neurological deficits secondary to embolic events (0.4–1.6%) (84).

The most common lesions treated with the PAO technique are internal carotid artery (usually petrous, cavernous, or cavernous ophthalmic) giant aneurysms, giant serpentine aneurysms of the M2 and M3 segments of the middle cerebral artery, and P2–P3 segments of the posterior cerebral artery, as well as the unilateral or bilateral vertebral arteries or vertebrobasilar junction (16, 74, 81). The use of coils with the modern detachable systems has several advantages compared with balloons in occluding a parent vessel, including better control of the catheters and deployment systems, allowing a more precise placement, avoidance of the traction that was necessary to deliver the balloons, less risk of migration especially when deployed partially into a thrombosed aneurysm, and no risk of recanalization secondary to balloon deflation (32) (*Fig. 2*).

Endovascular trapping instead of PAO was first advocated by Berenstein et al. (13) in 1984. Several theoretical advantages can be advocated with the use of this technique: lower rates of failure secondary to collateral flow into the aneurysmal lumen, reduced compaction of the coils in endosaccular techniques, and fewer thromboembolic complications secondary to reduction in dead space for propagation of thrombus. The trapping technique shares some of the fundamental limitations that the PAO poses, especially the tolerance to occlusion of the parent artery that is also obtained with this technique. Therefore, the discussion mentioned above regarding balloon test occlusion applies for the trapping technique. The anatomical characteristics of the aneurysm may favor a trapping technique, which is the case of more distal giant aneurysms of the internal carotid artery or vertebrobasilar circulation (*Fig. 3*). In the recent series of giant vertebrobasilar aneurysms treated with endovascular techniques by Lubicz et al. (81), nine out of 13 patients were treated with trapping techniques. They concluded that trapping of the aneurysm with isolation of the vertebral artery was ideal in obtaining mechanical obstruction to flow and reopening of the aneurysm. In this series, all aneurysms thrombosed except one that was treated with PAO instead of trapping. A water-hammering effect (71) of the

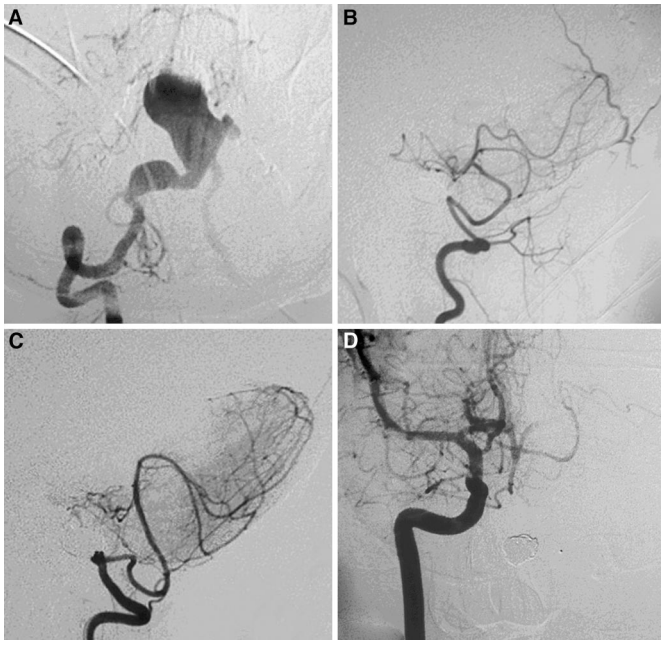

FIGURE 2. A, *digital subtraction angiogram anteroposterior view after right vertebral contrast injection in a 28-year-old woman with subarachnoid hemorrhage. There is a large fusiform aneurysm involving the distal right vertebral artery and the basilar artery.* B *and* C, *GDC embolization of the distal right vertebral artery was performed initially, followed by balloon test occlusion of the left vertebral artery. The patient tolerated the test, and permanent occlusion of the left vertebral artery was performed. Angiograms show right vertebral injection (*B*), lateral view and left vertebral artery injection (*C*), lateral view. The vertebral arteries are patent to the origin of the bilateral posteroinferior cerebellar artery with no further filling of the fusiform aneurysm.* D, *digital subtraction angiogram anteroposterior view after injection of the right internal carotid artery demonstrates good collateral flow over the posterior communicating artery, with basilar artery retrograde filling but no aneurysmal opacification.*

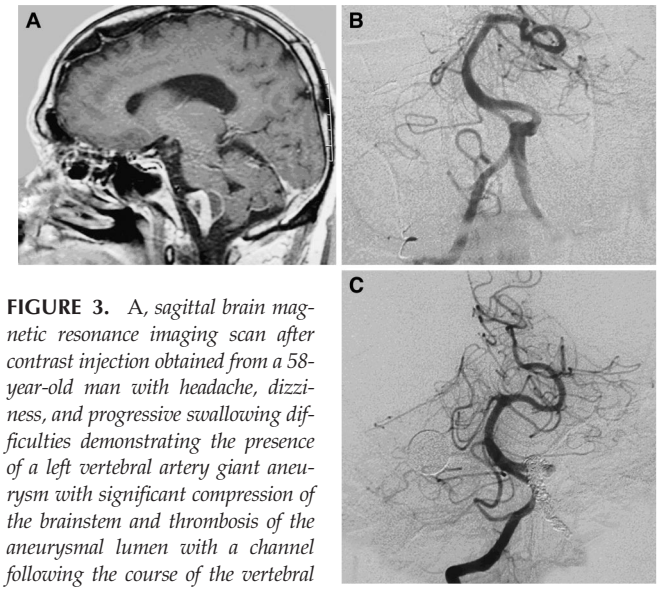

FIGURE 3. A, *sagittal brain magnetic resonance imaging scan after contrast injection obtained from a 58-year-old man with headache, dizziness, and progressive swallowing difficulties demonstrating the presence of a left vertebral artery giant aneurysm with significant compression of the brainstem and thrombosis of the aneurysmal lumen with a channel following the course of the vertebral artery.* B, *digital subtraction angiogram anteroposterior view of the left vertebral artery injection showing irregularity of the left vertebral artery distal to the takeoff of the posteroinferior cerebellar artery and proximal to the vertebrobasilar junction. The rest of the aneurysmal mass is not visualized secondary to thrombosis.* C, *digital subtraction angiogram anteroposterior view after GDC embolization and injection of the right vertebral artery demonstrating occlusion of the intraaneurysmal channel with no retrograde flow. The patient had persistent symptoms after trapping, and he underwent surgery for decompression.*

basilar artery was attributed to be the cause of failure on the treatment of this giant vertebral aneurysm. Interestingly, a case has been reported of continued aneurysmal growth with clinical deterioration of a vertebral artery giant aneurysm after endovascular trapping (59). The growth of this aneurysm occurred even in the absence of filling of its lumen during angiography. After surgical removal of the lesion, marked proliferation of the vasa vasorum of the aneurysm and occluded vertebral artery as well as inflammatory reaction were recognized in histological examination.

When the patient cannot tolerate the balloon test occlusion, revascularization procedures should be considered. In 1967, Yaşargil and Donaghy introduced the technique of intracranial arterial bypass as a strategy for prevention of stroke in patients with carotid intracranial occlusion (126). Microsurgical creation of a bypass followed by endovascular PAO or trapping has been performed successfully in numerous cases (*Table 2*) (7, 26, 47, 56, 64, 103). The advantages of a combined technique where direct occlusion of the artery is performed by endovascular methods include: lower risk of injury to surrounding neural structure, particularly cranial nerves in the cases of cavernous carotid aneurysms, less brain retraction, better visualization of the lumen of the vessel, which may be particularly difficult to access if significant surrounding thrombus or calcifications are present, and immediate evaluation of the effectiveness of trapping or PAO (*Fig. 4*).

The technique using direct arterial bypass with the superficial temporal artery or occipital artery, high-flow saphenous vein bypass, or interarterial anastomosis has proven to be a useful resource to improve the chances of adequate circulation distal to an intracranial arterial occlusion (83). Special attention should be paid to isolate the aneurysm as soon as possible from the intracranial circulation, given the risk of rupture associated with increase in the flow by the bypass (53, 83).

The introduction of a modified excimer laser-assisted nonocclusive anastomosis bypass technique (115, 124) represents a major technological advance in the construction of extracranial-intracranial bypasses, allowing the creation of the bypass without occlusion of the recipient vessel. This technique may have significant impact in the future of cerebrovascular surgery (72).

Reconstructive Techiques

Reconstructive strategies include endosaccular embolization with balloons, coils, or liquid embolic materials with or without adjunctive techniques such as balloon-assisted embolization or stent placement. Debrun et al. (20) in 1981 were the first to obtain endosaccular occlusion of giant unclippable

TABLE 2. Combined endovascular occlusion and bypass surgery for giant aneurysms[a]

Series (ref. no.)	No. of aneurysms	Technique	Results	Follow-up	Complications
Barnett et al., 1994 (7)	7	7 STA-MCA bypass; 6 balloons; 1 Crutchfield clamp	5 improved; 1 unchanged; 1 worsening	NI	1 mild VIth CN palsy
Hacein-Bey et al., 1998 (47)	1	STA-MCA bypass; coil PAO	Improved	12 mo	None
Ewald et al., 2000 (26)	8	4 STA-PCA bypass + 3 coil saccular embolization and 1 PAO	4 (100%) complete with bypass patency	4 wk–6 mo	1 IIIrd CN paresis
Hoh et al., 2001 (56)	48	3 EC-IC bypass; 1 A3-A3 anastomosis + coil embolization	2 GOS 5; 1 GOS 4; 1 GOS 1; 1 bypass failure	NI	Not specified per type of procedure
Kato et al., 2003 (64)	139	1 STA- MCA bypass + coil embolization	Complete	NI	Not specified per type of procedure
Martin et al., 2004 (unpublished data)	28	9 STA-MCA; 4 OA-AICA or PICA; 5 saphenous vein; 3 side-to-side anastomosis + coil embolization	66.7% good outcome; 16.7% moderate disability; 11.1% severe disability; 1 death (5.5%); 1 bypass failure	NI	2 postoperative hematomas; 2 CSF leaks; 2 new CN palsies

[a] STA, superficial temporal artery; MCA, middle cerebral artery; CN, cranial nerve; PCA, posterior cerebral artery; PAO, parent artery occlusion; EC, external carotid; IC, internal carotid; A3, segment A3 of the anterior cerebral artery; GOS; Glosgow Outcome Scale; NI, no information published; OA, occipital artery; AICA, anteroinferior cerebellar artery; PICA, posteroinferior cerebellar artery; CSF, cerebrospinal fluid.

aneurysms with preservation of the parent artery by using detachable balloons that were navigated into the aneurysmal lumen and then detached. Despite the early success reported with this technique, the balloon occlusion of intracranial aneurysms presented several limitations, including difficult navigation to some locations of the intracranial circulation, difficult detachment with risk of parent artery accidental occlusion, limited ability to adjust to the aneurysmal shape, which was associated with higher incidence of incomplete occlusions, high thrombus recanalization rates, balloon migration, and high morbidity and mortality rates (9.8% mortality; 10.2% morbidity) (16, 38, 54).

Since the introduction of GDC embolization in 1991 (45), balloon embolization has increasingly been abandoned and replaced by coil embolization, especially when embolization of the aneurysm with preservation of the parent artery is attempted. The detachment of the GDC system avoids any traction on the parent artery, the coils conform to the shape of complex aneurysms, allowing a higher density packing, navigation is easier than with balloons, and its deployment may be carried out more precisely. Also, the variety of sizes, shapes, and rigidities available in the GDC system significantly facilitate the procedure. These features added to better navigational systems with improved catheters and microguide wires have prompted the growing of endovascular techniques for the treatment of these lesions. Despite these advances, the rate of complete occlusion and the long-term success of coil embolization for large and giant aneurysms are very limited. The rate of complete embolization of giant aneurysms using Guglielmi detachable coils is 24.1%, with a high rate of residual necks (69%) (40). This significantly affects the clinical results of embolization and the effectiveness of the technique in resolving clinical symptoms, such as mass effect and thromboembolic events (57). Also, the long-term stability of the embolization is significantly affected by these factors, and it has been reported that recanalizations can be as high as 90% in giant aneurysms treated with endosaccular embolization (50).

Apart from aneurysmal size and neck, the density of initial coiling also may affect the rate of subsequent coil compaction and recanalization with further aneurysmal enlargement (65). Secondary to coil compaction, primary complete occlusion with coils of the aneurysmal lumen does not necessarily prevent recanalization, and therefore regrowth or rebleeding. In this setting, giant aneurysms may require either multiple embolization sessions (as high as 15–20%) (70) or additional surgical procedures (52).

In a recent series of 31 patients with giant or very large aneurysms, Gruber et al. (43) reported 73.3% excellent to good recoveries after GDC embolization with a 13.3% procedure-related morbidity rate and a 6.7% mortality rate. Symptoms secondary to mass effect improved in 45.5% of patients. However, in the angiographic follow-up, complete or almost complete occlusion was observed in only 71% of patients, and a single procedure was definitive treatment for only 12.5% of the giant aneurysms. A very high 6.5% post-GDC treatment hemorrhage rate (annual rate of 2.5%) was also reported by this group.

It seems that endosaccular embolization of giant aneurysms is limited by the long-term efficacy of the procedure and may be a resource for patients not amenable for surgical interven-

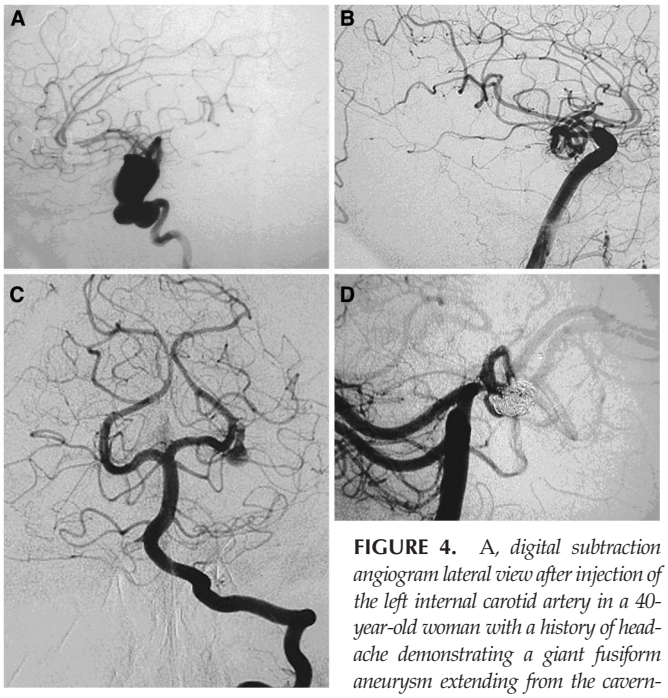

FIGURE 4. A, *digital subtraction angiogram lateral view after injection of the left internal carotid artery in a 40-year-old woman with a history of headache demonstrating a giant fusiform aneurysm extending from the cavernous portion of the left internal carotid artery to the supraclinoid region with involvement of the left posterior communicating artery. Given the anatomical findings, a balloon occlusion test was not performed. The patient underwent a left frontotemporal craniotomy with cerebral revascularization with a saphenous vein graft from the left external carotid artery to the left middle cerebral artery and surgical left internal carotid artery occlusion.* B, *postoperative digital subtraction angiogram lateral view after injection of the left common carotid artery demonstrating a patent extracranial-intracranial bypass.* C, *left vertebral artery injection showing filling of the superior third of the left internal carotid artery fusiform aneurysm from the posterior communicating artery. The patient underwent coil embolization of the residual fusiform aneurysm.* D, *postembolization lateral view angiogram of the left vertebral artery demonstrating complete occlusion of the aneurysm with preserved filling of the left internal carotid artery via the posterior communicating artery.*

tion or deconstructive permanent therapies. It also plays an important role in patients treated surgically with partial clipping of the neck, where further embolization procedures, after a more suitable neck has been created surgically, may complete the occlusion of the aneurysm.

In recognition of these difficulties, several innovations have been developed to increase the ability of packing giant aneurysms or obliterating their lumen with alternative methods. One of the most useful developments is the remodeling technique, introduced by Moret et al. (89) in 1997. This technique basically encompasses the traditional coil embolization while a balloon placed at the aneurysmal neck in the parent artery is inflated intermittently while the coils are deposited to prevent their migration and to facilitate higher density packing. Drawbacks of this technique include the need for simultaneous use of two microcatheters and a larger guide catheter, as well as the temporary interruption of flow in the parent artery, which may increase the risk of thromboembolic complications.

Recently, the development of intravascular stents represents a promising advancement that may overcome important technical limitations in the endovascular therapy of giant or wide-neck aneurysms. Basically, the stent acts as a scaffold in the parent artery while coils or other embolic materials are deposited into the aneurysmal lumen (120). One of the most significant limitations of this technique is the difficulty that may be found in the deployment of the stent in the parent artery, as well as the necessity of antiplatelet therapy before and after the procedure, which may become a limitation in some cases of ruptured aneurysms. In a series of 49 aneurysms in 48 patients treated with this technique by Benitez et al. (12), difficulties in stent deployment were found in eight patients, whereas thromboembolic complications related with the device were observed in three patients. An additional limitation that may be found in giant aneurysms is the need to find adequate bridging in the neck of the aneurysm, which may be particularly challenging in large fusiform aneurysms.

With the experience in the use of coronary stents, the induction of intimal hyperplasia is a significant limitation; however, this phenomenon has not been observed in the published series of intracranial stents, (73) and long-term results are not available.

Considering the limitations of balloons and even coils to fill the lumen of giant aneurysms successfully, liquid embolic materials seemed to be a feasible alternative. However, liquid materials also pose particular challenges: the need to drain the aneurysm lumen first to prevent ruptures during injection of the embolic material, obtaining adequate control of a liquid in a liquid environment, and occlusion of the aneurysmal orifice without leakage into the parent artery with the subsequent disastrous ischemic complications (121). Mawad et al. (85) recently published a series of 11 patients with giant and large intracranial aneurysms treated with liquid embolic materials in association with stent placement. They used a nonadhesive liquid polymer that is injected slowly in the aneurysmal lumen after a balloon-expandable stent is placed at the neck of the aneurysm while the balloon is inflated intermittently. In this series, they obtained complete occlusion of nine aneurysms with two small residual necks. At the 6-month follow-up, there was one recanalization. They reported two complications: one case of transient hemiparesis and one death.

FUTURE OF ENDOVASCULAR TREATMENT OF INTRACRANIAL ANEURYSMS

Numerous challenging issues remain to be resolved in the treatment of giant intracranial aneurysms. The anatomic and hemodynamic characteristics that make their treatment particularly difficult should guide our efforts to provide improved therapies. A better understanding of the biological and molecular events involved in the growing of intracranial aneurysms has the potential of providing targets to be modified by endovascular techniques. Drugs or growth factors that stimulate myointimal hyperplasia and inhibit the destructive phase of the remodeling wall process could be delivered locally in embolic materials to induce a directed biological response that

theoretically could thicken the aneurysm wall, preventing hemorrhages, and eventually could thrombose the aneurysm lumen. Improvements in stent technology, specifically the development of covered stents or less porous stents with enhanced navigability into the intracranial circulation, may alter the aneurysm inflow sufficiently to produce complete exclusion of the circulation and thrombosis.

CONCLUSION

Giant intracranial aneurysms are some of the most challenging vascular pathological features in the central nervous system. Their peculiarities make the surgical and endovascular approaches difficult and frequently limited by risks and complications. The therapeutic approach to these lesions requires a sophisticated understanding of their unique anatomy and hemodynamic features, an extensive comprehension of the treatment strategies, and a keen decision-making process to individualize the treatment for any specific lesions.

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GIANT CEREBRAL ANEURYSMS: ENDOVASCULAR CHALLENGES

OBJECTIVE: Giant (≥25 mm in diameter) cerebral aneurysms have a poor natural history, with high risks of subarachnoid hemorrhage or progressive disability or death caused by mass effect or stroke. Surgical treatment may be effective but carries a high burden of morbidity and mortality. Thus, attempts at endovascular solutions to these complex lesions have been developed to offer therapy at reduced risk.

METHODS: The authors reviewed their clinical experience and the current body of literature concerning giant cerebral aneurysms and present their perspective on the current state of the art in endovascular therapy for these aneurysms. A variety of techniques are described that can be used in an attempt to provide a solution to the wide variety of clinical dilemmas associated with the management of these difficult lesions. Preprocedural planning and periprocedural considerations are discussed briefly. The use of intracranial balloons and stents are described in conjunction with the use of detachable platinum coils. The developing concept of using stents alone to treat aneurysms is discussed. Alternative methods of treating giant aneurysms are discussed.

RESULTS: Current endovascular approaches, when properly selected and applied, can provide lower-risk therapies than conventional microsurgical approaches for patients harboring giant cerebral aneurysms. However, endovascular approaches do not, at present, provide results that are as durable as current surgical techniques for giant cerebral aneurysms.

CONCLUSION: Treatment of giant cerebral aneurysms via endovascular therapeutics requires the interventionist to possess an extensive armamentarium. Meticulous preprocedure evaluation, patient selection, and execution of the treatment plan enable safe and effective management. Current therapies do not provide an ideal solution for every patient, so one must consider creative and evolving solutions to these difficult clinical challenges. The procedural morbidity of open surgery versus the decreased durability of current endovascular techniques must be assessed carefully.

KEY WORDS: Balloon, Coil embolization, Giant cerebral aneurysm, Intracranial stent placement, Neuroform, Onyx

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Giant intracranial aneurysms are a difficult and complicated entity requiring a multidisciplinary approach. Only approximately 5% of intracranial aneurysms are giant (25 mm or larger in diameter) (1, 21, 43), but a significantly greater proportion of giant aneurysms occur in the pediatric population (12). These lesions are found most commonly in the internal carotid artery segments, especially the cavernous and paraclinoid segments, followed by the vertebrobasilar region. The remainder are found primarily in the middle cerebral artery and anterior cerebral artery regions (1, 12). Morphologically, giant aneurysms typically are divided into saccular and fusiform types, with fusiform aneurysms arising more commonly in the vertebrobasilar and middle cerebral territories (1). In 25 to 80% of giant intracranial aneurysms, the clinical presentation is subarachnoid hemorrhage (SAH) and/or intracerebral hemorrhage (1, 21, 35). Alternate presentations include mass effect, perforating vessel occlusion, distal embolic events, seizures, or even as an asymptomatic lesion found inciden-

tally on noninvasive imaging. The natural history for patients harboring untreated giant cerebral aneurysms is exceedingly poor, with more than 60% of patients with nonhemorrhagic presentations dying within 2 years and all surviving patients having marked neurological disabilities (36). The prognosis is even worse for those patients with SAH at presentation. The rate of SAH for conservatively treated intradural giant aneurysms is roughly 8 to 10% per year (45).

The treatment of giant intracranial aneurysms is generally directed toward complete exclusion of the aneurysm from the circulation, with preservation of all parent arteries, but this is not always technically feasible with acceptable risk. For those patients in whom the lesion is potentially treatable by surgical means, the surgical options are beyond the scope of this article, but have included direct clip reconstruction, aneurysm trapping with or without surgical bypass, proximal vessel occlusion with or without surgical bypass, and Selverstone clamping (delayed proximal occlusion). For patients in whom the lesion is not amenable to such definitive treatment, attention should be directed toward addressing the particular presenting symptoms. For some patients with distal embolic symptoms and untreatable giant aneurysms, anticoagulation may be warranted despite the risk of SAH. For patients with a clinical presentation of compressive mass effect, attempts should be made to debulk the mass or, at a minimum, to eliminate the pulsatility of the aneurysm.

Combined morbidity and mortality rates for surgical treatment of unruptured giant aneurysms (including cognitive dysfunction) vary between 20 and 45%, depending on location and age of the patient, with older patients and patients with posterior circulation lesions faring worse (45). Modern surgical mortality rates for treatment of both ruptured and unruptured giant aneurysms vary from 6 to 22% (13, 23, 38). Good or excellent outcomes have been reported in 61 to 87% of cases in modern series (13, 23, 38). Patients with SAH and mass effect at presentation have the worst surgical outcomes (23).

Patients harboring giant aneurysms tend to be older than those with smaller aneurysms (12) and have multiple medical comorbid conditions, and, as such, are at higher risk for complications associated with general anesthesia. In addition, giant aneurysms have a higher rate of arterial wall calcifications, atherosclerotic plaque, and intraluminal thrombus, making direct clip reconstruction more complex. The longer temporary arterial occlusion times required during surgical treatment of a giant cerebral aneurysm lead to an increased risk of cerebral ischemia. In addition, adjunctive treatment techniques, including profound hypothermia and circulatory arrest, are occasionally necessary, each of which incurs a separate complication risk. These characteristics have motivated the search for less invasive endovascular methods for the treatment of these lesions.

Similarly, the treatment of giant intracranial aneurysms presents challenges to the endovascular surgeon. The ideal aneurysm patient for the endovascular surgeon is one in whom the aneurysm is devoid of intraluminal thrombus, has a small neck with a large dome-to-neck ratio, and is roughly spherical in shape. The typical giant cerebral aneurysm does not possess these features; indeed, quite the opposite is the case. In addition, the mainstay of endovascular therapy does not immediately remove the mass effect associated with many giant aneurysms and may exacerbate this phenomenon in the periprocedural period.

In this text, the authors describe currently available and developing techniques for endovascular treatment of giant cerebral aneurysms; techniques that were born out of a need to provide a solution to the poor natural history of these lesions and the high risks associated with surgical treatment. Some of the statements represent the opinions and practice patterns of the senior author (LNH), and may be considered controversial. This bias reflects experience gained in attempts by the senior author to continue the development of endovascular treatment for giant intracranial aneurysms and heavily favors the use of stents to attempt to reconstruct the arterial lumen and preserve parent artery patency when feasible.

PRETREATMENT EVALUATION

Catheter-based angiography, three-dimensional (3-D) computed tomographic (CT) examination, and magnetic resonance angiography are helpful in confirming the diagnosis and/or consideration of an endovascular, surgical, or combination therapy approach. The performance of diagnostic cerebral angiography is crucial before final decisions about treatment options are made. Angiography provides invaluable information regarding not only the anatomical and morphological features of the lesion, but also the potential for collateral circulation should vessel occlusion be entertained as a treatment option. Cross-compression views can aid in determining patency of posterior communicating and anterior communicating arteries as appropriate. In addition, potential donor arteries for surgical bypass can be assessed. Multiple angiographic projections or 3-D angiography can be extremely useful at delineating the relevant pathological anatomy. A four-vessel study is performed to define any additional aneurysms. Balloon test occlusion is performed concurrently if permanent vessel occlusion (endovascular or surgical) is considered as a treatment option or as a bailout maneuver.

3-D CT angiography provides valuable information regarding the relative composition of the aneurysm (thrombus or calcifications) and provides delineation of some anatomic aspects of the aneurysm and any additional aneurysms. The technique is quick, noninvasive, and can aid in decision making (surgery versus endovascular therapy versus combination therapy) in acute emergencies, such as when dealing with a concomitant hemorrhage that is producing significant mass effect. This technique is dependent on the quality of 3-D image reconstruction, however, which can lead to misinterpretation, especially when the aneurysm is intimately associated with bony structures or multiple surgical clips or coils.

Magnetic resonance angiography is useful for screening, but typically not for treatment decision making. Magnetic resonance imaging can be quite useful to evaluate for intra-

aneurysmal thrombus, mass effect, edema, and any potentially associated ischemic lesions.

TREATMENT PLANNING

Ideally, the goal of treatment is complete exclusion of the aneurysm from circulation, with preservation of all native arteries. This is not always achievable. In addition, the risk of such a treatment may, in some cases, be greater than the natural history of giant aneurysmal lesions. Reducing or eliminating aneurysmal flow by redirection or proximal vessel occlusion is sometimes preferable and can incur less periprocedural risk. Decision making should revolve around treating the patient's presenting symptoms and relevant risks for future neurological injury, but must be constrained by an understanding of the natural history of the lesion in the individual patient from the available literature, the patient's age, and the likelihood of long-term survival on the basis of comorbid conditions.

ANESTHESIA CONSIDERATIONS

The choice of anesthesia during treatment can significantly affect the outcome of a neuroendovascular procedure. Use of local anesthesia plus intravenous conscious sedation allows the operator to perform limited neurological examinations during the course of the procedure. This allows the operator to identify a complication immediately and, potentially, to reverse a maneuver that has led to a neurological decline. Without that information, the operator is left to note subtle angiographic abnormalities and may not identify the cause of the neurological decline until after the procedure. Avoidance of general anesthesia also reduces the cardiovascular risk of the overall procedure. However, if a complication does occur, the potential exists for further harm until the patient's airway can be secured and additional maneuvers (ventriculostomy, further embolization) can be performed. One must be prepared to intubate on a moment's notice. Not all patients are candidates for conscious sedation because of poor neurological status, young age, excessive anxiety, or an inability to lie still.

General anesthesia offers the advantages of control of the airway as well as reduction or elimination of patient movement during the procedure. Thus, the operator can perform the procedure with fewer distractions, less need for additional roadmaps, and with greater control. There are drawbacks, though, because the operator can monitor only the patient's vital signs, and possibly somatosensory evoked potentials. Moreover, the cardiovascular risks associated with general anesthesia are highly dependent on the comorbid conditions of the patient.

Our particular bias is toward local anesthesia with intravenous conscious sedation, if at all possible, to be able to assess the patient's neurological condition throughout the procedure. We reserve general anesthesia for those patients who are not candidates for conscious sedation for the reasons previously noted.

ANTIPLATELET REGIMENS AND PERIPROCEDURAL ANTICOAGULATION

Patients scheduled to undergo elective stent placement receive aspirin (325 mg by mouth daily) and clopidogrel (75 mg by mouth daily) for a minimum of 4 days before the procedure. Those undergoing stenting on a more urgent basis receive aspirin (650 mg by mouth) and clopidogrel (600 mg by mouth) 4 hours before the procedure. If stenting is performed as an emergency bailout maneuver, we administer an intravenous bolus dose of glycoprotein IIb-IIIa inhibitor (180 μg/kg eptifibatide at our institution), then clopidogrel (600 mg by mouth) and aspirin (650 mg by mouth) immediately after the procedure. Eptifibatide (2 μg/kg/min) is continued as an intravenous drip for 4 hours after the procedure to allow the clopidogrel to reach therapeutic levels of platelet inhibition. In the rare case of a patient with an acutely ruptured aneurysm undergoing stent placement, the glycoprotein IIb-IIIa inhibitor can be given after the stent is in place and the first or second coil is in proper position.

Proper decision making regarding periprocedural systemic anticoagulation is essential when using complex endovascular techniques for aneurysm treatment. We routinely administer heparin (an intravenous bolus of 50–70 units/kg) to obtain an activated coagulation time of 250 to 300 seconds before catheterization of intracranial vessels for elective and emergent patients except those with SAH. Anticoagulation is used more judiciously in patients with SAH. In these patients, we typically administer a 25- to 35-unit/kg bolus of heparin after the first coil is placed successfully, followed by a similar bolus after intra-aneurysmal flow is reduced. We do not reverse the effect of the heparin with protamine sulfate during or after the procedure unless there is evidence of intraprocedural wire perforation or contrast extravasation. The heparin is allowed to wear off after the procedure.

For patients with SAH, CT examination is performed immediately before treatment to assess for latent intracerebral hemorrhage (whether caused by aneurysm rebleeding or ventriculostomy placement), because such hemorrhage will prevent our use of stents or glycoprotein IIb-IIIa antagonists. Because of the degree of systemic anticoagulation, the arterial access site is typically secured by use of a closure device at the conclusion of the procedure.

ENDOVASCULAR TREATMENT OPTIONS

Proximal Vessel Occlusion

Proximal vessel occlusion was first described for the treatment of carotid aneurysms by Cooper (5) in 1809. Initial experience demonstrated continued filling and rupture of aneurysms as well as clinically significant ischemic complications with more proximal surgical occlusions (34). The use of an endovascular approach for carotid or vertebral artery occlusion offers the ability to position the occlusion as close to the aneurysm as desired to limit collateral flow through the an-

eurysm and to test the patient's collateral circulation before permanent occlusion. Proximal occlusion is performed after successful balloon test occlusion or in conjunction with surgical bypass after failed test occlusion (41).

Proximal vessel occlusion is often a preferable option for those who are poor candidates for endoluminal reconstruction because of complex aneurysm shape, advanced age, or severe vessel tortuosity. This can be accomplished through an endovascular approach by several methods, including direct coil embolization, double detachable balloon placement, or coil embolization with proximal or distal balloon occlusion. Detachable balloons represent the least expensive solution for aneurysms in which endoluminal reconstruction is problematic. The senior author (LNH) preferred to use detachable balloons for proximal vessel occlusion in the past, but their availability in the United States is limited at this time.

Debrun et al. (6) described nine patients with giant unclippable aneurysms who passed balloon test occlusion, then subsequently underwent attempted detachable balloon occlusion of the aneurysm or carotid lumen. The vessel lumen occlusion technique seemed safer than attempts to balloon occlude only the aneurysm lumen. Lubicz et al. (25) described their experience with endovascular proximal artery occlusion with detachable balloons for giant vertebrobasilar artery aneurysms in 13 patients. In their series, one patient died (because of recurrent SAH) and four patients had transient worsening acutely in their symptoms (mass effect in three patients and stroke in one patient). All surviving patients had good or excellent outcomes in the long term, with marked reduction in filling documented in nine out of 12 aneurysms. A recent report described 21 patients with unruptured cerebral aneurysms, including nine giant aneurysms, treated via a more complex combined endovascular and surgical method (Ponce FA, Albuquerque FC, McDougall CG, Hann PP, Zabramski JM, Spetzler RF: Combined endovascular and microsurgical management of giant and complex unruptured aneurysms. **Neurosurg Focus** 17:E11, 2004). Most procedures consisted of surgical bypass and endovascular proximal occlusion. Two patients with giant aneurysms died (one death was related to the surgical procedure and another to delayed infarction). Gobin et al. (14) presented five patients in whom giant aneurysms were treated primarily with coil occlusion of the parent artery and aneurysm. There were no permanent neurological events.

At present, we prefer to position a nondetachable balloon immediately distal or proximal to the level determined for occlusion. The vessel then is occluded with multiple coils (*Fig. 1*). Attempts are made to keep the segment involved in coiling as short and tightly packed as possible. The process may involve using a large, more robust microcatheter and more stable guide catheter or sheath access. For patients in whom the aneurysm fills from collateral circulation, we attempt to begin the coil embolization from within the aneurysm and extend that coiling proximally along the parent vessel. The occlusion continues until the vessel appears densely packed for 1 to 2 cm of vessel length. The balloon is then deflated, and

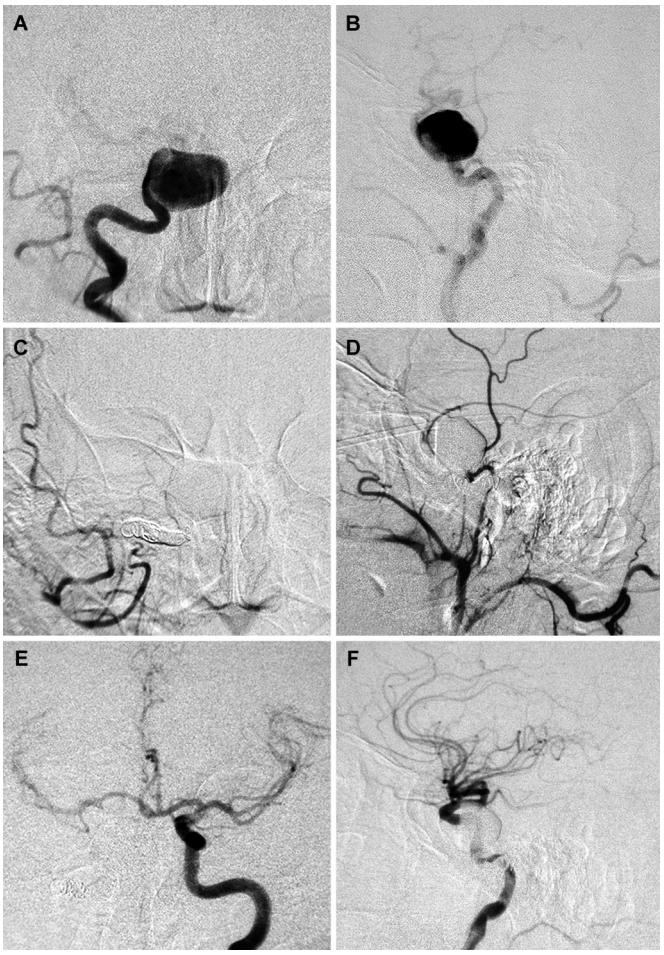

FIGURE 1. *Images obtained from a 62-year-old man with headache and ischemic episodes.* A *and* B, *angiograms demonstrating right internal carotid artery (ICA) injection and a giant cavernous segment aneurysm, anteroposterior (AP) and lateral views.* C *and* D, *angiograms demonstrating right common carotid artery injection after occlusion with multiple coils of the horizontal petrous ICA segment and no residual filling of aneurysm, AP and lateral views.* E *and* F, *angiograms demonstrating left ICA injection and no residual filling of the aneurysm, AP and lateral views.*

angiographic runs are performed to check for occlusion of that vessel segment. Additional coils are placed if there is residual flow, either in an attempt to extend the coiled segment or, preferably, to increase the packing density in the segment. As soon as complete occlusion is achieved, the deflated balloon is withdrawn. Typically, the artery remains occluded after removal of the balloon; additional coils may be placed if this is not the case. After the initial detachable coils have been deployed to provide a framework for stable positioning, pushable coils can be used to provide a lower cost option.

Delayed formation of flow-related aneurysms has been described after proximal vessel occlusion, most commonly of the anterior communicating artery complex (2). This risk must be considered when contemplating proximal vessel occlusion as

a treatment method, especially in young patients. The presence of an aneurysm contralateral to the aneurysm proposed for proximal occlusion is considered a relative contraindication to proximal occlusion.

Proximal occlusion should be undertaken with great caution when dealing with patients with acute SAH. The risk of delayed ischemic events associated with cerebral vasospasm is significant and will be worsened by proximal vessel occlusion. Proximal occlusion reduces the perfusion pressure of the distal cerebral arterial bed and complicates, or eliminates intra-arterial access for the performance of balloon angioplasty or selective administration of vasodilator therapy. Delayed proximal occlusion may be preferable in patients with SAH, whether that represents partial occlusion of the aneurysm, or leaving the aneurysm unsecured during the period of cerebral vasospasm.

Coil Embolization

Some giant aneurysms have a configuration amenable to endovascular coiling alone. The long-term results for giant aneurysms have not been as favorable as those for smaller aneurysms. Murayama et al. (33) reported their initial experience involving coil embolization of 73 giant aneurysms. Only 26% of patients experienced initial complete occlusion, although this improved to nearly 40% in the second half of the study. Overall clinical outcomes (not specified according to aneurysm size) were as follows: no worsening of deficits in 91%, appearance of a new deficit in 6%, and death in 3.4%. A subsequent recanalization rate of 59% was noted for giant aneurysms, with rates of approximately 40% even in initially completely occluded cases. Ten out of 12 patients in whom a delayed aneurysm rupture developed had large or giant aneurysms. Of the eight patients with angiographic follow-up, three out of eight (37.5%) demonstrated stable or progressive thrombosis and five out of eight (62.5%) showed some degree of minor recanalization. Sluzewski et al. (42) described their experience with 31 large and giant aneurysms (20–55 mm) in 29 patients. Long-term clinical outcomes were good in 79% of patients, but the initial treatment was insufficient (requiring subsequent coiling, surgery, or proximal occlusion) in 58% of cases. Gruber et al. (15) presented their 7-year experience in the treatment of giant intracranial aneurysms, demonstrating eight out of 12 (66.7%) giant aneurysms with more than 95% immediate occlusion. Four deaths (33.3%) occurred, one as a result of complications arising from SAH, one as a result of delayed ICA occlusion and massive infarction, one resulting from rebleeding (of a minimally embolized aneurysm), and one resulting from unrelated causes. It is clear from these results that although coil embolization alone, typically, is well tolerated clinically, it is not sufficient to provide a complete and durable long-term result in most patients.

In terms of technical considerations for coil embolization of giant intracranial aneurysms, the best angiographic projection of the aneurysm neck and parent vessel, or vessels, should be obtained. Placement of the microcatheter in a deep position and use of a larger microcatheter that will reduce the catheter back out may be helpful to improve the degree of coil packing. Ideally, 0.018-inch system coils should be used initially to provide the most stable framework from which to coil the bulk of the aneurysm. We prefer to continue to deposit sequentially smaller 3-D coils as feasible to increase the chances of good coverage of the aneurysm neck. There is some indication that the use of predominantly 3-D coils can improve packing density and neck coverage, thereby potentially reducing the delayed occurrence of recanalization (39). Because of the larger size, there may be multiple, smaller compartments in a giant aneurysm that still undergo filling with arterial blood near the end of the coiling procedure. It may be necessary to recatheterize and coil a portion of these compartments during the same or another session.

FIGURE 2. *Illustration demonstrating balloon-assisted coil embolization. The balloon catheter is positioned and inflated to occlude the aneurysm neck during coil deposition. The microcatheter is positioned into the aneurysm lumen alongside the balloon catheter proximally.*

The relatively poor results noted for coil embolization of giant aneurysms have led to significant effort into devising adjunctive methods to improve long-term outcomes. Considerable controversy exists regarding the choice of coils currently available, whether bioactive or bare platinum. There are data supporting and opposing the use of coils coated with polyglycolic-polylactic acid copolymer (Matrix; Boston Scientific/Target, Fremont, CA) (11, 26). The use of hydrogel-coated coils (HydroCoil; MicroVention, Aliso Viejo, CA) is in its preliminary stages (Arthur AS, Wilson SA, Dixit S, Barr JD: Hydrogel-coated coils for the treatment of cerebral aneurysms: preliminary results. **Neurosurg Focus** 18:E1, 2005); at present, there is not sufficient data to suggest a significant difference in terms of long-term recanalization rates for giant aneurysms. Clearly, randomized trials with bioactive coils versus bare platinum coils are necessary to determine whether or not these emerging technologies afford substantial benefit for giant aneurysms compared with conventional bare platinum coil technology to justify their additional cost and potential problems. At our center, the use of bioactive coils currently is reserved for select patients in whom it is thought that these technologies may provide some significant benefit, such as those with aneurysms that have recanalized.

Balloon-assisted Coil Embolization

The use of balloons to occlude the aneurysm neck during coiling of wide-necked aneurysms was first described in 1994 by Moret et al. (32). Essentially, a microcatheter is placed into the

aneurysm's fundus, and a balloon catheter is centered over the neck of the aneurysm (*Fig. 2*). The balloon is subsequently inflated during placement of a coil and then deflated intermittently in between coils to allow antegrade flow. Sequential inflations and deflations are performed as additional coils are placed, until the aneurysm is completely coiled, at which point the balloon is removed. The concept is that the presence of the balloon prevents distal embolization, conforms the coil mass to the shape of the balloon, and the coil mass shape becomes stable, thereby protecting the parent artery as the individual coils interlock (28, 30, 31).

At present, there is not significant information on short- or long-term results for balloon-assisted coiling to conclude that it is effective for long-term occlusion of giant cerebral aneurysms. Upward of 40 to 50 coils can be required to fill a giant aneurysm, leading to 40 to 50 cycles of balloon inflations, for which the risk may be prohibitive. In addition, the ability to protect the parent artery lumen by means of balloon occlusion during the coiling procedure, especially when there is extensive fusiform dilation, is minimal. Temporary balloon occlusion exposes the patient to an increased risk of cerebral ischemia resulting from thromboembolic complication and vessel rupture. The increase in thromboembolic complications occurs because of stasis of blood or temporary occlusion of local perforating end arteries covered by the balloon. The risk of vessel rupture stems from the compliant design of most balloons used for these purposes and is associated with dramatic changes in volume and pressure in the balloon with minimal inflation volume changes.

At our center, balloon assistance is used for cases of ruptured wide-necked giant aneurysms, in which the use of antiplatelet agents is contraindicated, and for those patients in whom deployment of a stent is not feasible. The number of patients in the second category is decreasing as more deliverable self-expanding intracranial stents become available. We currently use the HyperGlide and HyperForm balloons (Micro Therapeutics, Irvine, CA) for these patients with limited options.

STENT-ASSISTED COIL EMBOLIZATION

Neck Reconstruction

The clinical use of a stent to reconstruct the neck of a ruptured wide-necked aneurysm for subsequent coil embolization was first described by Higashida et al. (17) in 1997. The initial stents used were balloon-mounted stents designed for peripheral or coronary circulation. Considerable difficulty was encountered with the delivery of the early coronary design stents to the intracranial circulation, owing to vessel tortuosity in the cranial base or distal cervical vertebral artery. The use of stents allows reconstruction of the neck for coil embolization and reduces the likelihood of coil herniation into the parent vessel (*Figs. 3–5*). Stent-assisted coiling of wide-necked aneurysms was improved greatly with the development of a self-expanding nitinol stent (Neuroform; Boston Scientific, Natick, MA) designed for the intracranial circulation (16, 20). Initial results in terms of safe placement of the stent have been excellent in patients with unruptured aneurysms (Jabbour P, Koebbe C, Veznedaroglu E, Benitez RP, Rosenwasser R: Stent-assisted coil placement for unruptured cerebral aneurysms. **Neurosurg Focus** 17: E10, 2004). Follow-up results from clinical series are becoming available, but typically involve both the first- and second-generation Neuroform devices, which differ primarily in deliverability. An initial report of Neuroform stent-assisted coil embolization with a relatively short (3–6 mo) follow-up period included four patients with giant aneurysms; partial occlusion was achieved in two patients, and near-total occlusion was achieved in two others (9). Of the three patients available for follow-up in this series, one had progressive thrombosis and two had angiographic evidence of recanalization. The giant aneurysms represented a small portion of the cases for this study. These aneurysms, that would not otherwise be suitable for endovascular therapy, could be treated with the use of one or more stents. Lylyk et al. (27) presented six patients with giant aneurysms treated with Neuroform stents and coils, but the results obtained for giant aneurysms are not separated in this series consisting of 46 patients with 48 intracranial aneurysms. Overall, the stent placement was optimal in 81.2% of patients (every patient with the second-generation device). Complete occlusion was noted in 85% of all aneurysm patients. The mortality rate was 2.1%, and the morbidity rate was 8.6%, which was largely the result of thromboembolic complications. Long-term follow-up occlusion rate results were not presented, except that there was apparently no evidence of in-stent stenosis. At present, there is insufficient good clinical data to prove that Neuroform stent-assisted coiling leads to reduced recanalization rates in giant cerebral aneurysms. It is clear that stent assistance allows coil embolization of aneurysms that would otherwise be difficult or impossible to embolize with coils, and that stents are deliverable to most aneurysm sites. It is our impression that stent assistance allows for increased density of aneurysm coil packing.

FIGURE 3. *Illustration demonstrating stent-assisted coil embolization for neck reconstruction. The stent first is positioned to span the neck region. The microcatheter is positioned through the interstices of the stent and into the aneurysm fundus for coil placement.*

The radial outward force exerted by the Neuroform design is low. When a longer vessel reconstruction is needed, we purposely oversize the stent in an attempt to maximize this radial outward force. This technique reduces crushing of the stent with a larger aneurysm and the subsequent larger mass of coils packed around the stent. Currently, an additional advantage of choosing a stent of a slightly larger diameter and length is that

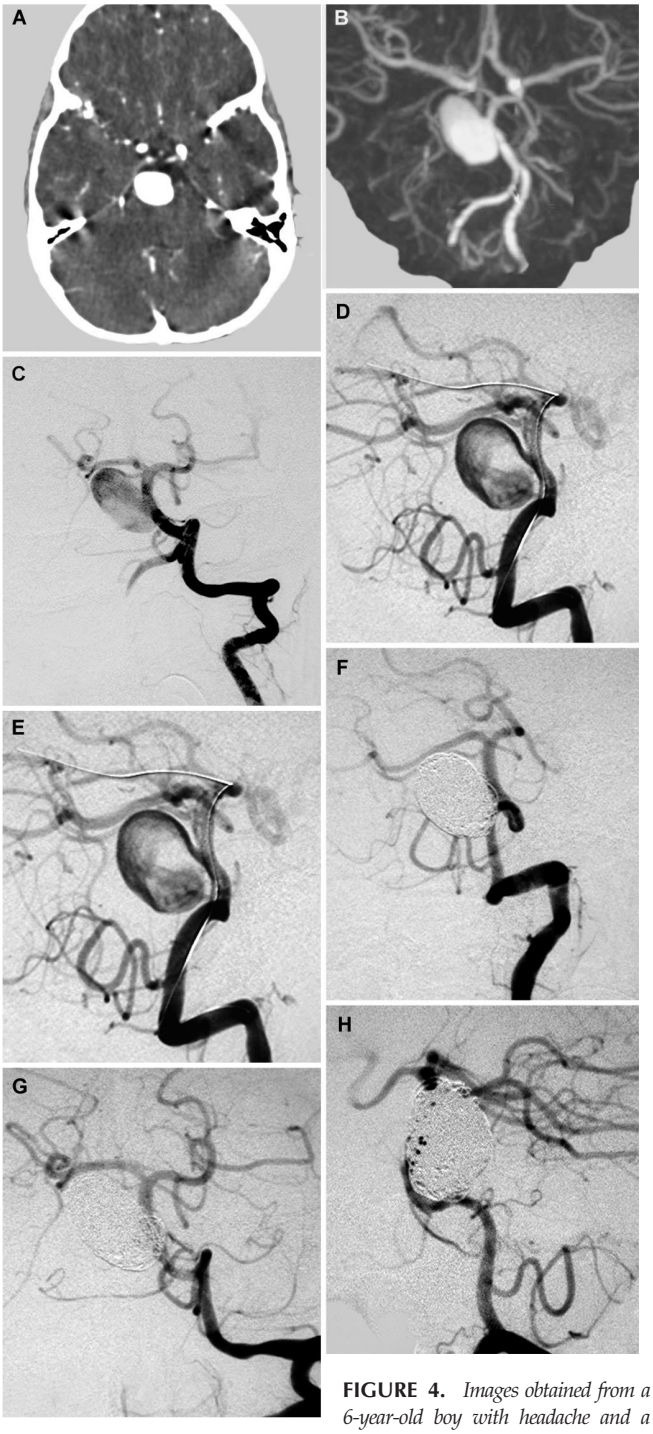

FIGURE 4. *Images obtained from a 6-year-old boy with headache and a large right compressive parapontine extraaxial mass.* A, *brain CT scan with contrast demonstrating an enhancing compressive mass.* B, *CT angiography demonstrating a giant right anterior inferior communicating artery aneurysm.* C *and* D, *anteroposterior and lateral views of left vertebral artery angiograms.* E, *working projection of left vertebral angiogram demonstrating coronary balloon-mounted stent deployed in position spanning the neck.* F, *final working projection view of angiogram demonstrating left vertebral injection and complete coil occlusion.* G *and* H, *final anteroposterior and lateral projections demonstrating complete coil occlusion.*

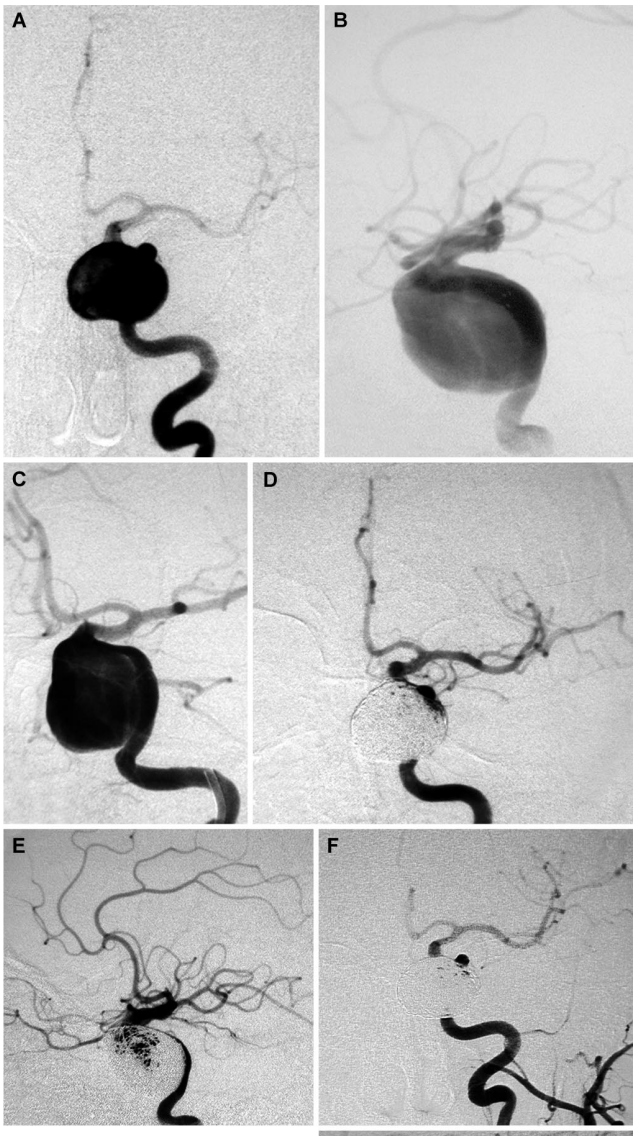

FIGURE 5. *Images obtained from a 41-year-old man with progressive diplopia (VIth cranial nerve palsy) and facial numbness.* A *to* C, *anteroposterior, lateral, and oblique angiograms of the giant internal carotid artery aneurysm demonstrating an extended neck region. Two Neuroform stents (Boston Scientific, Natick, MA) were placed subsequently.* D *and* E, *final anteroposterior and lateral angiograms demonstrating partial occlusion.* F *and* G, *anteroposterior and lateral angiograms demonstrating minimal progressive thrombosis obtained at the 2-month follow-up.*

the position of the stent is more stable during coiling and microcatheter manipulations. Although one could jail a microcatheter in the aneurysm with the stent and immediately proceed with

coil embolization, we have found that this increases the likelihood of coils protruding into the vessel outside the stent, where they can lock with the open-cell design of the currently available self-expanding stents. Our preference is to place the catheter through the struts of the stents when proceeding with coil embolization. If the stent appears to be in stable position or in an emergent setting, we consider coiling during the same session. If concerns exist regarding positioning or stability of the stent, we opt to perform coil embolization at a separate session 4 to 6 weeks later. Staging the procedure provides several advantages. It allows the stent to heal into the parent vessel wall and increases the stability of stent position. In addition, it reduces the chance of coils herniating into the parent vessel but outside of the stent, and the complications encountered when such coils lock with the stent (including coil fracture or unraveling, stent fracture, and stent movement). There is some histological evidence that Neuroform stent placement may narrow the aneurysm neck region to some degree because of an intimal response (24). This stent is designed for deliverability and for control of coil positioning, and as such has an extremely high porosity, leading to negligible hemodynamic effects.

The primary difficulty with the use of stents in intracranial vessels has been deliverability, which becomes increasingly difficult as the desired stent length increases. Proximal tortuosity leading to poor guide catheter access or tight vessel curvature (especially at the carotid siphon and proximal A1 segment) can result in an inability to navigate intracranial stents to the desired location. We have used a number of adjunctive techniques to allow intracranial stent placement, including the use of buddy wires to stabilize guide access, the use of guide catheters within stiff guide sheaths, and attempts to use circle of Willis collaterals to improve the geometry of stent placement. The delivery systems of self-expanding stent designs currently available in the United States are not sufficient for some wide-necked and giant aneurysms, and the upcoming release of the next generations of these stents is highly anticipated. In addition to difficulty with deliverability, the exact placement of these devices can be troublesome, especially when deploying the stent on a vessel curve. In such cases, the delivery system will tend to herniate proximally, leading to our preference to choose stents of slightly longer lengths. Advances in the design of closed-cell stents that can be resheathed will assist with these problems.

One difficulty with the use of stents in curved arteries is that the porosity of the stent increases on the outer radius of a curve as the stent bends. This increase in porosity can lead to reduced effectiveness in preventing coil herniation into the parent vessel. True bifurcation aneurysms (basilar apex, internal carotid artery, or middle cerebral artery bifurcation) tend to be associated with sharp vessel curvature and, in addition, to have a more complex neck configuration. Such morphological features can result in the failure of a single stent to provide adequate protection of the parent vessels. To assist coil embolization of bifurcation aneurysms, Y-configuration stenting was developed (3). In this technique, a self-expanding nitinol stent is deployed from the proximal artery into one of the distal branches. A second stent then is placed through the first stent from the proximal artery to the other distal branch (*Fig. 6*). This technique can be difficult to perform because of the increased resistance encountered when passing the second stent delivery catheter through the interstices of the first deployed stent. In addition, although the Y-configuration technique creates two stent channels to protect the posterior cerebral artery segments, it may not fully protect the basilar apex perforators if the 3-D shape of the bifurcation is complex and coils herniate outside of the stent construct and posteroinferiorly into the posterior basilar apex region. Also, a significant amount of nitinol material remains at the basilar apex in the parent lumen. Initial reports of periprocedural and intermediate-term follow-up results are promising for treatment of large and wide-necked aneurysms (37, 44).

An additional approach for the treatment of giant bifurcation aneurysms involves the use of the Neuroform stent in the so-called waffle cone technique (*Figs. 7* and *8*) (19). In this technique, a Neuroform stent oversized to the proximal artery is placed with the distal end flared open in the aneurysm, and then the proximal end is deployed into the parent artery proximal to the aneurysm. This technique essentially involves the reconstruction of a smaller neck and protects the distal branches of the parent vessel. A properly placed 3-D framing coil is still required to prevent compromise of the parent vessels, but the scaffold provided by the stent divides the aneurysm neck into smaller segments for coiling purposes. We have performed several such procedures in select cases at our institution. The distal aspect of the stent captures the framing coils, holding them within the aneurysm and allowing for neck reconstruction in bifurcation aneurysms. Potentially, the coil loops could lock into the distal ends of the stent to aid in the stability of the coil mass with regard to coil compaction. This technique can be effective in assisting coiling if the axis of the feeding artery points directly into the aneurysm, but is less useful when the aneurysm points tangentially away from the parent artery. In addition, the existence of a significant mismatch between the aneurysm neck size and the feeding artery helps to increase the angle of flaring of the stent in the region of the aneurysm neck. Proximal access anatomy presents a greater drawback with this technique, compared with traditional stent techniques, because of the more limited

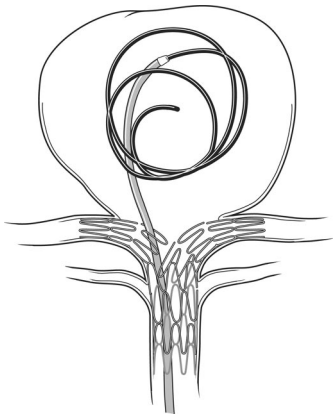

FIGURE 6. *Illustration demonstrating Y-configuration stent-assisted coil embolization for wide-necked bifurcation aneurysms. A Neuroform stent is deployed from one of the bifurcation arms into the proximal parent artery. A second stent is placed from the other bifurcation arm into the parent artery through the interstices of the first stent. A microcatheter is then placed through the stents into the aneurysm fundus for coil embolization.*

distal wire purchase for final positioning of the delivery system. Long-term results of the durability of this technique are pending.

Vessel Reconstruction

As an aneurysm grows, it can involve the proximal and distal parent artery, leading to the formation of a fusiform configuration with a poorly defined or absent neck region. One strategy to deal with this problem is to reconstruct a vessel lumen with one or more stents. This presents a considerably greater technical challenge than reconstruction of a wide neck. In this case, the midportion of the stent typically is not apposed to an arterial wall, and the coil embolization occurs in up to a 360-degree fashion in a cross-sectional plane. Angiographic visualization of the reconstructed vessel may be difficult, which can lead to coil loops herniating into the stent and, therefore, the reconstructed vessel. (Normally, one can visualize down the axis of the stent; this is not possible on curved segments, however.) Our preference is to use coronary stents for reconstruction of long segments of a fusiform aneurysm because these stents have a superior radial resistive force and lower porosity than self-expanding intracranial stents (*Fig. 9*). Balloon deployment of these coronary-type stents also allows for more precise positioning. Balloon-expandable stents can be more difficult to deliver than self-expanding stents, but recent developments in cobalt-chromium alloy stent technology include more trackable stent delivery systems that excel at deliverability to the intracranial circulation (e.g., Vision balloon-mounted stent [Guidant, Indianapolis, IN], Driver balloon-mounted stents [Medtronic, Minneapolis, MN]).

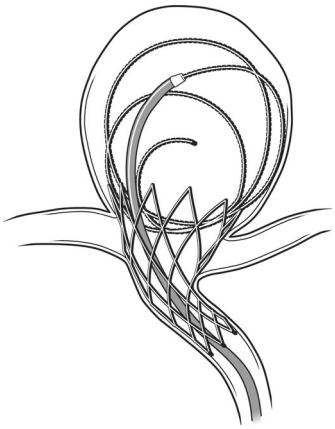

FIGURE 7. *Illustration demonstrating waffle cone configuration stent-assisted coil embolization for wide-necked aneurysms. An oversized Neuroform stent is deployed into the aneurysm fundus to allow flaring of the distal end. The stent is withdrawn until the flared segment cinches at the neck orifice. The remaining stent is deployed into the proximal parent vessel.*

Recent additional techniques have been described in which Neuroform stents have been used to assist coil deposition in this extreme situation of vessel reconstruction. For giant or fusiform aneurysms that have a circumferential dilatation, Fiorella et al. (10) described the placement of a long stent or multiple stents, then subsequent placement of a balloon inside the stented region for temporary inflations to prevent stent crushing or loops herniating into the reconstructed vessel.

POROUS STENT HEMODYNAMICS

There is increasing evidence from in vitro (40) and animal (22) studies, a report (7), and our clinical experience (*Figs. 10* and *11*) that single or multiple porous stents can be used to occlude

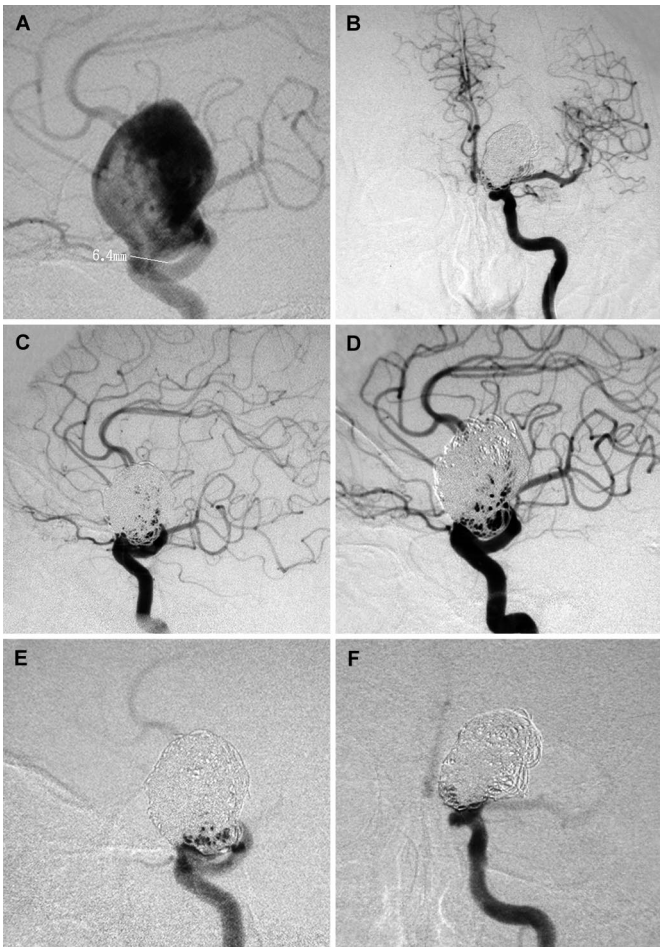

FIGURE 8. *Images obtained from a 74-year-old woman 2 weeks after rupture of a giant ophthalmic aneurysm.* A, *lateral projection angiogram demonstrating giant wide-necked ophthalmic segment aneurysm.* B *to* D, *anteroposterior, lateral, and oblique final angiograms demonstrating partial occlusion.* E *and* F, *angiogram demonstrating minimal progressive thrombosis of the aneurysm fundus with some coil compaction at the neck region obtained at the 3-month follow-up.*

cerebral aneurysms permanently. This can be accomplished via a variety of strategies; at present, however, our understanding of the exact degree of porosity for a particular aneurysm is lacking. The continued development of our knowledge of hemodynamics of aneurysms, including the effect on aneurysm growth and rupture, rheology, and coagulation, will allow us to better define the degree of stent porosity that will lead to occlusion of the aneurysm without sacrificing perforating arteries. These strategies, however, are more applicable to fusiform or sidewall aneurysms than true bifurcation aneurysms.

Several factors influence the effect of porous stents on intracranial aneurysms, including vessel size, aneurysm geometry (including dome-to-neck or aspect ratio), porosity, and parent vessel curvature (18). As the stent porosity decreases, the stent is more likely to occlude the aneurysm but becomes more difficult to deliver to the intracranial circulation. Ideally, the porosity of a

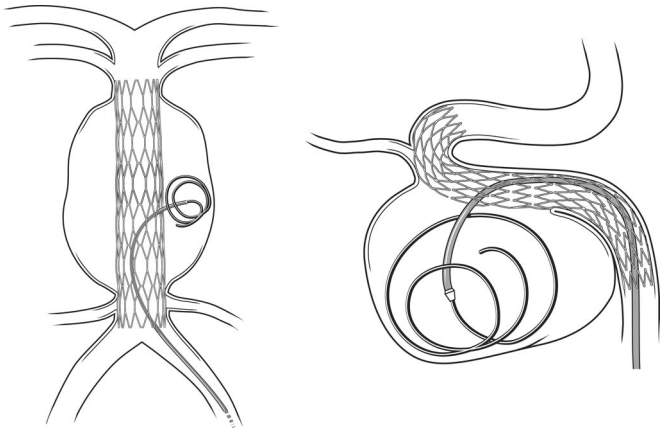

FIGURE 9. *Illustrations demonstrating two perspectives of stent-assisted coil embolization for vessel reconstruction. The aneurysm has a more fusiform appearance, requiring more extended or multiple stent placement. Coil embolization proceeds via the microcatheter positioned through the stent interstices.*

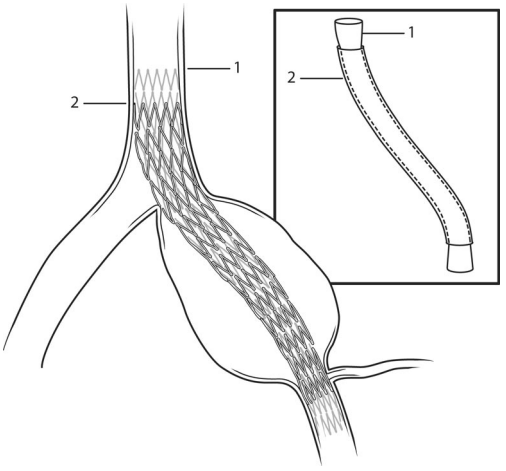

FIGURE 10. *Illustration demonstrating two coronary stents (*1 *and* 2*) positioned to span this fusiform aneurysm. The combined effect of the stents is to lower the porosity and to promote thrombosis.*

stent could be matched to the hemodynamic requirements of an aneurysm. At present, multiple coronary stents are placed into the parent artery of the aneurysm in an attempt to alter the hemodynamics of the aneurysm flow such that the inlet flow becomes laminar, as is the case with normal outlet flow. We have observed in our clinical cases that if a turbulent pulsatile inlet flow persists, the aneurysm is unlikely to undergo progressive thrombosis. On occasion, placement of a stent actually can lead to a more cohesive jet of flow, which can predispose the aneurysm to rapid growth and rupture. Either of these findings would suggest that a second stent should be placed inside the initial stent.

In an attempt to deal with the difficulty encountered during the deployment of less porous stents, there has been interest in the design of asymmetric stents that have a less porous segment to occlude the aneurysm orifice and a more porous segment to preserve the perforating vessels and to stabilize the stent. Whether the design is a stent, a covered stent combination, or a less porous segment incorporated with a standard stent (*Fig. 12*), the concept is the same. The difficulty with these devices is to position them appropriately, in both longitudinal and radial positions. There are no reports of clinical application of such devices in humans at present.

Liquid Embolic Techniques

Use of ethylene vinyl alcohol copolymer liquid embolic agents dissolved in dimethyl sulfoxide (Onyx; MicroTherapeutics, Inc., Irvine, CA) to embolize giant cerebral aneurysms has been limited in the United States. Results of the Cerebral Aneurysm Multicenter European Onyx trial, which was designed to treat those aneurysms that were considered high risk for surgical or conventional endovascular therapy, included a 1-year complete occlusion rate of 78.9% in 56 out of 71 aneurysms treated for which angiographic follow-up was available (29). Mortality occurred in four (4.1%) out of 97 patients during the index hospitalization, with half of the deaths resulting from procedure complications. Three additional patients died of unrelated causes during the 12-month follow-up period. Permanent morbidity, including hemorrhage, stroke, or worsening cranial nerve deficit, occurred in eight (8.2%) out of 97 patients. Ten percent of aneurysms required retreatment within 3 to 12 months of the index procedure (5% of giant aneurysms required retreatment). Parent artery occlusion was demonstrated on follow-up angiography in nine patients (five were asymptomatic and two experienced permanent neurological deficit). All parent artery occlusions occurred within 3 months of the embolization procedure. Cil et al. (4) described successful treatment of 15 giant aneurysms with Onyx, with recanalization in eight out of 15 aneurysms, of which three required treatment. The overall mortality rate in this series of 67 patients with 72 aneurysms was 4.4%. Liquid embolic agents have potential application in aneurysms that are not amenable to more conventional techniques, but the learning curve to using these techniques is significant. Availability of, and experience with, this agent at our center was limited to participation in clinical trials. Approval of Onyx for aneurysm use in the United States will add significantly to our ability to treat these difficult lesions in the future.

Access: Cut-Down Techniques

For those patients in whom significant proximal tortuosity prevents sufficient guide catheter or sheath access for proper delivery of stents or coils, we have, on occasion, performed an extracranial carotid or vertebral artery cut down to deliver stents to the intracranial circulation. This allows more direct access to the aneurysm and can avoid some complications of attempting access through tortuous proximal arteries (e.g., dissection and/or occlusion). Certain less porous types of stents cannot be delivered to the intracranial circulation by any other means.

For the extracranial vertebral artery cut down, the vertebral artery is exposed as it traverses over the posterior arch of C1, either through a midline approach (for familiarity), or paramed-

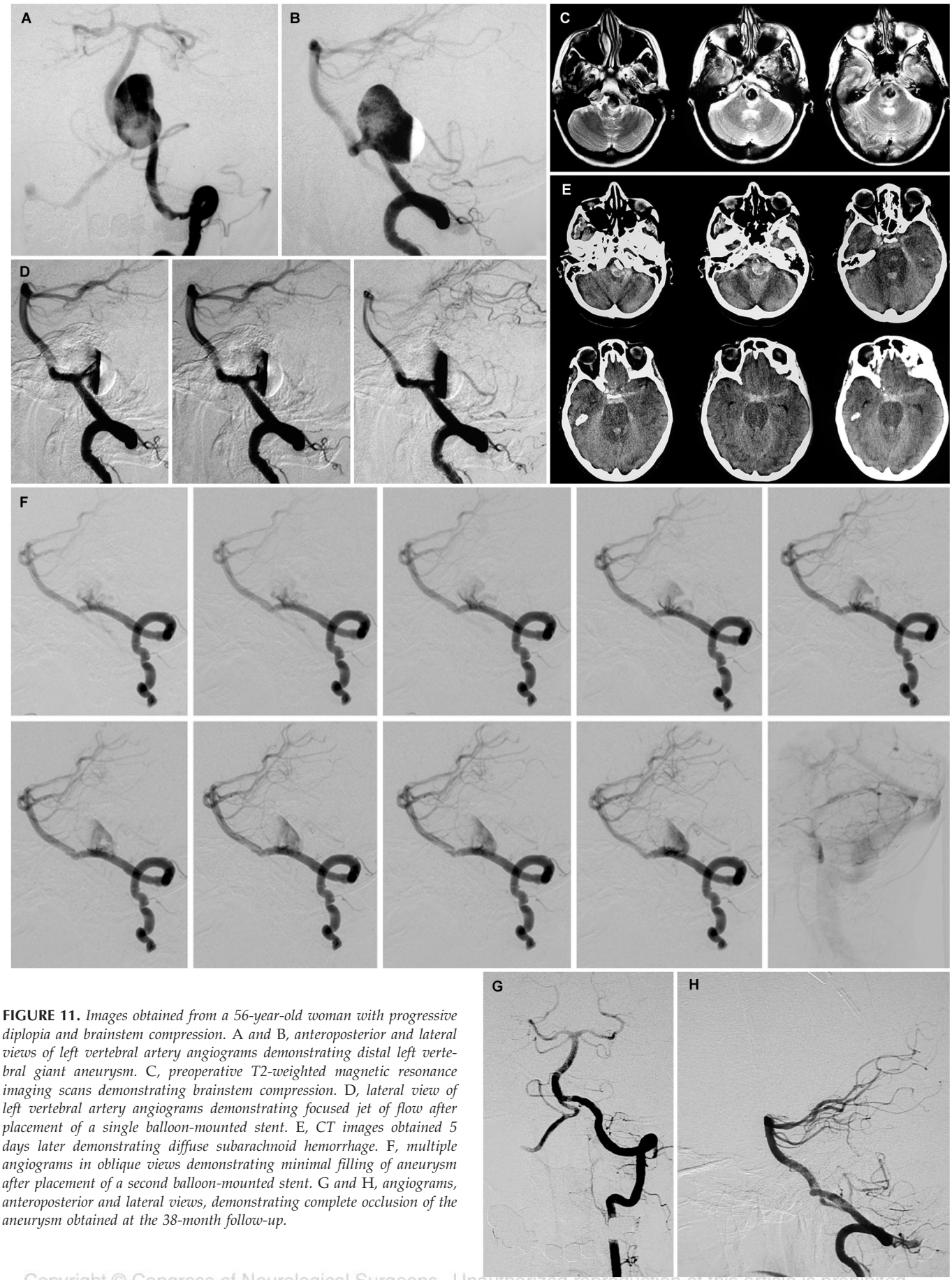

FIGURE 11. *Images obtained from a 56-year-old woman with progressive diplopia and brainstem compression.* A *and* B, *anteroposterior and lateral views of left vertebral artery angiograms demonstrating distal left vertebral giant aneurysm.* C, *preoperative T2-weighted magnetic resonance imaging scans demonstrating brainstem compression.* D, *lateral view of left vertebral artery angiograms demonstrating focused jet of flow after placement of a single balloon-mounted stent.* E, *CT images obtained 5 days later demonstrating diffuse subarachnoid hemorrhage.* F, *multiple angiograms in oblique views demonstrating minimal filling of aneurysm after placement of a second balloon-mounted stent.* G *and* H, *angiograms, anteroposterior and lateral views, demonstrating complete occlusion of the aneurysm obtained at the 38-month follow-up.*

ian approach (for more direct access). Two purse-string sutures are placed in the vertebral artery, and an access needle is entered into the center of the purse-string suture. Typically, a 6-French sheath is then positioned into the artery over a wire. Often, it is necessary to tunnel the sheath through the skin lateral to the cervical incision to assure proper angulation of the sheath with respect to the vertebral artery segment being catheterized. An angiographic run is then performed. If no abnormalities are encountered, systemic heparinization is initiated. The stent placement and/or coil embolization proceeds in routine fashion. At the termination of the procedure, the sheath is removed, and the purse-string sutures are tied down. The wound is closed with drains in place because of the heparinization and the likely use of antiplatelet medications. The approach for the extracranial carotid cut down is similar, but is performed in the common carotid artery, owing to its larger size and for ease of access and hemostatic control.

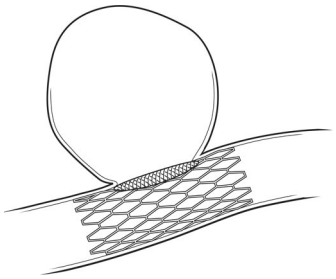

FIGURE 12. *Illustration demonstrating stenting of an aneurysm with a variable porosity stent. The less porous portion of the stent is positioned over the aneurysm neck region.*

We have performed extracranial carotid or vertebral cut down in eight patients, all with immediate procedural success; with one delayed, postoperative death associated with subacute stent thrombosis resulting from premature cessation of antiplatelet medications. Use of these techniques may become less frequent with continued development of intracranial stents with improved deliverability, including those with covered or partially covered designs.

COMPLICATION AVOIDANCE AND MANAGEMENT

Reduction of endovascular complications in the treatment of giant aneurysms lies primarily in prevention, because many complications are not readily treatable. Proper patient selection, assessing the most reasonable approach to each particular aneurysm, and careful attention to detail are keys to avoiding complications. At institutions in which these complex lesions are treated, an honest assessment must be made in terms of the locally available treatment techniques, and their relative risks at that institution (whether they are surgical, endovascular, or combination approaches).

Procedure-related thromboembolic complications occur in 2.5 to 11% of intracranial aneurysms treated by coil embolization, with permanent deficits in 2.5 to 5.5% of patients (46). Primarily, they are a result of platelet aggregation and distal embolization or complete thrombosis of the vessel. There is usually a nidus responsible for such platelet aggregation, be it stent struts, errant coil loops, or herniation of nascent thrombus from the aneurysm into the parent lumen during coil placement. Treatment of such complications can involve use of glycoprotein IIb-IIIa inhibitors or thrombolytics, with our bias toward glycoprotein IIb-IIIa inhibitors. If there is flow restriction by errant coil loops, it may be necessary to place a stent to prevent complete occlusion as a bail-out maneuver (8).

Vessel perforations caused by wires represent a significant risk, owing to the combination of antiplatelet and anticoagulant medications administered for complex revascularization procedures. Wire perforation can occur because of small, poorly visualized perforators, excessive wire or catheter motion caused by vessel tortuosity, or excessive force during wire or catheter manipulation. To manage this complication, we quickly reverse the intravenous heparin with intravenous protamine (1 mg/100 units heparin; typically, 30 mg is sufficient for most adults). Angiographic runs are performed to assess for further contrast extravasation. Temporary balloon occlusion can be used to tamponade any continued extravasation. The procedure should be aborted, a CT scan should be performed, and an immediate neurosurgical consultation obtained for potential ventriculostomy or craniotomy and hematoma evacuation.

Frank aneurysm rupture can occur during endovascular treatment and is more likely when treating acutely ruptured aneurysms. This represents a more serious issue than simple wire perforation, because the wall defect is typically larger and less likely to seal without intervention. Reversal of anticoagulation and rapid placement of coils to occlude the ruptured portion of the aneurysm is the typical treatment for this complication type, but proper occlusion depends on the aneurysm configuration. Quick cessation of hemorrhage should be the goal, and not a perfect angiographic occlusion. This goal may be more difficult to achieve in fusiform or extremely wide-necked aneurysms, where temporary balloon tamponade may be necessary to assist the coil embolization.

Femoral artery access site complications can lead to significant lower extremity ischemia, retroperitoneal hemorrhage, hypotension, or even death. Proper prevention of these complications involves meticulous single wall puncture technique based on proper anatomical landmarks to avoid puncturing above the inguinal ligament. Some clinicians advocate micropuncture kit use for femoral artery access for those patients in whom a dual regimen of antiplatelet and anticoagulant agents is used. Reversal of anticoagulation may be necessary if groin or retroperitoneal hemorrhage is suspected. Some cases can be treated with local compression or by increasing the size of the groin sheath. Access closure devices routinely are used, and we look forward to improvements in closure technology.

CONCLUSION

Current endovascular techniques for the treatment of giant cerebral aneurysms seem to have lower periprocedural risks for the patients, but are not satisfactory in terms of the long-term durability of aneurysm occlusion. It is in the context of the elevated risk of hemorrhage and other untoward events in the natural history and the associated high surgical morbidity

and mortality of these lesions that these more complicated endovascular revascularization techniques are a relatively low-risk alternative. These lesions present severe technical challenges. Nevertheless, continued development of techniques and devices that are based on our understanding of the engineering and biology of giant aneurysms will lead to future solutions for these difficult problems. Reversing the hemodynamic and biological forces leading to continued aneurysmal growth and rupture should be the immediate goal of treatment, with eventual healing of the artery codifying the long-term goal.

DISCLOSURES

Ricardo A. Hanel, M.D., has received industry grant support from Boston Scientific Corporation. L. Nelson Hopkins, M.D., has received industry grant support and consultant fees from Boston Scientific, Cordis, EndoTex, and Micrus. He holds stock or is a shareholder in EndoTex and Micrus, and has received honoraria from Bard, Boston Scientific, Cordis, and Medsn. Elad I. Levy, M.D., has received industry grant support from Boston Scientific and Cordis and has received honoraria from Boston Scientific and Cordis.

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ENDOVASCULAR MANAGEMENT OF CEREBRAL VASOSPASM

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CEREBRAL VASOSPASM REMAINS a leading cause of death and disability in patients with ruptured cerebral aneurysms. The development of endovascular intervention in the past two decades has shown promising results in the treatment of vasospasm. Endovascular techniques that have been used in humans include intra-arterial infusion of vasorelaxants and direct mechanical dilation with transluminal balloon angioplasty. This article reviews the current indications and role of endovascular therapy in the management of cerebral vasospasm, its clinical significance, and potential future therapies.

KEY WORDS: Cerebral vasospasm, Endovascular therapy, Transluminal balloon angioplasty, Papaverine

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After the initial effects of hemorrhage, cerebral vasospasm remains the second leading cause of death and disability in patients with ruptured cerebral aneurysm. In the International Cooperative Trial on the Timing of Aneurysm Surgery, conducted in the early 1980s, vasospasm permanently affected 13.5% of the patients and accounted for 33% of all death and disability (42, 43). With modern treatment, including administration of nimodipine, magnesium, "triple H" therapy, endovascular intervention, and improved critical care, the number of patients permanently affected by cerebral vasospasm seems to be lower; the estimated proportion of patients who are dead or disabled from vasospasm ranges from 5 to 9% (11, 17, 71, 74, 76), and vasospasm accounts for 12 to 17% of all cases of death and disability after subarachnoid hemorrhage (SAH). Nevertheless, this number is still substantial, and efforts to prevent this potentially devastating complication continue.

Cerebral vasospasm is defined as the delayed-onset narrowing of the cerebral arteries occurring after SAH. Angiographic vasospasm occurs in approximately 70% of patients with aneurysmal SAH (18), but clinical manifestations (i.e., delayed ischemic neurological deficit [DIND]) occur in only 30 to 50% of patients with angiographic vasospasm (28, 30). If clinical vasospasm is present, associated angiographic vasospasm is usually severe (77). Independent predictors of symptomatic vasospasm include thick clot in the basal cisterns, early rise in middle cerebral artery (MCA) flow velocity on transcranial Doppler, a Glasgow Coma Scale score of less than 14 on admission, and rupture of an anterior cerebral (ACA) or internal carotid artery (ICA) aneurysm (70).

Endovascular therapy is typically reserved for the treatment of DIND that does not respond to hyperdynamic therapy (triple H therapy). However, the timing and clinical criteria for the institution of endovascular therapy are not well established. If DIND is present and other causes, such as electrolyte abnormalities, hydrocephalus, procedure-related stroke, and seizures, are excluded and the patient is not responding to aggressive triple H therapy, most clinicians think that the patient should be evaluated and, if possible, treated with endovascular therapy within hours of the onset of DIND. Previous reports have shown that patients who are treated early seem to have the largest benefit. In patients with lateralizing signs, detection of DIND may not be difficult. However, patients with midline aneurysms tend to present more often with subtle mental status changes. In these patients, we have previously defined a drop of more than 2 points on the Glasgow Coma Scale score as indicative of DIND (58).

The goal of endovascular therapy in the management of cerebral vasospasm is the reestablishment of adequate cerebral perfusion. This can be accomplished by either pharmacological or mechanical dilatation. Endovascular techniques that have been used in humans include intra-arterial infusion of Papaverine (IAP), nimodipine, nicardipine, or

verapamil, and transluminal balloon angioplasty (TBA). In addition, the endovascular management of cerebral aneurysms by endosaccular placement of coils has facilitated procedures such as cisternal irrigation and clot lysis (36), procedures that were successful in preventing vasospasm, but were abandoned in surgical patients because of the hemorrhagic complications related to craniotomy and surgical dissection (26). This article reviews the current indications and role of endovascular therapy in the management of cerebral vasospasm and touches on potential future therapies.

INTRA-ARTERIAL INFUSION OF VASOACTIVE AGENTS

Papaverine

Papaverine hydrochloride is the most common agent used for pharmacological dilatation of vasospastic cerebral vessels. Papaverine is a member of the benzylisoquinoline group of alkaloids. It was originally prepared as a crude alkaloid derivative of opium, but is now manufactured synthetically. It is a potent, nonspecific, endothelium-independent smooth muscle relaxant, which mainly produces diffuse dilatation of arteries and arterioles, but is also capable of dilating veins (14, 15). Its exact mechanism of action is unknown. It is thought to be related to inhibition of cyclic adenosine monophosphate (cAMP) and cyclic guanosine 3,5 monophosphate (cGMP) phosphodiesterase activity, which decreases cAMP and cGMP turnover in the smooth muscle cell (9, 52, 55, 66, 69).

IAP is usually administered superselectively via a microcatheter positioned proximal to the spastic vessel. The typical Papaverine concentration infused is 0.3% (300 mg Papaverine in 100 ml of normal saline). This dose is usually administered to the affected vessel or vascular territory for 20 to 30 minutes (6, 52). In the anterior circulation, the microcatheter is placed in the supraclinoid carotid artery above the origin of the ophthalmic artery. This allows infusion in both the middle and anterior cerebral circulations, with dilution kept to a minimum. If the spasm is present predominantly in either the ACA or middle cerebral artery (MCA), but not both, then superselective catheterization is required to prevent flow through the route of least resistance into the less affected territory. Infusion with the catheter located proximally in the common carotid artery can cause runoff to other vascular territories and can limit the effectiveness on the distal spastic vessels. In the posterior circulation, the catheter is placed immediately proximal to the vessels affected by vasospasm. Infusion of the distal vertebral (VA) or proximal basilar artery below the origin of the anterior inferior cerebellar artery may be limited because of diffusion into perforators supplying the lower brainstem.

Although Papaverine can lead to immediate reversal of angiographic vasospasm, its effect is usually transient, even with prolonged infusion (12, 24, 27, 40, 41, 47, 48, 50, 59, 61, 73). In almost all patients, vasospasm recurs within 1 day after infusion. This is probably attributable to the short half-life of Papaverine in the circulation (45–60 min). However, multiple daily treatments with IAP can be effective for distal refractory vasospasm and can carry patients through the period of the most severe spasm. In animal experiments, Papaverine has been shown to be most effective in the first 3 days after the onset of vasospasm, but the vessels have tended to become unresponsive in the chronic phase (i.e., 5–9 d after the onset of vasospasm) (53, 82).

Clinical improvement with IAP infusion is modest, varying between 25 and 52% in most series (*Table 1*). However, the data come only from small consecutive case series, and IAP has not been subjected to testing in randomized clinical trials.

Complications associated with IAP include raised intracranial pressure (ICP), seizures, transient hemiparesis, mydriasis, hypotension, cardiac dysfunction, and respiratory arrest (5, 10, 13, 44, 51, 79, 80). Infusion proximal to the ophthalmic artery leads to mydriasis, which is usually transient, but permanent visual impairment and monocular blindness have been reported (12). In the posterior circulation, infusion may result in cardiac dysfunction and respiratory arrest, probably as a result of depression of respiratory and cardiovascular centers in the brainstem. The development of hypotension is dose related and associated with infusion into multiple territories and higher infusion rates. The cause of neurological impairments, such as hemiparesis and seizures, is poorly understood. Microcrystal formation of Papaverine in areas of low flow may lead to the development of microemboli, which subsequently lodge in the distal circulation (52), and Papaverine is known to precipitate when in contact with contrast media or heparin-containing solutions. Seizures may be attributable to a proconvulsant effect of Papaverine at high doses, although Papaverine has been used in epilepsy research as an anticonvulsant agent because of its inhibitory effects on adenosine uptake (10). More recently, concern has also been raised about potential neurotoxic effects of IAP (78). However, this was based on a small magnetic resonance imaging study (i.e., five patients who presented with signal changes and neurological decline after IAP).

Raised ICP was a significant problem in a recent series from the University of Cincinnati (2). The authors reported on 50 patients treated with IAP for symptomatic cerebral vasospasm. In 21 cases, IAP was prematurely terminated because of a sustained increase of ICP, and five patients died as a result of intractably high ICP. The authors did not note a significant impact on outcome with IAP and found that TBA was more effective and was associated with fewer complications. They recommended against the use of IAP in patients with diffuse bilateral vasospasm because of the likelihood of developing elevated ICP, and they felt that IAP should be reserved for selected cases, such as opening a vasospastic vessel for subsequent TBA or treating vasospasm refractory to medical management and not amenable to TBA for technical reasons. Overall, the use of IAP as primary therapy is declining in most institutions in the United States. IAP is now generally used for adjunctive therapy or in selected cases with isolated distal vessel vasospasm.

TABLE 1. Efficacy of intra-arterial Papaverine administration[a]

Series (ref. no.)	Study design	No. of patients	Treatment	Angiographic improvement (%)	Clinical improvement (%)	Favorable outcome (%)	Complications
Kaku et al., 1992 (40)	Case series	10	IAP	91	80		
Kassell et al., 1992 (41)	Case series	12	IAP	57	25		
Livingston et al., 1993 (48)	Case series		IAP				
Clouston et al., 1995 (12)	Case series	14	IAP	95	50	70	One permanent monocular blindness, one ICA dissection w/o complications, one seizure
Terada et al., 1997 (79)	Case series	12	IAP	92	25	67	One seizure
Polin et al., 1998 (68)	Case control	31	IAP	No difference in outcome of patients treated with IAP versus control			
Katoh et al., 1999 (44)	Case series	4	IAP	N/A	25	50	One hypertension
		10	Prophylactic IAP[b]	N/A	N/A	90	Five decreased LOC, 1 hypertension, one hemiparesis, one decerebrate posturing, all transient
Firlik et al., 1999 (27)	Case series	15	IAP	78	26	N/A	One worsening vasospasm, one transient brainstem depression, one seizure, one hypotension
Morgan et al., 2000 (56)	Case series	85 (52 DIND)	Prophylactic IAP[b] + TBA (5 patients)	N/A	N/A	76	Transient hemiparesis 0.4%, seizures 2.2%, respiratory arrest 7%
Andaluz et al,, 2000 (2)	Case series	50	IAP + TBA (16 patients)	87	26	28	20 elevated ICP, ICP-related death 10%, one transient hemiplegia, one transient mydriasis, one transient brainstem depression, one aneurysm perforation. No complications from TBA

[a] DIND, delayed ischemic neurological deficit; IAP, intra-arterial Papaverine administration; ICA, internal carotid artery; ICP, intracranial pressure; LOC, loss of consciousness; TBA, transluminal balloon angioplasty.
[b] These patients were treated with IAP before onset of clinical vasospasm

Intra-arterial Calcium Channel Blockers

Direct intra-arterial infusion of calcium channel blockers has received renewed interest (*Table 2*) (3, 8, 25). In the past, calcium channel blockers were thought to act by a direct effect on the vascular smooth muscle cell via interaction with the calcium-dependent process of muscle contraction. Clinical trials were subsequently conducted with the intravenously and orally administered calcium channel blockers nicardipine and nimodipine (1, 34, 35, 63, 65, 75). Only with the latter was there a modest improvement of outcome, but no angiographic reversal of vasospasm was shown, indicating that the drug was effective through some mechanism other than smooth muscle relaxation (65). Direct intra-arterial infusion of nimodipine into the ICA was also tested around that time. Grotenhuis et al. (33) reported on six patients with vasospasm who were treated with intra-arterial nimodipine, but there was no effect on vessel caliber, and no clinical improvement was seen.

In a recent study, 25 patients with symptomatic vasospasm who were treated with infusion of nimodipine into the carotid artery or VA were retrospectively reviewed (8). Seventy-two percent of these patients were good-grade patients on admission (World Federation of Neurosurgical Societies Grade I–III), and 56% had Fisher Grade III SAH (29). Standard treatment included triple H therapy, but none of the patients were

TABLE 2. Efficacy of intra-arterial calcium channel blocker administration

Series (ref. no.)	Study design	No. of patients	Treatment	Angiographic improvement (%)	Clinical improvement (%)	Favorable outcome (%)	Complications
Grotenhuis et al., 1984 (33)	Case series	6	Nimodipine	0	0	Not stated	None
Biondi et al., 2004 (8)	Case series	25	Nimodipine	43	76	72	None
Feng et al., 2002 (25)	Case series	29	Verapamil	34	29 (5/17 procedures)	Not stated	None
Badjatia et al., 2004 (3)	Case series	18	Nicardipine	100	42	Not stated	None

treated with balloon angioplasty. Nimodipine was infused into the symptomatic carotid artery unilaterally in 21 cases, the bilateral carotid arteries in seven cases, and the VA in three cases, with a dose of 1 to 3 mg per vessel. The patients also received intravenous nimodipine at a rate of 2 mg/h, which was continued to 21 days posthemorrhage in patients who developed vasospasm. There were no apparent complications, and clinical improvement was observed in 19 (76%) patients, resulting in a good outcome in 17 of these 19 (89.5%; 68% of total). After a follow-up period of 3 to 6 months, 18 (72%) out of 25 patients had a favorable outcome. However, successful dilatation of infused vessels occurred in only 13 (43%) out of 30 procedures, raising some question as to the cause-and-effect relationship between drug and outcome.

Intra-arterial verapamil and nicardipine were also studied in consecutive case series. In a study of 29 patients, verapamil resulted in angiographic improvement in one-third of the cases, with an average increase of vessel diameter by 44%, but neurological improvement was noted in only five (29%) out of 17 cases in which verapamil was used as the sole treatment (25). In a smaller series, intra-arterial administration of nicardipine was somewhat more successful (3). Eighteen patients were treated with 0.5 to 6 mg of nicardipine per vessel, with angiographic dilatation seen in all vessel segments and neurological improvement in 42% of patients. An advantage of intra-arterial infusion of any of these drugs is that multiple treatments can be given.

TRANSLUMINAL BALLOON ANGIOPLASTY

Although human studies have shown that TBA produces a long-lasting dilatation of vasospastic vessels, the precise mechanism of action of TBA is not well understood. Proposed mechanisms include disruption and dysfunction of the smooth muscle cells, the extracellular matrix of the vessel wall, or the connections in the basement membrane between smooth muscle cells and the extracellular matrix (39a, 48a, 82a). In general, TBA does not seem to cause major structural damage to the vessel wall, unless high balloon pressures are applied (46). TBA typically results in smooth muscle flattening, mild matrix interruption, endothelial flattening, or denudation. Vasospastic and normal vessel segments do become less responsive to both vasoconstrictors and vasodilators immediately after TBA (49).

Zubkov et al. were the first to report that TBA was effective in humans, with excellent success in carefully selected patients with large vessel spasm (83). In the two decades since that initial description, advancements have been made in balloon and catheter technologies, making this technique more widely applicable and safer (4, 19–21, 23, 37–39, 45, 61, 62, 67). The original balloons used were relatively stiff latex balloons, but soft, flow-guided silicone balloons, which (at least in theory) reduce the risk of catastrophic vessel rupture, became available in the late 1980s, followed more recently by wire-guided balloons. Flow-guided balloons tend to be less traumatic to the vessels, but may impose difficulties navigating into the ACA or posterior cerebral arteries because of acute vessel angulation or tortuosity. Over-the-wire systems allow for easier navigation into vessels inaccessible by flow-guided balloons, but they are associated with an increased risk of vessel perforation and rupture (62). Compliant and noncompliant over-the-wire balloons are available. Compliant balloons are less traumatic to the vessel wall and more trackable through tortuous vessels. However, the smallest diameter available at this time is approximately 3.5 to 4 mm, and is, therefore, larger than even the largest the proximal ACA or MCA. This may impose risk during balloon inflation in these vessels. The noncompliant balloons may be more traumatic because of their stiffness, but they come in smaller diameters (e.g., 2–2.25 mm) and cannot be overinflated as easily. It should be noted that none of the balloons currently in use for cerebral angioplasty are Food and Drug Administration approved for this procedure, and all are thus used "off label."

For the procedure, the intracranial arteries are catheterized superselectively, most commonly using a transfemoral approach. Creation of a digital roadmap is essential to facilitate the procedure by allowing balloon manipulation with a superimposed image of the vessels being angioplastied. To prevent thromboembolic complications, the patients are heparinized unless there is an absolute contraindication to doing so. A clotting time of 2 to 3 times baseline, or generally greater than 300, is desirable before catheterization of the intracranial vessels. The patients are usually placed under general anesthesia or, if intubated already, are paralyzed and sedated to prevent patient movement, which may increase the risk of complications such as vessel rupture. However, if anesthesia is unavailable in a timely fashion, angioplasty can be performed with sedation only. In either case, care should be taken to prevent a drop in blood pressure during use of sedative medications or anesthetic agents because cerebral per-

fusion pressure must be maintained. Vessels amenable to angioplasty include the supraclinoid ICA, the M1 and sometimes M2 segments of the MCA, the A1 and (less commonly) A2 segment of the ACA, the intracranial segment of the VA, the basilar artery, and the P1 and (less commonly) P2 segment of the posterior cerebral artery (61). Angioplasty of the A1 segment remains technically challenging, and treatment of this vessel is possible in fewer than 10% of the patients because of its relatively small size and acute angulation as it arises from the ICA bifurcation (7, 19, 32, 39). As Newell et al. (61) have pointed out, it is important to attempt to treat patients with ACA spasm, particularly when the contralateral ACA is hypoplastic. Neurological sequelae from ACA infarcts can be significant and include lower-extremity weakness, hypesthesia, personality changes, transcortical motor aphasia, abulia, and bladder and bowel incontinence (16). Angioplasty of the supraclinoid carotid artery sometimes improves flow into the ACA, but, in some cases, Papaverine may be needed to at least transiently increase flow or to facilitate balloon navigation into the vessel.

Initially, the use of TBA was limited to the treatment of patients with symptomatic vasospasm that had become refractory to other treatment modalities, such as calcium channel blockers and triple H therapy. In addition, it was thought that TBA should not be performed in patients with low-density areas on computed tomographic scans because of the risk of reperfusion hemorrhage (61). Further experience indicated that initially asymptomatic vessels with a milder degree of vasospasm would often develop severe spasm if left untreated. For this reason, and also to maximize pial collateral flow, the practice at most institutions is to treat all accessible vessels that exhibit angiographic vasospasm during the first treatment session. Small- and medium-sized low-density areas on computed tomographic scans may improve after angioplasty of the vessels supplying the affected territories, and, thus, these changes are not considered an absolute contraindication for treatment with TBA (61). However, TBA is not recommended in patients with large MCA strokes, unless an M2 branch not supplying the infarcted area can be accessed. In each patient, the risk of reperfusion hemorrhage versus the possibility of salvaging territory at risk, but not yet infarcted, should be balanced.

The clinical success rate of TBA is variable (*Table 3*). A number of reasonably large consecutive case series evaluating the efficacy of TBA are now present in the literature (7, 39, 61, 67, 72). The angiographic improvement with TBA seems to be high, reaching 80 to 100% in most series. Clinical improvement is less frequent, but it remains more common than with IAP, and it ranges from 30 to 80%. Early treatment seems to be associated with increased efficacy, as will be described later in this article (see "Timing of Endovascular Intervention"). In the largest series published to date, 109 patients with symptomatic vasospasm were treated with TBA (61). Forty-seven (44%) of the patients improved within 72 hours after treatment, 31 (28%) remained unchanged, and 31 (28%) deteriorated.

These numbers seem to be confirmed in a meticulous prospective study on the prevention and treatment of vasospasm with TBA (balloon prophylaxis of aneurysmal vasospasm study [BPAV]). Preliminary analysis of the available blinded BPAV data (see below) revealed 29 patients in whom therapeutic angioplasty had been performed (*Table 3*). Therapeutic angioplasty was performed within 24 hours of the development of medical refractory DIND. Out of all patients who developed DIND, 68% required TBA. The number of patients requiring therapeutic TBA was much lower in the prophylactic TBA than in the control group; respectively, 12 and 27% of patients underwent therapeutic TBA ($P < 0.025$). A total of 102 vessel segments were subjected to angioplasty. Angiographic improvement was noted in 97% of cases, but clinical improvement was seen in only 38% of cases. Transcranial Doppler velocities were lower after treatment in 80% of cases and elevated in 13%.

No randomized clinical studies are currently available that assess the effect of TBA on outcome, nor is much known of the long-term effects of TBA. Nevertheless, the effect of angioplasty in the setting of cerebral vasospasm has been found to be lasting, and re-treatments are rarely needed. Furthermore, the angioplastied vessels normalize in luminal diameter over time based on follow-up angiography. Complications resulting from TBA for cerebral vasospasm are uncommon and include vessel perforation, unprotected aneurysm rerupture, branch occlusion, hemorrhagic infarction, and arterial dissection. Vessel rupture is reported in 4% of cases, usually with catastrophic outcome, and rebleeding from unclipped aneurysms is found in roughly 5% of cases (7, 21, 22, 67, 81).

Prophylactic TBA

Despite the success rate of TBA in treating symptomatic vasospasm, substantial numbers of patients are left with severe neurological deficits from vasospasm. Recent data from animals, as well as observations in humans, have indicated that the prophylactic treatment of vessels exposed to perivascular or subarachnoid blood may be effective in preventing vessels from undergoing subsequent vasospasm (54).

A pilot study investigating the effect of prophylactic TBA in humans was conducted at our institution (57, 58). Patients enrolled were those with the highest risk of developing cerebral vasospasm (i.e., Fisher Grade III SAH), and these patients underwent ballooning after treatment of the ruptured aneurysm, but within 3 days postrupture. A silicon flow-guided balloon was used for the procedure. Target vessels for the anterior circulation were the A1 segment of the ACAs, the M1 segment of the MCAs, and the supraclinoid segment of the ICAs. The posterior circulation target vessels were the P1 segment of the PCAs, the basilar artery, and the dominant VA intradural segment. Prophylactic TBA was considered satisfactory when it could be performed in at least two of the three parts of the intracranial circulation (right and/or left carotid system and/or vertebrobasilar system) and included the aneurysm-bearing part of the circulation.

A total of 18 patients were treated with prophylactic TBA in the pilot phase (*Table 3*). None of the patients developed DIND. Outcome analysis revealed a favorable outcome in 83% of patients (i.e., 12 patients with good recovery and three patients with

TABLE 3. Efficacy of transluminal balloon angioplasty[a]

Series (ref. no.)	Study design	No. of patients	Treatment	Angiographic improvement (%)	Clinical improvement (%)	Favorable outcome (%)	Complications	Note
Higashida et al., 1989 (37)	Case series	13	TBA	100	77	69	One patient had hemorrhagic infarct 24 hours later and died.	36 vessels treated
Newell et al., 1989 (62)	Case series	10	TBA	Not stated	80	80	Two out of 10 rebled from unprotected aneurysm 1 week s/p TBA; one patient had MCA stroke: no source of emboli.	31 vessels treated
Fujii et al., 1995 (31)	Case series	19	TBA	94	63	89	None stated	36 vessel segments dilated
Eskridge et al., 1998 (19)	Case series	50	TBA	Not stated	61	Not stated	Two (4%) died immediately as a result of vessel rupture.	170 vessel segments dilated
Bejjani et al., 1998 (7)	Case series	31	TBA +/− Papaverine	Not stated	72	90	No complications from the dilatation; three (10%) retroperitoneal/ inguinal hematomas.	81 vessels dilated
Polin et al., 2000 (67)	Case series	38	TBA +/− Papaverine	82	29	53	None reported	
Newell et al., 2001 (61)	Case series	109	TBA +/− Papaverine	Not stated	44	Not stated	Not stated	
Muizelaar et al., 2001 (57)	Case series	18	Prophylactic TBA	N/A	N/A	83	One patient had vessel rupture.	
Oskouian et al., 2002 (64)	Case series	12	TBA	Not stated	50	58	None from angioplasty	
Murayama et al., 2003 (59)	Case series	10	TBA +/− Papaverine	100	Not stated	70	None from angioplasty	
BPAV study (2004)	Case series	29	TBA	97	38	N/A	One arterial dissection	

[a] TBA, transluminal balloon angioplasty; MCA, middle cerebral artery; N/A, not available; BPAV, balloon prophylaxis of aneurysmal vasospasm study.

moderate disability). Three patients died, two of whom had developed pulmonary complications and one who had a vessel rupture during prophylactic TBA. The vessel rupture was caused by unintended balloon entry and inflation in the posterior inferior cerebellar artery caused by patient movement and resultant roadmap misregistration. Subsequently, all patients were treated while under general anesthesia, and no other complications associated with TBA were observed.

According to the same protocol, patients with Fisher Grade III SAH are currently being randomized to balloon treatment versus standard medical and endovascular management in the National Institutes of Health-funded balloon prophylaxis of aneurysmal vasospasm trial. This study is conducted in five centers in the United States, one center in Canada, and one center in the Netherlands. At the time of this writing, 151 out of the 185 projected patients have been enrolled. The data remain blinded to treatment effect, but adverse events related to the endovascular procedures require unblinding and are shown in *Table 4* . Overall, 469 neurointerventional procedures were performed in 132 patients. Balloon prophylaxis was performed in 73 patients. A total of 415 vessel segments underwent prophylactic ballooning: ICA (n = 124), MCA (n = 123), ACA (n = 21), posterior cerebral artery (n = 50), posterior communicating artery (n = 4), basilar artery (n = 48), and VA (n = 45) segments. In all patients, we were able to balloon two of three parts of the cerebral circulation. Five patients (7%) had

TABLE 4. Complications of neurointerventional procedures in 132 patients enrolled in the balloon prophylaxis of aneurysmal vasospasm trial

	Procedures	Complications	Complication rate/ procedure (%)	Vessels treated	Complications	Complication rate/ vessel (%)
Cerebral angiogram	295	3	1			
Coil	68	2	3	68	2	3
Therapeutic angioplasty	33	1	3	102	1	1
Prophylactic angioplasty	73	5	7	415	5	1
Total	469	11	2	585	7	2

complications directly related to the procedure under investigation. In three patients (4%), balloon prophylaxis caused a fatal vessel rupture. One patient had an uneventful vessel perforation by a guide wire, and another patient developed temporary vasospasm during the angiogram, but this temporary vasospasm resolved spontaneously. When taking into consideration the number of vessel segments that received ballooning, our complication rate is 1% per ballooned vessel.

TIMING OF ENDOVASCULAR INTERVENTION

The timing of intervention is an important determinant of the outcome after treatment of vasospasm and persistence of neurological deficit. Early intervention seems crucial to successful treatment. Newell et al. (60) have suggested that IAP performed within 6 to 12 hours after the onset of ischemic symptoms was beneficial, whereas treatment initiated beyond that time interval was not. Similarly, for TBA, treatment seems more effective when initiated early. In a recent study by Rosenwasser et al. (72), 84 patients with clinical vasospasm underwent endovascular treatment with TBA and/or superselective IAP in cases of distal vasospasm. Fifty-one patients were treated within 2 hours after onset of clinical symptoms, and 33 patients underwent treatment more than 2 hours (up to 17 h) after neurological decline. In the first group, 90% of patients had angiographic improvement, and 70% of patients sustained clinical improvement. In the second group, angiographic improvement was very similar at 88%, but clinical improvement was only seen in 40% of the patients. Thus, the time window may be even shorter than was previously appreciated (45), supporting investigation into prophylactic interventions for vasospasm (58). Moreover, prophylactic treatment can be performed at a time that secondary insults are not yet so important, as opposed to the period when patients are already in vasospasm and increasingly vulnerable to ischemic injury.

CONCLUSION

In the past two decades, the development of endovascular intervention, together with aggressive intensive care unit management, has greatly assisted in the treatment of cerebral vasospasm. TBA seems to be more effective than pharmacological treatment, and up to 80% of patients can be treated at a relatively small risk. Interpretation of the available studies should be performed with caution, however, because the body of published work consists nearly exclusively of retrospective institutional case series (i.e., Level III significance). Randomized clinical trials are needed to assess outcomes after these interventions, although in cases of TBA randomization, this may be difficult because of a loss of clinical equipoise. On a cellular and molecular level, a better understanding of the mechanism of action of TBA is required because this can potentially lead to the development of treatment strategies that are less invasive. Clinically, definitive criteria to evaluate and compare treatment paradigms are lacking, and standards to assess the effectiveness of therapy in these patients need to be developed (61). In summary, the framework has been laid for improving the treatment of cerebral vasospasm, and forward strides have been made in the endovascular treatment of cerebral vasospasm. However, much work remains to be done to eradicate the devastating complications of ruptured cerebral aneurysm.

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NEUROSURGERY'S Science Times

THERAPY OF BRAIN ARTERIOVENOUS MALFORMATIONS: MULTIMODALITY TREATMENT FROM A BALANCED STANDPOINT

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THE THREE THERAPEUTIC modalities for arteriovenous malformation (AVM) treatment (surgery, embolization, and radiotherapy) developed in the past years with specific tools, each tool with its own qualities. Soon after the implementation of embolization for treatment of AVMs, this technique was used in combination with microsurgery; since the development of radiosurgery, treatment algorithms combining embolization with surgery and eventual subsequent radiosurgery, embolization with radiosurgery, or surgery with subsequent radiosurgery have been reported. These different combinations have been in use under the term *multimodality treatment* for many years, but the algorithms regarding the combination of tools, which tool has priority, and how the risk levels of each tool are assessed shows great variability among institutions. Centers with a surgical background see embolization as a technique to increase surgical feasibility and radiosurgery as a tool to complete subtotal AVM excision. Institutions with an endovascular background embolize AVMs with the aim of maximal occlusion rates and view surgery or radiosurgery as a technique to be used if the goal of total endovascular occlusion cannot be achieved. Radiosurgeons receive patients after incomplete embolization or surgical extirpation or a combination of both.

KEY WORDS: Brain arteriovenous malformations, Embolization, Multimodality treatment, Radiotherapy, Surgery

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This article presents an analysis of the qualities of three tools in regard to such factors as procedural invasiveness, occlusion capacity, speed of efficacy, and long-term reliability. The value of the tools regarding their independence from size, brain functionality, angioarchitecture, and flow is also detailed.

To formulate a decision to combine the tools for brain arteriovenous malformation (AVM) therapy in the form of a multimodality concept, the qualities of the tools should be seen from a neutral standpoint. The principle of multimodality algorithms is to combine the advantageous elements of each tool to increase procedural safety and efficacy and to avoid the negative elements and thus prevent risk accumulation.

DEVELOPMENT OF THREE TOOLS

Surgery

The first operation on a cerebral AVM was reported in 1889 by Giordano (16). Although this procedure involved only ligating a feeding vessel on the brain surface, Péan (47) in the same year exposed and excised a brain AVM in a 15-year-old patient with a right-sided cerebral AVM. He reported on the complete excision of this lesion. In the following years, the majority of descriptions of brain AVM surgery were made by Cushing and Bailey (6), who began performing surgery for cerebral angiomas in 1909, and Dandy (8) who described the history, pathology, and surgical treatment of "arteriovenous aneurysms" in his book *Surgery of the Brain*. He described not only the principle of arteriovenous shunts but also the classic symptomatology of AVM patients and the principle of AVM surgery. At the end of this chapter, Dandy raised the question of whether radium or x-ray radiation of brain AVMs could be beneficial (8).

Dandy also focused on diagnostic tools for these lesions. In addition to the analysis of clinical symptoms, he mentioned plane radiographs (calcifications), auscultation of the cranium, ventriculography, and finally a new diagnostic tool

invented by Moniz in 1927 called *arteriography*. This technique enabled physicians not only to diagnose the presence of an AVM but also to learn about its location, size, and architecture. With the help of angiography, Berastrand et al. (2) performed the first successful the radical removal of a brain AVM in 1932. In the following years, the primarily imperfect angiographic techniques improved and became widely available. In addition to Bergstrand et al. (2), surgeons such as Penfield and Erickson (48) and Pilcher (50) published larger series of AVM surgery with decreasing rates of mortality. In the 1950s, a large number of authors reported on brain AVM surgery with a mortality from 5 to 20% (31, 42, 58). Surgery for large AVMs or AVMs in eloquent areas of the brain, however, was still questionable until the late 1960s when Yaşargil (64) published his monograph on AVM surgery using the operating microscope, bipolar coagulation, and microinstruments. Additional techniques, such as temporary occlusion of vessels (15), fluorescein angiography (12), and intraoperative flow measurement (41), completed the armamentarium of microsurgery for brain AVMs.

Embolization

At the beginning of the 1970s, as microtechniques started to become the surgical standard and the first large series of brain AVMs operated by microtechniques were published (13), the first attempts were made to achieve occlusion of AVM vessels via an endovascular route. After an initial period in which spheres or pallets were introduced in a free way into the flow of the internal carotid artery (see "History of Endovascular Surgery" in this issue), catheter techniques were improved to allow more selective approaches to AVM feeding arteries and finally to the nidus itself (53). The development of microcatheters to allow for such superselective approaches went from fully flow-driven catheters with balloon mounted tips via guide wire supported catheters with "progressive softness" to the type of microcathethers in use today. These catheters combine the pulling capacity of the blood flow with the ability to guide the catheter (especially its tip) by soft microguidewires. A broad range of different microcatheters and guidewires is currently available, allowing for endovascular access to almost every point in the vascular tree as long as the vessel and catheter diameter allow this. The performance of these surface-coated flow-driven and guide-wire supported microcatheters is excellent, and the goal of entering the nidus can be reached more frequently than in earlier years.

But the improvement in endovascular approaches to brain AVMs was not only caused by the technical developments. Improved quality of neuroimaging, especially of digital subtracted angiography, together with increasing experience, led to a better understanding of functional vascular neuroanatomy. In 1998, Valavanis and Yaşargil (60) published on the endovascular treatment of brain AVMs and presented their concept of a topographic classification of the AVM nidus and the functional classification of the feeding arteries. The understanding of the angio-architecture of the AVM nidus, its contributing arteries, and draining veins directly influenced the result of the endovascular procedure, not only by an increase in occlusion rates but also by improved procedure safety.

Although progress was achieved in catheter and guidewire material and in the understanding of where to place the catheter tip to inject the embolizing substance, few developments were made in the chemistry of the embolizing substances. Isobutyl-2-cyanoacrylate, which was invented by Zanetti and Sherman (66) in 1972, was replaced by the similar substance *n*-butylcyanoacrylate (NBCA) (Histoacryl, Braun Meesungen, Germany), which is used in mixture with the oily dye Lipiodol (Guerbet, France) to become visible under x-ray. The ratio of acrylic glue to dye influences not only the visibility of the substance but also the speed of polymerization and setting. This ratio, as well as the speed of injection and the volume injected under radiographic control, must be decided by the endovascular therapist. These handling parameters, along with understanding of the neuroanatomy, experience, and skill determine the result of each endovascular "shot" into an AVM nidus. The problem of a "too deep penetration" through the nidus into the venous system caused by a too high blood flow and a too slow polymerization led to the development of modified acrylates. Substances such as Glubran-2 (NBCA + monomer, GEM, Pesaro, Italy) is said to have a special anti-inflammatory effect. Neuroacryl (Provasis Therapeutics, San Diego, CA) may allow for slower and better penetration of the nidus (4). The polymerization time is longer than with NBCA, and the glue mass is more cohesive, resulting in a more controlled form of embolization. Another new polymer with a longer polymerization time and less adherent capacity, allowing for slower filling and a more controlled filling of the nidus, was proposed by Jahan et al. (27) in 2002. In a comparative analysis of this ethylene vinyl alcohol copolymer (Onyx; MicroTherapeutics, Irvine, CA) to NBCA, Akin et al. (1) described in an animal study in 2003 that the softness of the settled Onyx allowed for easier surgical handling of the specimen embolized. Another report about this new endovascular substance was given by Florio et al. (14), who published in 2003 on the embolization of brain AVMs in 10 patients with the recorded complications of two transient and one mild permanent neurological deficit, two clinically silent cases of moderate subarachnoid hemorrhage, four catheters glued to the injection site, and three cases of treatment discontinuation caused by continuous reflux of Onyx into the afferent artery peduncle.

Radiosurgery

In 1951, Leksell (34) combined a stereotactic guiding device with radiotherapeutic modality. In 1968, he had designed the first gamma knife stereotactic radiosurgical unit in Stockholm, which was designed primarily for functional neurosurgical procedures (35). It was not this but a second gamma unit that was designed especially for the therapy of intracranial AVMs or brain tumors and was used at the Karolinska Institute in Sweden for more than 13 years. The next gamma knife units

were implemented in Buenos Aires, Argentina, and Sheffield, England, in the 1980s.

Although Leksell had decided to use a cobalt source as radiotherapeutic principle, other authors built the principle of combining a stereotactic guiding device with a radiotherapeutic modality on different radiation principles. Kjellberg et al. (30), in 1962, described a stereotactic instrument for use with the Bragg peak of a proton beam to focus radiation on intracerebral AVMs (28, 29). Fabrikant et al. (11) and Hosobuchi et al. (25) irradiated AVMs with the helium-ion-beam of a 230 MeV cyclotron in 1984, and, finally, isocentric linear accelerators became available at the beginning of the 1980s, which were evaluated and used in clinical practice (20, 22). In 1989, Colombo et al. (5a) reported on the results of 97 patients with cerebral AVMs treated with Linear accelerator radiosurgery. Seventy-nine patients experienced at least one hemorrhage, and four patients had progressive neurological symptoms. The lesions varied in diameter from 4 to 40 mm, and doses from 18.7 to 40 Gy were delivered in one or two sessions. On the mean follow-up of 17 months, 52% of the patients showed complete obliteration of the malformation. The authors suggested that even with incomplete obliteration, a significant decrease in risk of hemorrhage could be obtained. In 1989, Betti et al. (3) stated the clear relationship between lesion volume and percentage of occlusion at follow-up. In AVMs with a diameter of less than 12 mm, total occlusion could be achieved in 81.3%, whereas in AVMs with 25 to 60 mm diameter, only one out of eight patients showed AVM disappearance at 17 months follow-up. Five patients, all of whom had bled previously, experienced subarachnoid hemorrhage after treatment; two of these patients died. The authors mentioned that the result obtained with the linear accelerator system seemed to be comparable with those obtained with the gamma unit.

Results of a larger series of AVM patients treated with the gamma knife were published in 1979 by Steiner et al. (57), who found in 68 patients an occlusion rate of 84.1% on 2 year angiographic follow-up. More recently, Pollock et al. (51) reported on a series of 144 patients with AVM at follow-up greater than 5 years after gamma knife radiosurgery. Excellent outcomes (obliteration without deficit) could be achieved in 73% after one or more radiosurgical procedures. Twenty (14%) patients sustained major deficits or died. Eleven percent of the patients had unchanged neurological examinations but persistent arteriovenous shunting. The authors reported an 8% rate of hemorrhage leading to permanent deficit or death in the 2 to 5 year latency period, which represents the major drawback of radiosurgery as opposed to surgery or embolization.

Similar data were given by Zabel et al. (65), who reported in 2005 on a series of 110 patients with AVM after Linac based radiosurgery. Complete obliteration was shown to be 67% after 4 years; in AVMs less than 3 cm, total occlusion was significantly higher. Intracranial hemorrhage occurred in 8.2% a median 13.9 months after the applied single dose Linac based radiosurgery.

Fractionated stereotactic radiation therapy using the Linac accelerator was used by Lindqvist et al. (36) in 1986 to treat large intracranial AVMs not suited for open surgery or radiosurgery. In two out of 26 patients, complete obliteration could be shown angiographically 5 years after treatment. The rationale for the use of fractionated treatment of AVMs was addressed by Hall and Brenner (18) in 1993. Veznedaroglu et al. (61) recently presented a series of 30 patients with large inoperable AVMs of 14 cm^3 or greater. All patients received radiotherapeutic fractions; 72 patients received a cumulative dose of 42 Gy, and 23 patients a cumulative dose of 30 Gy. Patients in the 42 Gy cumulative group showed, with at least 5 years follow-up, an AVM obliteration rate of 83%. Those in the 30 Gy cumulative group had an obliteration rate of 22%. The authors concluded that fractionated stereotactic radiotherapy for large AVMs achieves obliteration at a threshold dose, including large residual niduses after embolization.

DIFFERENT TOOLS AND ONE CLASSIFICATION

Initial classifications of brain AVMs were purely descriptive, had no functional elements, and followed pathological principles (6, 7, 63). The first classification aimed at predicting surgical feasibility was published by Luessenhop and Gennarelli (38) in 1977. These authors focused on the vascular supply of the malformation and demonstrated a clear relationship between morbidity and mortality and AVM grading. Another classification based on angio-architecture was proposed by Parkinson and Bachers (44) in 1980. Although these classifications did not become commonly used, the classification proposed by Spetzler and Martin (55) in 1986 received much attention and has become most widely accepted and used even more as a standard for assessing the surgical risk since having been validated in a prospective fashion by Hamilton and Spetzler (19) in 1994. This classification seems simple, consisting only of three components, nidus size, the presence of deep venous drainage, and the eloquence of the brain surrounding the AVM. The value of this classification for the prediction of a surgical result has been proven in the literature (9, 24) as well as in daily applications of AVM surgery all over the world. The fact that in some series or under certain circumstances this classification does not fit to the results (21) shows the influence of subjective assessment and individual surgical performance. The inhomogeneity of Grade III AVMs (from 3/0/0, via 2/0/1, and 2/1/0-1/1/1) led authors such as de Oliveira et al. (43) in 1998 and Lawton (32) in 2003 to propose modifications of the Spetzler-Martin classification.

In recent years, several proposals have been made to use more complex classifications, including not only AVM architecture but also other diagnostic features, such as transcranial Doppler sonography (45) and hemodynamic and clinical elements (49). The classification by Spetzler and Martin remains, probably because of its simplicity, the most frequently used

TABLE 1. Classification of cerebral arteriovenous malformations for endovascular use as used in Vienna circa 1990[a]

	Grade 0	Grade I	Grade II	Grade III
Function of feeders		Pial	Pial + perforating	Perforating
Number of feeders	1–2	>2		
Size of nidus (cm)	<2	2–4	>4	

[a] The algorithm is similar to that of Spetzler and Martin (55) for use in arteriovenous malformation surgery, allowing the comparison of surgical and endovascular feasibility.

and published classification, used finally not only for the prediction of surgical outcome but also to stratify AVMs for radiosurgical (5, 51, 65), endovascular (37), and endovascular plus radiosurgical therapy (23, 39). Particularly in series of multimodality treatment, this classification has been used to "select the appropriate treatment" (10, 59). The principle of this selection consists obviously of choosing for surgery those patients in whom Spetzler-Martin classification predicted good surgical feasibility. Other patients were subject to a combination of embolization and radiosurgery just because they were less feasible for surgery. Factors predicting endovascular or radiosurgical outcomes were not assessed.

Factors predicting surgical outcome in Spetzler-Martin's classification are AVM size, deep venous drainage, and the eloquence of the surrounding brain. Surgical manipulation around the AVM, disturbance of the microcirculation, the possible damage to the brain parenchyma in the resection plane, and the possible trauma in the event of complications such as intra- or postoperative hemorrhage or ischemic events make the influence of "AVM size" and "eloquence of the surrounding brain" on surgical outcome very understandable. The presence or nonpresence of deep venous drainage, however, may not influence surgery as directly as the previous two factors. The mechanism lies rather in the fact that deep venous drainage occurs normally in deep brain AVMs. Although in 30% of cases, unexpected deep venous draining pattern can be observed (60), in the majority of cases, deep draining will represent deep AVM components, frequently with perforating feeding supply, making surgery more difficult.

Factors predicting feasibility or outcome of endovascular treatment are both morphological and functional. In early years, AVM size and number of feeders were thought to play the most important role (62). In 1996, Gobin et al. (17) reported on the influence of the Spetzler-Martin grading to the rate of complete AVM obliteration. In those years, the Vienna classification for endovascular treatment focused on AVM nidus size, number of feeders, and functionality of feeders (*Table 1*). The algorithm of this classification was similar to that of Spetzler and Martin; the aim was to allow a differentiation of an individual AVM according to surgical or endovascular feasibility. With improved knowledge of functional AVM micro-architecture, a more complex view of endovascular feasibility arose. In 1998, Valavanis and Yaşargil (60) reported on the topographic classification of brain AVMs and pointed to angio-architectural features with positive or negative influence on complete AVM occlusion (*Tables 2* and *3*). This listing of positive and negative elements is currently the most accurate predictor of endovascular feasibility, even if it is not a simple "classification algorithm."

Factors predicting outcome after radiosurgery for AVMs are AVM nidus volume, the geometry of nidus distribution (solid or spotted), the eloquence of the surrounding brain, and the presence of a bleeding history. In regard to the influence of AVM size to outcomes, the Spetzler-Martin classification has been used in some of the published series beside the applied radiation dose (5, 65). Inoue et al. (26) published in 1995 on a specific classification of AVMs for radiosurgery and categorized the lesions as Moya-type, shunt-type, or mixed-type. In 2002, Pollock and Flickinger (50a) mentioned that the grading scales previously used to predict patients' outcomes are unreliable for the prediction of results of AVM radiosurgery. The scoring that he

TABLE 2. Topographic classification of brain arteriovenous malformations[a,b]

- Convexity or superficial AVMs (72%)[c] (so-called cortical AVMs)
  - Sulcal AVMs (28%)[c]
    - Pure sulcal
    - Sulcal-subcortical
    - Sulcal-subcortical-ventricular
  - Gyral AVMs (12%)[c]
    - Pure gyral
    - Gyral-subcortical
    - Gyral-subcortical-ventricular
  - Mixed sulco-gyral AVMs (29%)[c]
    - Sulco-gyral
    - Sulco-gyral-subcortical
    - Sulco-gyral-subcortical-ventricular
  - Diffuse AVMs (proliferative angiopathy) (3%)[c]
- Subcortical AVMs (2%)[c]
- Deep or central AVMs (26%)[c]
  - Subarachnoid (fissural, cisternal) (12%)[c]
  - Parenchymal (intrinsic) (7%)[c]
  - Plexal (intraventricular) (1%)[c]
  - Mixed (6%)[c]

[a] AVM, arteriovenous malformation.
[b] *From* Valavanis A, Yaşargil MG: The endovascular treatment of brain arteriovenous malformations. **Adv Tech Stand Neurosurg** 24:131–214, 1998 (60).
[c] Data derived from magnetic resonance scans and angiographic evaluation of the 387 cases of this series.

TABLE 3. Classification system of feeding arteries of brain arteriovenous malformation with consideration of their functional and endovascular[a]

Direct types of feeling arteries
Monoterminal
Dominant
Supplementary
Multiterminal
Dominant
Supplementary
Pseudoterminal
With flow reversal distally
A. Dominant
B. Supplementary
Induced by wedged catheter
Indirect types of feeding arteries
Transit arteries
With single or multiple supplementary feeding branches
Rarely, with dominant feeding branches
Retrograde collateral feeding arteries
Leptomeningeal
A. Usually supplementary
B. Dominant after proximal occlusion of dominant feeders
Subependymal
A. Usually supplementary
B. Dominant after proximal occlusions of dominant feeders

[a] *From* Valavanis A, Yaşargil MG: The endovascular treatment of brain arteriovenous malformations. **Adv Tech Stand Neurosurg** 24:131–214, 1998 (60).

proposed included AVM volume, patient age, and AVM location. He demonstrated that this AVM score could predict patient outcome after radiosurgery. In 2005, Zabel et al. (65) published a retrospective analysis of factors effecting AVM obliteration and saw significant influence by Spetzler-Martin's grading representing AVM volume. In addition, they found that the rate of complete AVM occlusions was significantly improved after doses higher than 18 Gy and in males.

Classifications with the aim to predict patient outcome after AVM therapy must be based on specific factors determining these outcomes. Some of these factors are more or less present in all three tools used for AVM treatment, whereas others are very tool specific. It is therefore unreasonable to use one single classification for predicting outcomes of multimodality treatment. In another section of this contribution, we will try to list and analyze these factors again in relation to treatment modalities.

AVM: MULTIMODALITY TREATMENT FROM DIFFERENT PERSPECTIVES

The existence of three modalities for the therapy of AVMs led early to the idea of combination of tools. The interest vascular neurosurgeons had circa 1980 in implementing new endovascular technologies into therapeutic concepts for brain AVMs to facilitate surgical extirpation is mentioned in the article on endovascular neurosurgery in this issue. In 1980, Wolfgang Koos (Vienna, Austria) stimulated the author of this article to develop endovascular techniques supporting AVM surgery. The basis for an ongoing development of neuroendovascular procedures and experience in Austria was created. In the same year, Stein and Wolpert (56) published on concepts and treatment of AVMs of the brain. They described "embolization which involves the placement of small spheres into the lesion under radiographic control as a moderately safe procedure that can reduce the size of but rarely eliminates these malformations" (56). The authors conclude that embolization has been used effectively in preparing these lesions for surgical extirpation.

Before the introduction of guidewire supported microcatheters, endovascular therapy for brain AVMs could not achieve total occlusion in a higher percentage of the cases. Embolization was therefore seen as a therapeutic step followed by microsurgical extirpation. In 1988, Pelz et al. (46) described 15 cases of preoperative embolization of which, in 10 cases the surgeons thought that the embolization had significantly aided the operative removal by decreasing blood loss, reducing the size of draining veins, and removing portions of the nidus itself. No patient suffered unanticipated significant neurological deficit after embolization. This latter statement was contradicted by Hamilton and Spetzler (19), who reported in 1994 on the outcome of AVM patients being operated after embolization. Of 16 patients with Spetzler Grade IV and V AVMs who had poor outcomes after combined treatment, nine were caused by surgical and seven to endovascular technical complications. Combining therapies means combining the inherent risks; this circumstance should be taken into account when a decision for the combined use of therapeutic tools is made. The major advantage of multimodality treatment is that each of the tools can be used in its low-risk segment. The availability of another tool to continue the treatment makes it unnecessary to use the one tool under high-risk conditions. If this principle is not respected, multimodality therapy may increase rather than decrease the overall risk. Deruty et al. (10) saw a deterioration as a part of multidisciplinary treatment in 25% of all embolized cases.

For neurosurgical centers with a pure microsurgical background, surgery remained the standard treatment for brain AVMs even after the availability of "alternative tools." Their therapeutic efficacy was accepted for specific groups or subentities of AVMs; these techniques were included in a multimodality concept when microsurgery as the "gold standard" could be associated with unacceptably high rates of surgical morbidity or low rates of complete removal. This was especially the case in deep AVMs, such as those located in the thalamus, basal ganglia, or brainstem, or large or giant AVMs. In 1995, Lawton et al. (33) reported on a series of 32 patients with deep AVMs of all sizes. They differentiated between surgically accessible AVMs (22 patients) undergoing microsurgical resection, half of those after preoperative transfemoral embolization. Ten patients having AVMs in the basal ganglia seen as surgically inaccessible underwent embolization and postembolization radiosurgery. The principle of this treatment algorithm followed surgical accessibility and used the "alternative techniques" to increase surgical feasibility. In 1997, Smith et al. (54) reported on the multimodality treatment approach used in Phoenix, Arizona. In their series of 54 patients, 60% underwent surgery alone, 17% were treated by radiosurgery alone, and no patient was treated by embolization alone. In 43%, the surgical approach was aided by prior embolization and subsequent radiosurgery. All patients in Grade I or II had undergone microsurgery only.

In their series of large and critically located AVMs treated by a multimodality approach, Mizoi et al. (40) found in only one out of 54 patients complete nidus occlusion after embolization alone. In 10 out of 54 patients, embolization was used before surgery, and in 31 out of 54 patients embolization was used before radiosurgery. The authors described embolization as primarily an approach with the aim of nidus reduction with minimum procedure related complications. The endovascular therapy is followed either by surgery in patients with ruptured AVMs and noneloquent areas or by radiosurgery. In his description of the treatment paradigm for brain AVMs in the Karolinksa Hospital in Stockholm, Sweden, Sodoman et al. (54a) reported in 2003 on a decision tree in which the AVMs were classified primarily by volume. AVMs smaller than 10 cm^3 are classified by endovascular accessibility for an endovascular versus surgical approach. AVMs between 10 and 20 cm^3 underwent targeted embolization before radiosurgery or surgery. AVMs larger than 20 cm^3 did not receive therapy. The treatment algorithm presented by Uno et al. (59) in 2004 classifies the AVM according to Spetzler-Martin and includes the factor of previous hemorrhage in the treatment decision in Grade IV and V. Endovascular therapy is used in this concept only to facilitate surgery.

The way the three available tools for AVM therapy are combined varies greatly from institution to institution. Whereas some algorithms see microsurgery as the basis and previous embolization or subsequent radiosurgery as adjunctive therapies, other decision trees focus on endovascular accessibility and apply microsurgery or radiosurgery according to the result of the endovascular therapy (23). Embolization or microsurgery applied after radiosurgery is uncommon. In the Stanford series in 2003, Chang et al. (5) reported on embolization as well as microsurgical resection following previous radiotherapy. The reason for this strategy was failed stereotactic radiosurgery. A concept of primary radiosurgery followed by endovascular or microsurgical therapy has not been presented, to the knowledge of the author.

The reason for the large variability in treatment algorithms lies in the specific historical development and situation of each institution. Multiple local factors, such as availability of tools or the individual training and development of the deciding physician, will influence the way AVM tools are combined. Centers with a microsurgical background will focus on surgical accessibility with accessory endovascular and radiosurgical therapy, whereas endovascular centers will see AVMs as primarily endovascular targets, with the possible option of surgical extirpation or radiation if endovascular surgery does not result in 100% occlusion. Radiosurgical institutions receive patients after incomplete embolization or if, after combined endovascular and microsurgical therapy, the lesion did not disappear angiographically. Even if some of these treatment algorithms succeed in producing high percentages of AVM disappearance with low complication rates, the principles behind decision-making are far from a neutral analysis of the pros and cons of each therapeutic tool. The application of a therapeutic tool for brain AVMs after another tool has been used may occur on the basis of a treatment concept or as a consequence of a therapeutic failure. Some of the treatment algorithms presented (especially those using embolization as the "start-up" procedure) accept treatment failures as the basis of the multimodality algorithm.

PATIENTS' NEEDS AND TOOL PROPERTIES

As in any other therapeutic decision-making, the choice of the therapeutic mechanism with all the risks included must be assessed in consideration if the "patient's needs" in each individual case (52). For the AVM patient, these needs depend on the individual type of AVM that contains different natural risks, which shall be eliminated by the therapy.

Each therapeutic tool or principle has its specific pros and cons. In addition to the tool-related factors are other factors influencing the performance of the tool. These factors include the amount of training, skill, and dexterity of the operator(s) and team as well as the medical environment.

The ultimate factor that determines success or failure is the intellectual process of decision-making. The deciding physician must be familiar with the patient's needs. All the components subsumed under this term, including the patient's clinical history and current symptoms, social and familiar background and psychological status, AVM architecture, morphology, and hemodynamics, must be put together in a list of factors of different urgency and importance.

AVM-related factors representing a higher or high bleeding risk, such as previous hemorrhage, intranidal aneurysms, singular or even impaired venous drainage, will have high pri-

TABLE 4. Three tools for treatment of brain arteriovenous malformations: pros and cons[a]

	Embolization	Surgery	Radiosurgery
Low procedural invasivity	2	1	3
Occlusion capacity	1–2	3	2
Speed of efficacy	2–3	3	1
Long-term reliability	2–3	3	3
Independent from size	3	2	1
Independent from brain functionality	3	1	2
Independent from angio-architecture	1	2	3
Independent from flow	1	3	2

[a] 1, no/low; 2, medium; 3, yes/high.

ority. Other factors, such as the elimination of seizures or focal symptoms, will have less priority. Permanent or waving headache may impair the patient's quality of life, as will the psychological effect of knowing about the "bomb in the head." But there are more risks to be eliminated or kept as low as possible to fulfill patient's needs. The avoidance of a new neurological deficit in dealing with an AVM in an eloquent area, long-term reliability of the AVM exclusion, or a low procedural invasivity are just some of the many factors influencing the quality of the therapeutic performance.

On the other side stand three tools, each being very different from the other, with different qualities, advantages, and disadvantages. It is crucial that the deciding physician not only be familiar with the qualities of the tools but also have detailed knowledge regarding all the complex functions, capabilities, and possible pitfalls.

Table 4 shows on the left side necessities from the therapeutic point of view (patient's needs) being assessed against the therapeutic tools. This assessment is made under the principle of optimal technical performance. The influence of negative "human factors," failures in assessing risk conditions, and other technical failures are not taken into consideration.

Low procedural invasiveness is greatest in radiosurgery as long as the optimal dose/volume relation is respected. Embolization is less invasive than in surgery (under the precondition of optimal technical performance).

Occlusion capacity is best in surgery. Embolization may reach high occlusion capacity in the hands of select experts. In the majority of AVM embolizations, the occlusion rate will be lower than after surgery and slightly lower than after radiosurgery.

Speed of efficacy will be best in surgery and embolization. Endovascular techniques allow the immediate occlusion of intranidal aneurysms or high-flow shunts. Careful analysis of functional AVM anatomy allows the reduction of potential bleeding risk as quickly as surgery. For radiosurgery, the low speed of efficacy (i.e., the persistence of the risk of bleeding in the latency period) is crucial.

Long-term reliability is high in surgery and radiosurgery. Partial embolization, however, carries the risk of reperfusion.

Independence from size is highest in embolization. A large AVM with multiple feeders requires multiple endovascular approaches, potentially increasing the therapeutic risk. With surgery, size plays an important role; for radiosurgery, size (volume) is the determining factor.

Independence from brain functionality is best in embolization. After a technically correct selective approach to a nidus, the functionality of the surrounding brain can be neglected. For radiosurgery, the importance of brain functionality increases with AVM volume, and for surgery, brain eloquence is a crucial factor.

Independence from angio-architecture is best in radiosurgery. For AVM surgery, angio-architecture plays a significant role, and for the endovascular therapy, this factor is crucial.

Independence from blood flow is best in surgery. For radiosurgery, it plays a significant role (high-flow, large-diameter AVM shunts are less responsive to radiation). For endovascular therapy, flow is a determining factor.

The process of decision-making starts with a ranking of the patient factors according to their importance and clinical significance (*Table 5*). Highest priority will have an estimated risk of rebleeding or bleeding. The result of this process will be the stratification of the specific patient's needs with the priority of those elements representing an acute risk of a life-threatening event. Step two will be the analysis of the lesion. All AVM-related factors, such as location, size, surrounding brain func-

TABLE 5. Decision algorithm to allow use of therapeutic tool(s) with most appropriate capability to solve "patient needs"[a]

Step 1	Listing of patient-related factors (such as clinical history, current symptoms, psychological status, familiar and social background) and ranking according to clinical importance ("patient needs")
Step 2	Analysis of AVM morphology ("classification") (such as location, size, vascular architecture, flow, etc.) in consideration of surgical, endovascular, and radiosurgical feasibility
Step 3	Choice of treatment modality according to specific capability of each tool to fulfill "patient needs" in given morphological AVM condition with lowest invasiveness and risk (*Table 4*); if necessary, planning of multimodality therapy to reduce overall risk by using each tool in its low-risk segment

[a] AVM, arteriovenous malformation.

tionality, type of feeding and draining vessels, compartmental architecture, and presence of special risk elements such as intranidal aneurysms, will be collected and transformed to an estimated risk of natural course as well as to an assessment of feasibility and therapeutic risk. The last step will be to choose, from the three treatment modalities, the one whose therapeutic capabilities will conform with the patient's therapeutic necessities. If the use of one single tool will expose the patient to a too high therapeutic risk, a combination of tools will be chosen to keep the use of each modality in its low-risk range.

As an example, we may sketch out the case of a patient with a deep seated basal ganglia AVM who experienced multiple ventricular hemorrhages. This patient requires the extinction of his bleeding source without too much delay. From the three modalities, microsurgery would be most effective to solve this problem quickly but with the price of high invasivity in this specific AVM location. The next glance goes to embolization. For the use of this modality, this AVM with a singular feeding branch from a M1 perforator has appropriate architecture. In view of the need of quick release of the bleeding risk together with an acceptable level of therapeutic invasivity, embolization will be chosen for this AVM. If, for architectural or technical reasons, a part of the nidus remains open when the endovascular options have been exhausted, an additional tool will be chosen to complete the therapeutic goal. If the AVM remnant is small in volume, radiosurgery may be the choice on the basis of the fact that small or very small volumes allow a more efficient dosimetry and may lead to the total disappearance of the AVM in an acceptable timeframe. In case the embolization was insufficient and a large nidus with a high shunt volume remained, surgery will be chosen with regard to the previous hemorrhages to achieve quick release of the bleeding risk. Under these circumstances, the higher risk for surgery in this AVM location will have to be accepted.

This decision philosophy is based on the priority of patient's symptoms, clinical history, psychological status, and familial and social background. The resulting therapeutic aims (such as elimination of bleeding risk, seize of focus symptoms or seizures, etc.) are brought into examination in light of the patient's AVM (its location, size, vascular architecture, flow conditions, etc.). To solve the resulting therapeutic proposition, the one tool is chosen whose positive capabilities may solve the problem with the highest efficacy and lowest therapeutic risk. If the capability of the one tool is not enough, the remaining AVM will undergo subsequent therapy by a second or even a third tool. The combination of tools is primarily used as a planned strategy but may also occur if the chosen primary tool fails to reach the therapeutic target.

CONCLUSION

Brain AVMs are complex lesions representing a source of acute risk, permanent or transient symptoms, or potential future danger for the patient. The three therapeutic modalities are different not only in their technical principles and philosophy but also in their specific qualities. The choice of the "right" tool for an individual AVM will be influenced (under ideal circumstances) solely by the qualities of the tool, which should be capable of solving the specific problems of the individual AVM. If the tool is not capable of completely treating the AVM without high risk, tools may be used in combination. The choice of combining tools for a multimodality treatment should follow the principle of choosing the beneficial qualities of each tool and avoiding the drawbacks as much as possible. In daily practice, local factors, such as availability of tools and personal background and development, will influence the choice of therapy. The responsible physician should be aware, however, that the decision to choose therapeutic modalities for AVMs in combination requires a precise analysis of the therapeutic needs and tool qualities from a most neutral standpoint.

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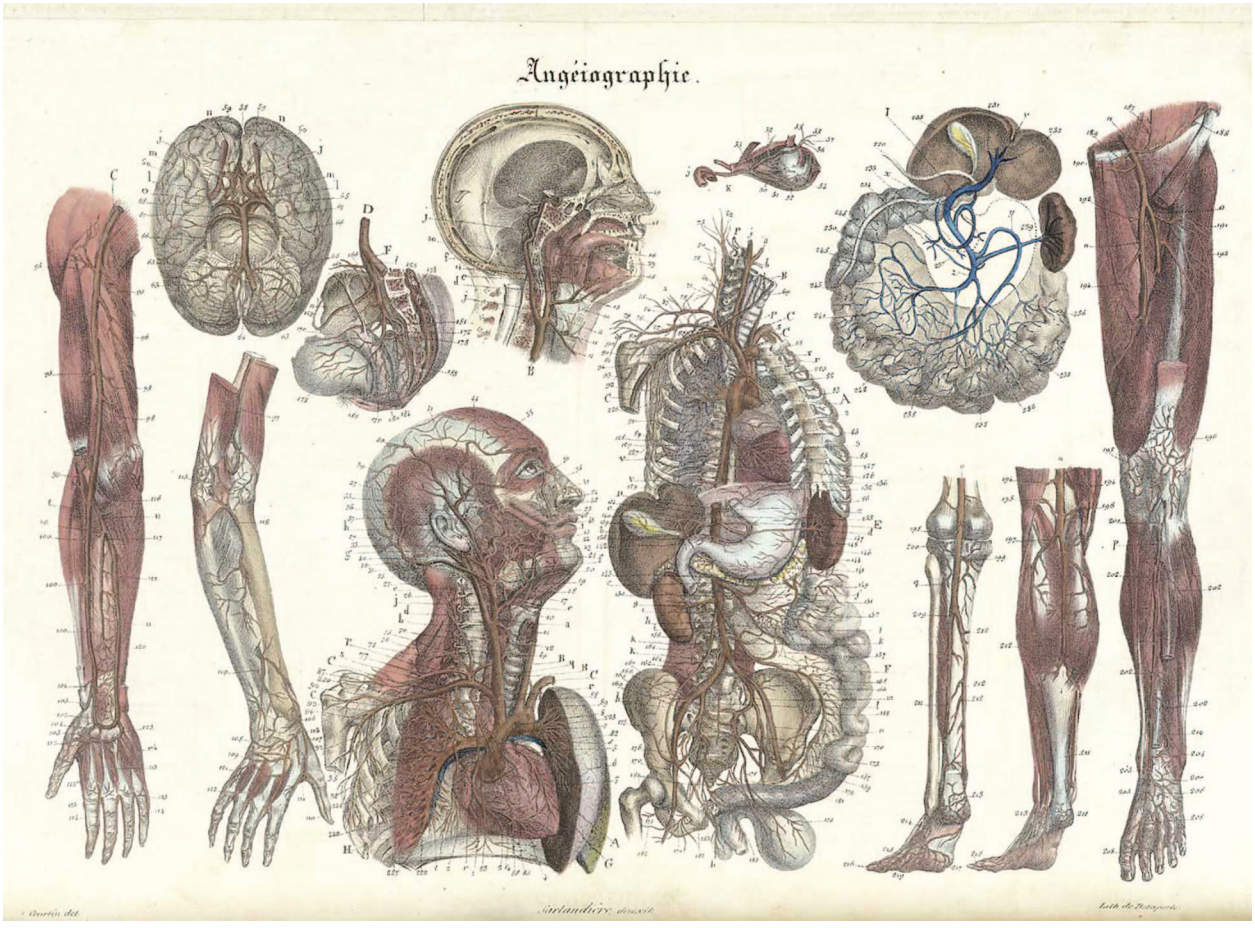

Jean-Baptiste Sarlandière, 1787–1838, ***Anatomie Méthodique, ou Organographie humaine en tableaux synoptiques, avec figures****. Paris: Chez les libraires de médecine, et chez l'auteur, 1829 (courtesy of the U.S. National Library of Medicine, National Institutes of Health, Bethesda, Maryland).*

A Novel Technique and New Grading Scale for the Embolization of Cerebral Vascular Malformations

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OBJECTIVE: Effective transarterial embolization of a dural arteriovenous fistula or pial arteriovenous malformation (AVM) requires penetration of a durable occlusive agent into the fistula or AVM nidus. Cyanoacrylate glue often cannot traverse the tortuous vessels that typically supply such malformations, leading to proximal occlusion and recruitment of collateral flow. Other embolic agents, such as polyvinyl alcohol particles, achieve better penetration, but their effects are short lived, often leading to recanalization. The authors sought to overcome these obstacles by developing a technique to enhance glue penetration into the fistula or AVM nidus itself.

METHODS: After placing a guide catheter in the proximal feeding artery, a microcatheter is advanced coaxially to its limit. As glue is injected through the microcatheter, a column of 5% dextrose in water (D5W) is pushed manually through the guide catheter lumen to propel the glue forward. This technique has been bench tested in a standard flow model of vascular malformations, using a pump capable of delivering various rates of D5W. It has also been validated in treating 17 patients with cerebral dural arteriovenous fistulae or AVMs, with real-time adjustment of D5W flow according to the extent of glue penetration.

RESULTS: In the bench model, the extent of glue penetration, as graded by a new scale of liquid agent embolization proposed by the authors, correlated directly with the rate of D5W flow ($P = 0.5$, analysis of variance). In vivo, this technique has enhanced the penetration of glue into the fistula or AVM nidus, resulting in longstanding embolization of these malformations.

CONCLUSION: Coaxial injection of D5W through the guide catheter can propel cyanoacrylate glue through tortuous feeding arteries and can enhance its penetration into dural fistulae and AVMs, leading to more effective endovascular treatment of these malformations.

KEY WORDS: Arteriovenous malformation, Dural arteriovenous fistula, Embolization, Grading scale, *n*-butylcyanoacrylate, Technique

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Transarterial embolization (TAE) has become a mainstay in the treatment of cerebral dural arteriovenous fistulae (dAVF) and pial arteriovenous malformations (AVMs). In some cases, TAE alone may affect cure, palliate symptoms related to increased flow (e.g., tinnitus or congestive heart failure), or convert a high-risk dAVF with cortical venous drainage into a low-risk one (3, 14, 19, 28). In others, TAE can serve an adjunctive role by reducing flow through main arterial feeders, either before or after transvenous occlusion of the affected sinus, microsurgery, radiosurgery, and other therapies (2, 3, 5, 14, 19, 24, 28, 31).

Effective TAE of a dAVF requires penetration of a durable occlusive agent into the fistulous connection (2, 20, 28). Cyanoacrylate glue and mechanical devices (platinum coils, detachable balloons) often cannot traverse the tortuous vessels that typically supply such malformations, leading to proximal occlusion and recruitment of collateral flow (5, 30). Other agents, such as polyvinyl alcohol (PVA) particles, achieve better penetration, but their effects are short lived, often leading to recanalization (2, 27). The use of ethanol can be associated with cranial neuropathy, stroke, and other unacceptable morbidities (5, 29). The same limitations apply to pial AVMs

supplied by meningeal branches of the external carotid or vertebral arteries.

We sought to overcome these obstacles by developing a technique to enhance penetration of cyanoacrylate glue into the fistula or AVM nidus itself. *Figure 1* schematically illustrates this method. After placing a guide catheter in the proximal feeding artery of an AVM or dAVF, a coaxial microcatheter is advanced to its limit. As cyanoacrylate glue is injected through the microcatheter under continuous fluoroscopic monitoring, a column of 5% dextrose in water (D5W) is pushed through the guide catheter lumen with a syringe attached to a rotating hemostatic valve. This coaxial flow of D5W around the microcatheter propels glue forward, achieving deeper penetration into the nidus or fistula. The force of manual injection through the syringe can be altered according to the distribution achieved by the glue, allowing real-time adjustment of D5W flow and consequent glue permeation.

MATERIALS AND METHODS

Preclinical Testing

In benchtop experiments, a standard flow model was used to test the D5W push technique. This model consists of two impermeable membranes separated by channels that simulate blood vessels of varying caliber. The models replicate the feeding arteries, nidus, and draining veins of a vascular malformation and were provided by Cordis Neurovascular (Miami Lakes, FL), which uses them to train physicians in the use of Tru-Fill, their proprietary *n*-butylcyanoacrylate (NBCA) glue.

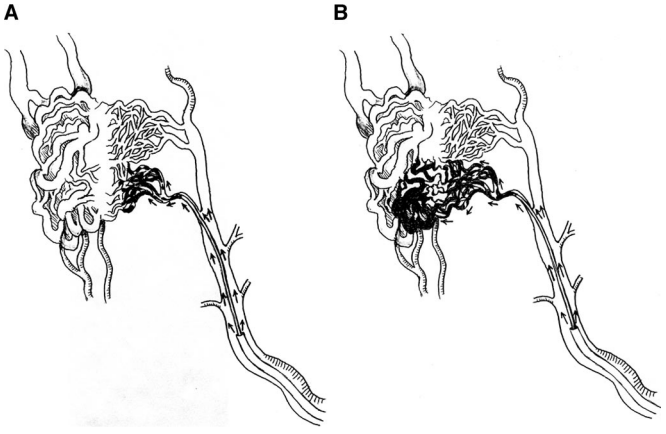

FIGURE 1. *Schematic illustration showing the D5W push technique. After placing a guide catheter in the proximal feeding artery of an AVM or fistula, a coaxial microcatheter is advanced to its limit.* A, *as cyanoacrylate glue (*black*) is injected through the microcatheter, a column of D5W is pushed through the guide catheter lumen with a syringe (*arrows*).* B, *this coaxial flow of D5W around the microcatheter (*small arrows*) propels glue forward, achieving deeper penetration into the nidus or fistula. The force of manual injection through the syringe can be altered according to the distribution achieved by the glue, allowing real-time adjustment of D5W flow and consequent glue permeation.*

The model was perfused continuously with sheep plasma (Hema Resource & Supply, Aurora, OR) using a recirculating pump (Flowtek, Las Vegas, NV). The pump delivers pulsatile flow at frequencies similar to human heart rhythms. A 5-French guide catheter (Envoy; Cordis Neurovascular, Miami Lakes, FL) was advanced to a consistent landmark at the proximal (arterial) end of the AVM model and connected to a digital power injector (Angiomat; Mallinckrodt, Hazelwood, MO) through a rotating hemostatic valve. The injector pushed D5W through the guide catheter at four different rates (0.0, 0.2, 0.4, and 0.6 ml/s) with a force of 1200 lb/inch^2. These parameters were selected after pilot studies suggested that rates of 1 ml/s and more resulted in penetration beyond the venous end of the model.

A microcatheter (Prowler-10; Cordis Neurovascular) was primed with D5W, placed coaxially within the guide catheter, and advanced to a consistent landmark in a simulated feeding artery proximal to the AVM nidus. Tru-Fill was diluted 1:3 volumetrically with ethiodized oil to confer radiopacity and to reproduce ratios typically used in clinical application. The glue and ethiodized oil mixture was then injected manually through the microcatheter, propelled by the flow of D5W through the guide catheter. The injection was terminated when glue refluxed back to a simulated feeding artery aneurysm proximal to the microcatheter tip. All injections were performed by one person (APA), who was blinded to the randomly selected rate of D5W flow.

For each of the four rates, four models were tested. The microcatheter, flow model, and sheep plasma were replaced after each experiment. However, the same guide catheter was used throughout the study. The degree of penetration into the AVM model was assessed radiographically with digital subtraction serialographs using the A-plane of a Philips Integris imaging system (Philips Medical Systems, Bothell, WA). The object-image distance was kept constant throughout. The serialographic images were printed onto radiographic film and then interpreted by two experienced interventional neuroradiologists (GPT, DWL) who were blinded to the rate of D5W flow corresponding to each image. The degree of glue penetration into the flow model was graded on a scale of 1 to 5, using a new classification that we propose for liquid agent embolization of vascular malformations (*Table 1*, *Fig. 2*). The mean score and standard deviation for each rate of flow then was calculated. The four rates were compared using a one-way analysis of variance (21).

TABLE 1. New grading scale for glue embolization of vascular malformations

1. Glue penetration into feeding artery only
2. Glue penetration into proximal nidus or fistula
3. Glue penetration into distal nidus or fistula
4. Glue penetration into immediate draining recipient
5. Glue penetration into distal vein or beyond

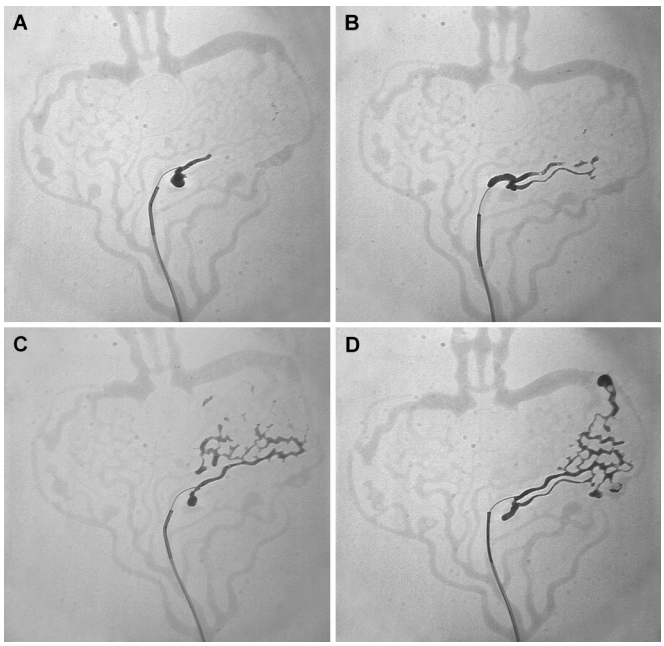

FIGURE 2. *Angiograms illustrating the new grading scale for liquid agent embolization of cerebral vascular malformations (see Table 1). In benchtop experiments, a standard flow model was used to measure the penetration of cyanoacrylate glue. This model simulates the feeding arteries, nidus, and draining veins of an AVM.* A, *glue penetration into feeding artery only.* B, *glue penetration into proximal nidus.* C, *glue penetration into distal nidus.* D, *glue penetration into immediate draining recipient.*

Clinical Application

The D5W push technique has been validated in treating 17 patients with cerebral dAVFs or pial AVMs supplied by transosseous meningeal branches of the external carotid or vertebral arteries. To date, we have not used it to embolize feeding branches arising from arteries of the subarachnoid space or those supplying spinal dAVFs.

RESULTS

Preclinical Model

The extent of glue penetration, quantified with the new scale proposed in *Table 1* and illustrated in *Figure 2*, correlated directly with the rate of D5W flow (*Fig. 3*). The mean scores (and standard deviations) of glue penetration for rates of 0.0, 0.2, 0.4, and 0.6 ml/s were 1.50 (0.5), 2.50 (0.87), 2.50 (0.71), and 3.17 (0.29), respectively. Using a one-way analysis of variance, this trend of increased glue penetration with increased rates of D5W flow was statistically significant (F test statistic = 3.48, with 3 and 12 degrees of freedom; $P = 0.5$).

Clinical Usefulness

In the 17 patients in whom this technique has been used, there have been no complications. Because of the potential for real-time adjustment of D5W flow according to the extent of glue penetration, there have been no cases of venous outflow occlusion. There have been no known cases of intracerebral hemorrhage or other bleed. Because of the staged nature of TAE, many of these patients underwent follow-up angiography. No recanalization of the arteries embolized by this technique has been encountered in these ensuing studies. An illustrative case is presented in *Figure 4*.

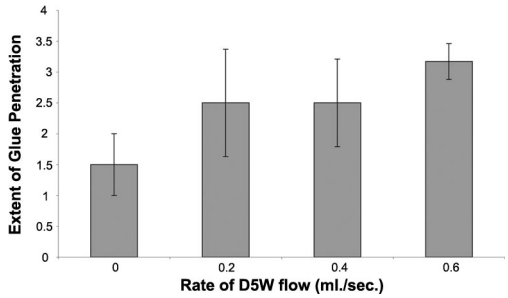

FIGURE 3. *Bar graph illustrating that the extent of glue penetration correlated directly with the rate of D5W flow. The mean score and standard deviation for the four rates of flow are shown (P = 0.5, analysis of variance). See* Figure 2 *and* Table 1 *for explanation of the grading scale.*

DISCUSSION

The natural history of cranial dAVFs is highly variable. Although some remain static, incidental findings on imaging studies, others can pursue an aggressive and potentially fatal course (1, 4, 15, 18). Treatment may be indicated to palliate symptoms related to increased flow, to restore perfusion to cerebral territories experiencing vascular steal, or to divert flow away from leptomeningeal veins, aneurysmal varices, and other vessels at risk of hemorrhage.

TAE of arterial feeders to the malformation remains a standard of treatment, either independently (3, 14, 19, 28) or as an adjunct to transvenous occlusion of the affected sinus, microsurgery, radiosurgery, and other therapies (2, 3, 5, 14, 16, 19, 24, 26, 28, 31). The objective of TAE is delivery of a durable occlusive agent directly into the fistulous connection itself (2, 20, 28). A variety of embolic materials have been used, including bare platinum coils, fibered coils, detachable balloons, Gelfoam (Upjohn, Kalamazoo, MI), silk suture, PVA particles, collagen, and cyanoacrylate liquid adhesives. Currently, the most commonly used agents are PVA and NBCA.

NBCA and mechanical devices often cannot traverse the tortuous vessels that typically supply such malformations, leading to proximal occlusion and recruitment of collateral flow, usually from vascular pedicles that are too small to catheterize or too dangerous to embolize (5, 10, 30). Conversely, deposition of embolic agents distal to the nidus or fistula may result in venous infarction or hemodynamic alterations that promote hemorrhage (9). Suspensions of PVA particles achieve better penetration, but their effects are short lived, often leading to recanalization and the need for retreatment (2, 7, 12, 16, 22, 27). These same limitations apply to pial

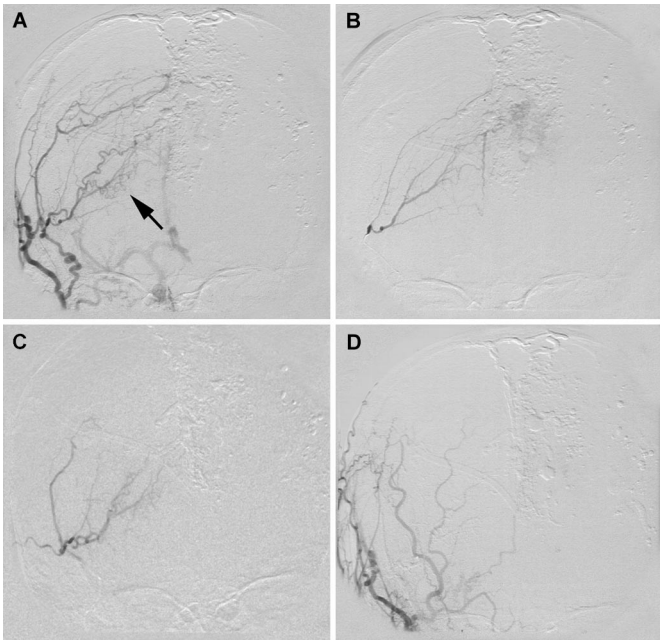

FIGURE 4. *Images obtained from a 17-year-old boy with a right frontoparietal AVM supplied by multiple branches of the internal and external carotid arteries illustrating the D5W push technique.* A, *external carotid artery angiogram performed through a guide catheter, frontal projection. Note the supply to the AVM from the anterior division of the middle meningeal artery (*arrow*).* B, *angiogram performed through a microcatheter after selective catheterization of this branch. Although the microcatheter was advanced to its limit, a significant distance still remained between its tip and the AVM nidus.* C, *glue cast after NBCA embolization using the D5W push method. Note how the cyanoacrylate glue was propelled into branches of the vessel beyond the microcatheter and into the AVM nidus.* D, *repeat external carotid artery angiogram performed through a guide catheter, frontal projection. Note that the supply to the AVM from the anterior division of the middle meningeal artery has now been eliminated.*

AVMs supplied by meningeal branches of the external carotid or vertebral arteries. We sought to overcome these shortcomings by developing a technique to enhance the penetration of cyanoacrylate glue into the fistula or nidus itself.

Despite the importance of TAE in the management of dAVFs, few reports have emphasized technical aspects of the procedure. In most cases, a concentrated mixture of NBCA and iodized oil is injected using a flow-related method. Some authors have reported better permeation of cyanoacrylate glue by wedging the microcatheter into the feeding artery and arresting blood flow before injection of a more dilute glue mixture (11, 20). However, in its original description, the wedged technique was only possible after approximately 70% of the shunt flow had been eliminated using the conventional flow-related method. Subsequent reports have also emphasized the importance of preparatory embolization of accessory pedicles with the flow-related approach to decrease competing inflow and fragmentation of the glue column. Furthermore, the wedge technique requires navigation to a sufficiently distal segment so that the diameter of the feeding artery matches that of the microcatheter tip. Such positioning is not always possible in the large caliber, tortuous conduits that typically supply dAVFs. Although the use of adenosine to induce systemic hypotension for flow arrest has been reported anecdotally, the safety and efficacy of this adjunct has not been established (23).

For these reasons, the D5W push method has merit in enhancing the penetration of cyanoacrylate glue into the fistula or nidus itself. This technique is indicated for embolizing feeding arteries the tortuosity of which limits the ability to navigate the microcatheter close to the fistulous connection. In general, it works best when the guide catheter can be positioned in the proximal aspect of the same vessel and there are no large branches originating from the intervening segment. This can often be achieved with divisions of the external carotid artery, but less so for those of the internal carotid or vertebral arteries. Thus, feeding vessels within the subarachnoid space may be embolized with the D5W push method, but the greater distance between the guide catheter and microcatheter tips, as well as the numerous branches arising from the intervening segment, dilute the force of the D5W column in propelling the embolic agent distally.

Other strategies for injecting NBCA far beyond the microcatheter tip include delaying its polymerization time by altering the monomer-to-ethiodol ratio or by adding glacial acetic acid (8, 17). However, miscalculating the rate of transit through the fistula or the polymerization kinetics of the glue can lead to unpredictable events, such as proximal occlusion or iatrogenic venous outflow restriction. Furthermore, the use of glue that is too diluted may lead to recanalization. The advantage of the D5W push technique over these methods is the ability to use a concentrated NBCA mixture coupled with dynamic, real-time adjustments that allow precise dispersion of the glue cast at the site of the fistula.

Recently, a nonadhesive liquid embolic agent composed of ethylene-vinyl copolymer dissolved in dimethylsulfoxide has become commercially available (Onyx; MicroTherapeutics Inc., Irvine, CA). Onyx been studied extensively as an embolic agent for cerebral AVMs (6, 13), and its use has been reported in the treatment of dAVFs as well (25). Its nonadhesive property minimizes the risk of gluing the microcatheter to the wall of the feeding artery. This allows more prolonged injection, which should obviate the barriers imposed by tortuosity and long distances between microcatheter tip and nidus. For this reason, the D5W push technique is not likely to augment the use of Onyx. Furthermore, the potential chemical interactions between D5W and the dimethylsulfoxide vehicle have not been characterized.

The benchtop experiments validate the D5W push technique in vitro, but its clinical usefulness is more difficult to quantify. One reason is that dynamic, real-time adjustments of the force of manual injection preclude the ability to correlate the depth of glue penetration with any single rate of D5W flow in vivo. However, it has been our subjective experience that the technique enhances the dispersal of NBCA compared with conventional methods of delivery. For instance, the glue cast

depicted in *Figure 4C* is more permeant than what is typically achieved without this adjunctive technique.

Finally, the new grading scale for liquid agent embolization of cerebral vascular malformations proposed in this study may become an important tool for further research and therapy. By specifying the anatomic portion of the vascular malformation permeated by the embolic material, the attendant risk and efficacy of TAE can be refined. Furthermore, this scale can be used for prognostic purposes in helping to define the role and outcome of adjunctive treatments after TAE, such as radiosurgery or microsurgical resection. However, as with the D5W push itself, the clinical usefulness of this grading scale requires further study.

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THE ROLE OF NEUROENDOVASCULAR THERAPY FOR THE TREATMENT OF BRAIN ARTERIOVENOUS MALFORMATIONS

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NEUROENDOVASCULAR EMBOLIZATION REPRESENTS a critical component of the multidisciplinary management of cerebral arteriovenous malformations. Safe and effective embolization may be performed only in the context of a well-designed, rational treatment plan that is fundamentally based on a clear understanding of the natural history of the lesion, as well as the cumulative risks of multimodality treatment. This article outlines the role of neuroendovascular embolization in arteriovenous malformation therapy with a specific emphasis on decision making in the context of formulating a treatment plan. The authors also provide a summary of the available embolic agents and their technical application, potential intraprocedural and periprocedural complications, and postprocedural management.

KEY WORDS: Arteriovenous malformation, Embolization, *n*-butylcyanoacrylate

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Arteriovenous malformations (AVMs) are highly complex vascular lesions that typically present in young patients (age, 20–40 yr) with hemorrhage, seizures, headache, or focal neurological deficits. The most common and compelling reason for treatment is the prevention of hemorrhage. Existing data indicate that only complete eradication of the lesion provides protection from future hemorrhage, whereas partial treatment is not helpful and may, in fact, increase the rate of future hemorrhage.

To a greater extent than any of the other vascular lesions of the central nervous system, the treatment of brain AVMs requires a multimethod and multidisciplinary approach. All patients should be evaluated by physicians with expertise in endovascular embolization, microneurosurgical resection, and radiosurgery. After a careful consideration of the clinical data and AVM anatomy, a risk-to-benefit ratio for treatment can be estimated. As soon as a treatment plan is agreed on, all parties must have a clear understanding of their individual roles to facilitate successful treatment.

FORMULATING A TREATMENT STRATEGY

The most critical step in the successful management of any patient's AVM is the formulation of a treatment strategy designed to optimize the risk-to-benefit ratio. This is predicated on an understanding of the natural history of the lesion, as well as the morbidity and mortality associated with various treatments.

AVMs are relatively uncommon lesions (3). They are, in most instances, symptomatic at the time of presentation, usually from hemorrhage (21). As such, the literature describing the natural history of AVMs is limited and is composed predominantly of retrospective analyses of selected populations (e.g., those not undergoing surgery, patients with symptoms other than hemorrhage at presentation) yielding biased and relatively variable estimates of the rate of hemorrhage and its associated consequences (1). Having said this, most estimates approximate a 2 to 4% per year risk of hemorrhage (7, 35). In the year immediately after a symptomatic hemorrhage, the rehemorrhage risk is generally thought to be considerably higher, on the order of 6 to 18% per year, gradually returning toward the 2 to 4% baseline with time (15, 21, 24, 35). The implications of an AVM hemorrhage are not as severe as those for aneurysmal subarachnoid hemorrhage, with most estimates approximating a 10% risk of death and 20 to 30% risk of major disability subsequent to AVM rupture (21).

The risk of surgical intervention is directly related to the angioarchitecture of the particular lesion. This relationship is best characterized with the Spetzler-Martin grading system (*Table 1*). In prospective studies, the Spetzler-Martin grade demonstrated a reliable correlation with surgical outcome. Hamilton and Spetzler (16) reported operative morbidity and mortality rates for the resection of Grade I and II AVMs (<1%) and Grade III AVMs (<3%) to be very low. However, much higher morbidity rates were observed for Grade IV and V AVMs, reaching 31 and 50%, respectively, in the early postoperative period and subsequently improving to 22 and 17%, respectively, at the time of the follow-up examination. Heros et al. (20) reported a similar relationship between Spetzler-Martin grade and outcome. These data form the foundation for most management decisions regarding AVM therapy.

In general, for Grade I and II AVMs, the risk of hemorrhage far outweighs the risk of surgical resection. As such, these lesions are generally resected surgically. For Grade I lesions, because of the low operative morbidity and mortality, preoperative embolization is not frequently pursued, given that the risk of the embolization procedure may approach or even surpass the risk of surgery. In some instances, stereotactic radiosurgery, rather than surgical resection, is used for treatment of a Grade II lesion. The most common example would be a small Grade II AVM in a highly eloquent region.

Grade III AVMs represent a complex and heterogeneous group, each requiring an individualized assessment. The heterogeneity of this category led Lawton (29) to further stratify these lesions into three additional angioarchitectural subcategories with low (2.9%), intermediate (7.1%), and high (14.8) risk of postsurgical death or new deficit, respectively. Most of these lesions are treated with either radiosurgery or preoperative embolization followed by surgical resection. When these lesions are approached surgically, preoperative embolization frequently plays an important role.

The surgical resection of Grade IV and V AVMs is generally associated with a risk of operative morbidity and mortality that exceeds the risks associated with the natural history of the lesion. Han et al. (17) analyzed outcomes in a series of 73 consecutive patients with Grade IV and V AVMs. These authors recommended no treatment for most patients in this group (55 out of 73) and reported a relatively low risk of hemorrhage in these patients (1% per yr). In addition, in this series as well as in several additional reports, partial AVM treatment substantially increased the yearly risk for hemorrhage. In accordance with these observations, treatment for Grades IV and V AVMs is recommended only in patients with progressive neurological deficits attributable to repeated hemorrhage or disabling symptoms, such as intractable seizures.

TABLE 1. Spetzler-Martin arteriovenous malformation grading system

Description	Points
Size (cm)	
<3	1
3–6	2
>6	3
Eloquence	
Yes	1
No	0
Deep venous drainage	
Yes	1
No	0

NEUROENDOVASCULAR THERAPY

The role of neuroendovascular therapy in the management of brain AVMs depends ultimately on the overall treatment plan. In general, five scenarios comprise the vast majority of rational management strategies (listed from most to least common):

1. Preoperative: embolization as a precursor to complete curative surgical resection;
2. Targeted therapy: embolization to eradicate a specific bleeding source;
3. Preradiosurgery: embolization as a precursor to radiation therapy;
4. Curative: embolization for attempted cure;
5. Palliative: embolization to palliate symptoms attributed to shunting.

Preoperative Embolization

AVM embolization is most frequently performed as a precursor to curative surgical resection (*Fig. 1*). In this setting, the overall goal of the embolization is to decrease the blood supply to the malformation, thereby decreasing the level of technical difficulty and associated morbidity of surgical resection. A successful embolization is effective in reducing the size of the AVM nidus, occluding deep feeding vessels that are difficult to access and control surgically, reducing intraoperative hemorrhage and providing better delineation of a surgical resection plane.

The neuroendovascular interventionist must always be cognizant of the surgical complication rate associated with the resection of any particular lesion and must make every attempt to assure that the risks of the embolization do not exceed those of the surgical resection (e.g., preoperative embolization of a Grade II AVM that is associated with a very low operative morbidity). The goal of the vascular neurosurgeon must be to achieve a complete, curative resection of the AVM. Accumulating data suggest that partial AVM resection does not reduce, but rather increases, the risk of future hemorrhage. Han et al. (17) observed a hemorrhage rate of 10.4% in patients with Grade IV and V AVMs after partial treatment, compared with a 1% risk in patients with no previous treatment. Miyamota et al. (37) found an annual risk of hemorrhage of 14.6% in patients who underwent palliative treatment of cerebral AVMs. Wikholm et al. (53) observed an increased rate of

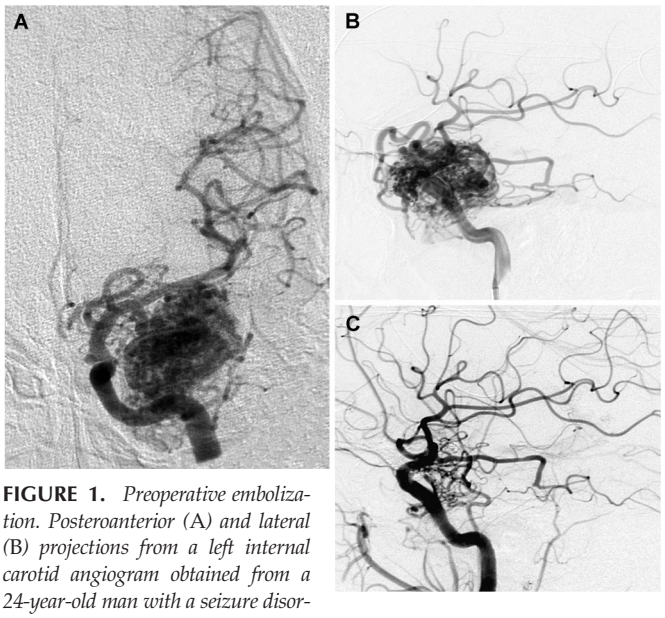

FIGURE 1. *Preoperative embolization. Posteroanterior (*A*) and lateral (*B*) projections from a left internal carotid angiogram obtained from a 24-year-old man with a seizure disorder demonstrating a Grade III AVM involving the anterior left temporal lobe.* C, *angiogram demonstrating that, after six pedicle embolizations performed during a single session, the volume of the AVM is reduced substantially.*

hemorrhage and death in patients undergoing partial treatment that resulted in less than 90% nidal obliteration.

The efficacy of modern AVM embolization using *n*-butylcyanoacrylate (NBCA) has been demonstrated in several clinical studies. Jafar et al. (22) demonstrated that preoperative embolization reduced the operative morbidity of large AVMs to a level similar to that of smaller AVMs that were not embolized before surgery. DeMerritt et al. (9) reported similar results with preoperative embolization of large AVMs improving postsurgical outcomes in comparison with a control group of smaller AVMs that were not embolized.

Targeted Therapy

With few exceptions, all treatment strategies for AVM management should ultimately be directed toward the complete eradication of the lesion. However, in some patients with Grade IV and V AVMs not amenable to surgical resection, partial treatment targeted to eliminate an identified bleeding source is undertaken.

Aneurysms are identified in association with AVMs in 7 to 20% of cases (25, 28, 32, 39). These aneurysms may be located on vessels that are remote from the nidus, on a feeding vessel (flow-related aneurysms), or within the nidus itself. In addition, intranidal pseudoaneurysms—composed of an organized hematoma that communicates with the intravascular space—may form after AVM hemorrhage. The presence of an aneurysm represents a risk factor for intracranial hemorrhage in patients with AVMs (5). Although both intra- and extranidal aneurysms are risk factors for intracranial hemorrhage in patients with AVMs, the increased risk of hemorrhage in the setting of an extranidal aneurysm may be attributed to aneurysm rupture rather than hemorrhage from the AVM nidus itself (25).

Remote and feeding vessel aneurysms can usually be identified by conventional angiography. Nidal aneurysms may occasionally be visualized on conventional angiographic views. Often, however, only superselective angiography performed using high frame rates can demonstrate these lesions. Nidal aneurysms are frequently obscured by overlying vessels or other portions of the AVM nidus on conventional angiographic views. As such, when an unresectable AVM hemorrhages one or more times, endovascular exploration for a nidal aneurysm represents a reasonable strategy. In these cases, if the AVM is not to be resected, a targeted embolization may be undertaken to eradicate the aneurysm either with a liquid embolic agent (nidal aneurysm) or coils (proximal, flow-related aneurysm or remote aneurysm; *Fig. 2*).

Preradiosurgery

A detailed discussion of the role of radiosurgery for the treatment of AVMs is beyond the scope of the present article. In general, the success of radiotherapy is inversely proportional to the size of the AVM nidus to be treated (27). AVMs with nidal volumes less than 10 ml (diameter < 3 cm) (2) are frequently curable by radiosurgery, with rates of cure at 2 years estimated at between 80 and 88% (31, 43). The theoretical goal of embolization in this setting would be to reduce the size of the AVM nidus into a range that is amenable to radiosurgical ablation (*Fig. 3*). In this setting, the use of a permanent embolisate, such as NBCA (see below), is mandatory to avoid recanalization of portions of the AVM that have been embolized, but not included in the radiation field. Additional goals of preradiosurgical embolization would include targeted therapy for components predisposed to hemorrhage (i.e., nidal or feeding vessel aneurysms) and the ablation of large arteriovenous fistulae that are typically more refractory to the effects of radiotherapy.

Despite the straightforward rationale for preradiosurgical embolization, very little data exist to support this approach. This is related in part to the extended latency period (2–3 yr) required for radiotherapy to have a definitive effect. Of the available case series, most were conducted in the late 1980s and early 1990s, and many used particulate embolysates (e.g., polyvinyl alcohol [PVA]). The use of a temporary embolisate for the permanent eradication of a component of AVM is contraindicated at this time, given the availability of more durable agents.

The largest series was reported by Gobin et al. (13), who described their experience with 125 patients undergoing embolization (predominantly with NBCA) as a precursor to radiosurgery. These authors were able to achieve total occlusion in 11.2% of AVMs after embolization alone, with an additional 76% of lesions reduced sufficiently in size to undergo radiotherapy. A 65% rate of total occlusion was observed after radiotherapy in patients undergoing combined treatment. More recently, Henkes et al. (19) reported a series of 30 pa-

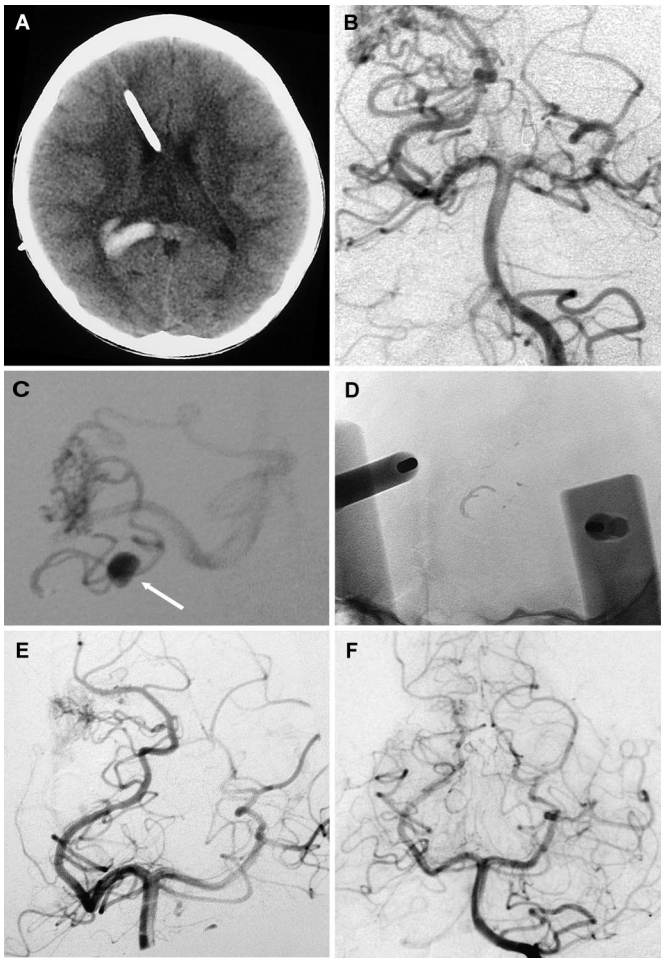

FIGURE 2. *Targeted therapy of an intranidal aneurysm with hemorrhage.* A, *computed tomographic scan demonstrating a small amount of parenchymal hemorrhage within the right major forceps and marginating the ependymal surface of the right lateral ventricle.* B, *conventional angiogram obtained using a catheter positioned within the left vertebral artery demonstrating a diffuse AVM nidus within the right medial parietal and occipital lobes with a small central nidal aneurysm.* C, *superselective angiogram obtained using a microcatheter positioned within a pedicle of the right PCA better defines the anatomy of the aneurysm* (arrow). D, *unsubtracted image (acquired in the same projection as the superselective angiogram) obtained after NBCA infusion demonstrating a glue cast distributed within the proximal aspect of the pedicle.* E, *postembolization angiogram demonstrating complete occlusion of the nidal aneurysm with the residual AVM nidus supplied by small, inaccessible branches of the right PCA. This patient subsequently underwent gamma knife radiotherapy with angiographic cure of the AVM demonstrated on follow-up angiography* (F).

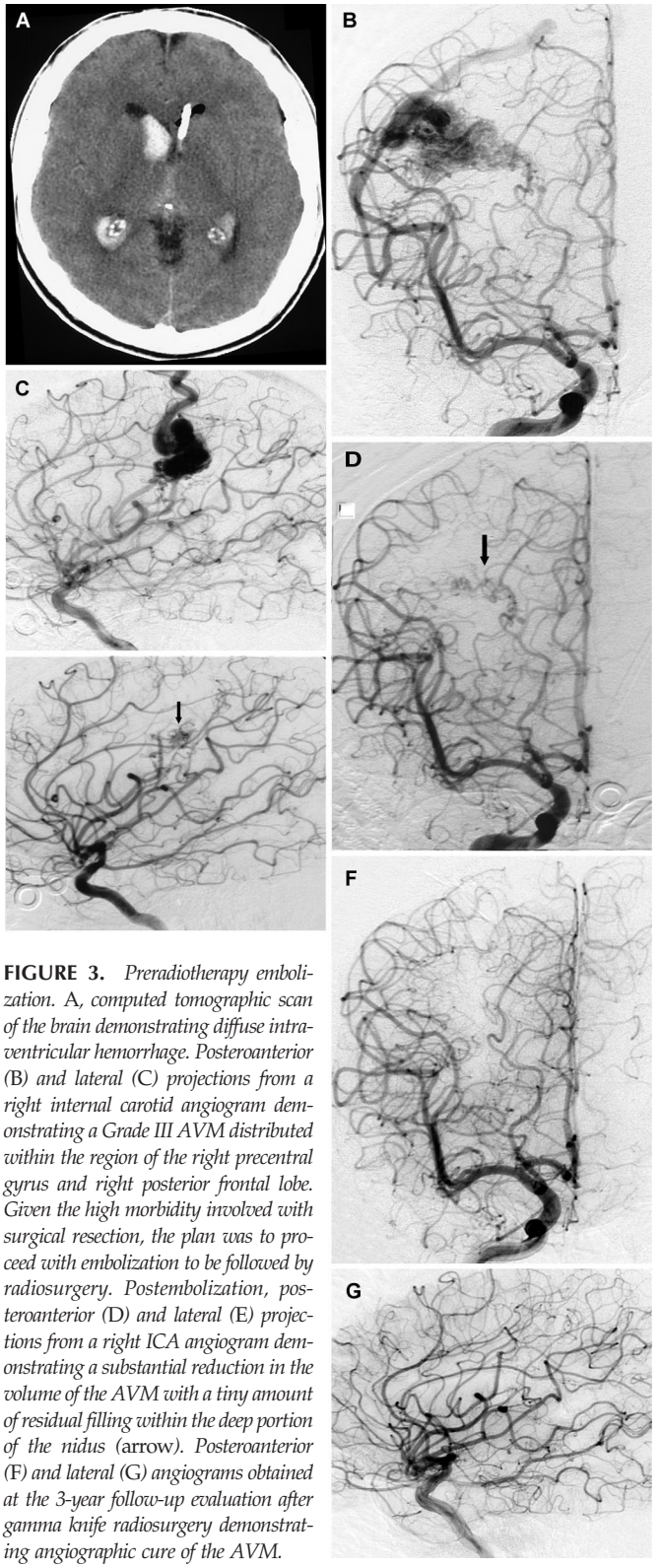

FIGURE 3. *Preradiotherapy embolization.* A, *computed tomographic scan of the brain demonstrating diffuse intraventricular hemorrhage. Posteroanterior* (B) *and lateral* (C) *projections from a right internal carotid angiogram demonstrating a Grade III AVM distributed within the region of the right precentral gyrus and right posterior frontal lobe. Given the high morbidity involved with surgical resection, the plan was to proceed with embolization to be followed by radiosurgery. Postembolization, posteroanterior* (D) *and lateral* (E) *projections from a right ICA angiogram demonstrating a substantial reduction in the volume of the AVM with a tiny amount of residual filling within the deep portion of the nidus* (arrow). *Posteroanterior* (F) *and lateral* (G) *angiograms obtained at the 3-year follow-up evaluation after gamma knife radiosurgery demonstrating angiographic cure of the AVM.*

tients undergoing combined embolization and radiotherapy, observing a less impressive 47% obliteration rate in a series of 30 patients. However, in this study, most of the treated AVMs were of very high grade. From the existing data, no compelling evidence exists to justify or refute the usefulness of preradiosurgical embolization.

Curative Therapy

Occasionally, a small AVM with a limited number of feeding pedicles can be cured completely using endovascular embolization alone (*Fig. 4*). Although the reported rates of complete endovascular obliteration vary, most estimates are in the range of 10%. However, it is important to note that these estimates are based on series that predate the introduction and widespread application of Onyx (MicroTherapeutics, Inc., Irvine, CA), and, therefore, may be expected to increase with this new technology. If curative therapy is the goal of embolization, it is critical that a permanent agent (e.g., NBCA or Onyx, not particles) be used.

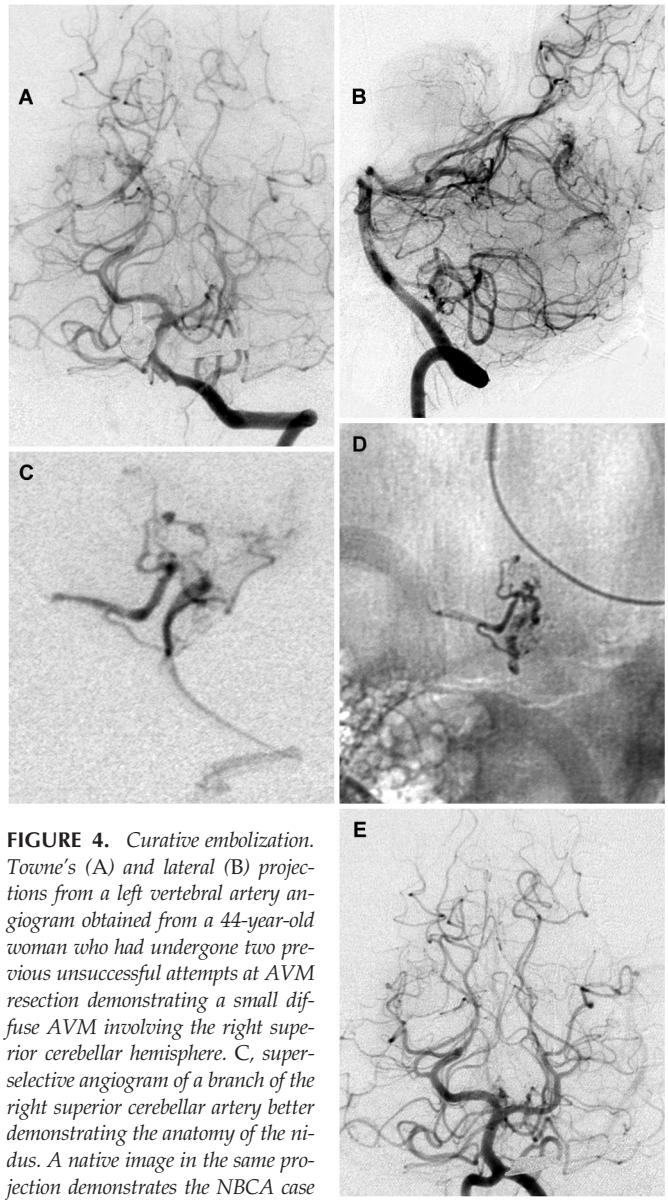

FIGURE 4. *Curative embolization. Towne's (*A*) and lateral (*B*) projections from a left vertebral artery angiogram obtained from a 44-year-old woman who had undergone two previous unsuccessful attempts at AVM resection demonstrating a small diffuse AVM involving the right superior cerebellar hemisphere.* C, *superselective angiogram of a branch of the right superior cerebellar artery better demonstrating the anatomy of the nidus. A native image in the same projection demonstrates the NBCA case coresponding to the configuration of the nidus visualized on the superselective angiogram.* D *and* E, *angiograms obtained after the embolization of this pedicle demonstrating the complete obliteration of the AVM nidus.*

Viñuela et al. (50) reported a 9.7% cure rate for embolization alone. Their cures were achieved exclusively in small AVMs with a small number of feeding pedicles. Gobin et al. (13) reported a cure rate of 11.2% (14 patients) in a series of 125 patients undergoing preradiosurgical embolization. These authors also reported that the chance of complete obliteration was inversely proportional to AVM volume and the number of feeding pedicles. Wikholm et al. (52) reported a complete obliteration rate of 13.3%, with success also being heavily dependent on the size of the AVM nidus—71% with AVMs smaller than 4 ml, 15% with AVMs of 4 to 8 ml. Fournier et al. (10) reported a cure rate of 14% with embolization alone. Yu et al. (55) recently reported a 22% cure rate with cyanoacrylate embolization alone in a series of 27 patients. Their success rate was 60% in patients undergoing embolization with the prospective goal of achieving a definitive cure. In all patients undergoing an attempted curative embolization, the nidus was accessible, was less than 3 cm, and was fed by fewer than three arterial pedicles. These authors found that the angiographic obliteration of the AVM was durable at 17 to 32 months with no recurrences. No complications of embolization were reported in the series. Valavanis and Christoforidis (48) reported substantially higher cure rates (40%) in a consecutive series of 387 patients. These authors identified the presence of direct, dominant feeding arteries, a monocompartmental nidus, and a dominant fistulous component of the nidus, without perinidal angiogenesis as being the key characteristics predictive of endovascular cure. These authors did not find size or number of feeding pedicles to be an important determinant of the potential for endovascular obliteration.

Palliative Therapy

Although controversial, some investigators theorize that large AVMs may cause progressive neurological deficits, intellectual deterioration, or persistent headaches as sequelae of the shunting of blood away from physiologically normal brain, i.e., a steal phenomena (2, 33). Given that the lesions responsible for this type of phenomena are large and typically are unresectable, some investigators have advocated partial embolization in an attempt to reduce the severity of arteriovenous shunting and to improve perfusion pressure in the surrounding functional brain parenchyma (17). Although, no large clinical series exist to support this strategy, several case reports have described success in small numbers of patients (26, 30). Fox et al. (11) reported improvement in limb weakness in three patients after subtotal embolization of large AVMs located near the motor cortex, attributing the improvement to a reduction in cerebrovascular steal.

Although evidence to support partial embolization in cases of suspected cerebrovascular steal is lacking (34), there is a reasonable amount of evidence that indicates that partial treatment of large AVMs—with either embolization or surgery—increases the risk of hemorrhage (17, 37, 52). In addition,

although studies have indicated diminished cerebral blood flow in brain regions around AVMs in groups of patients with steal syndromes, these studies are, at present, not sufficient to prospectively identify patients who will benefit from partial treatment. These factors must be taken into account before initiating the partial embolization of a large, unresectable AVM to control symptoms. From a practical standpoint, when this type of plan is undertaken, it is imperative to proceed cautiously during the embolization and, in particular, to avoid producing any restriction of venous outflow.

EMBOLYSATES

Liquid Embolics

Liquid embolics are the most widely used and most effective agents for AVM embolization. The most commonly used of the liquid agents are the cyanoacrylate polymers (e.g., NBCA). The dimethyl sulfoxide (DMSO) solvent-based system ethylene-vinyl alcohol (EVOH) copolymer (Onyx) is a liquid nonadhesive embolic agent that became available in the United States in late 2005. Finally, ethanol (ETOH), an agent that has been used effectively to treat peripheral AVMs, has been used with success by a few practitioners for the treatment of central nervous system lesions.

Cyanoacrylates

These liquid adhesive polymer agents offer several important advantages: 1) the potential for penetration deep into the AVM nidus; 2) permanent embolization with durable occlusion of the vessel or pedicle embolized; 3) the ability to be delivered through small, flexible, flow-directed catheters that can be manipulated safely and atraumatically into the most distal locations within the cerebrovasculature (*Fig. 5*); and 4) the ability to be delivered into the pedicle easily and quickly, with infusions generally requiring less than 1 minute.

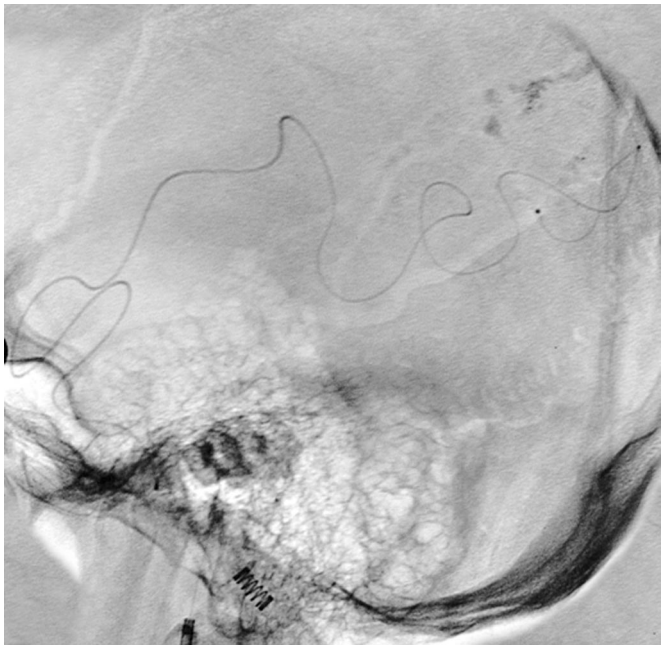

FIGURE 5. *Distal catheter position. Unsubtracted film obtained during the embolization of a left parietal lobe AVM providing an example of the extent to which the modern generation of flow-directed microcatheters (Elite 1.8-French; Boston Scientific, Natick, MA) can be efficiently and atraumatically manipulated into the most distal of locations within the cerebrovasculature.*

Several different polymers have been used. The first agent available was iso-butyl-2-cyanoacrylate. However, this was discontinued after studies demonstrated that the agent possessed some carcinogenic potential in animals. Currently, NBCA is the cyanoacrylate of choice for AVM embolization.

These agents are introduced as liquid monomers that subsequently polymerize to form a stable solid when they come into contact with a solution containing anion, such as the hydroxyl groups in blood. The rate of polymerization and the rate of injection determine how far the agent will travel within the cerebral vasculature before solidifying. The NBCA itself is radiolucent and must be mixed with a radiopaque agent, typically ethiodized oil (e.g., lipiodol, ethiodol); we use a 1.5:1 to 3:1 (oil-to-NBCA) mixture for most applications. In addition, to impart radiopacity to the NBCA, the oil acts as a retardant, slowing the rate of polymerization and acting to allow the NBCA to travel farther in the vessel before solidifying. Several investigators have observed that increasing the volume of ethiodized oil increases the time to polymerization (4, 42). Glacial acetic acid may also be added to the mixture in small quantities to retard the rate of further polymerization (14).

NBCA is, for all intents and purposes, a permanent embolic agent. After solidifying, the cyanoacrylates (if a sufficient volume has been injected) create an immediate occlusion of the embolized pedicle. An intense inflammatory reaction follows that leads to fibrous ingrowth that, in turn, produces a durable occlusion (53). Although recanalization can occur, it is rare after an adequate embolization.

Several disadvantages of the liquid adhesives include the high level of expertise required to control the injection safely to achieve adequate nidal penetration without allowing the agent to extend into the vein and the risk of NBCA adhering to the catheter, making withdrawal traumatic or impossible.

EVOH Copolymer-DMSO Solvent

EVOH is a polymeric agent that is, in some respects, similar to NBCA. This agent was applied first to the treatment of AVMs in the early 1990s (44) and is currently commercially available in the United States as Onyx. The most significant advantage of the EVOH copolymer is that it is nonadhesive, reducing the possibility of the catheter adhering to the injected polymer. This allows the operator a much greater degree of flexibility with respect to the volume and rate of the injection. The operator may temporarily halt an EVOH-DMSO infusion periodically to perform control angiography and to assess the status of the AVM nidus and draining veins before continuing the infusion.

Initial studies demonstrated that the DMSO component of the mixture induced vasospasm and angionecrosis (6, 40). Subse-

quent investigations indicated that these effects could largely be eliminated by limiting the volume of DMSO injected and limiting the rate at which it was introduced (38). Jahan et al. (23) did report one complication (proximal reflux) related to distal vasospasm that developed during an injection. This same group also reported histopathological evidence of angionecrosis in two AVM specimens resected 24 hours after embolization.

The EVOH-DMSO mixture itself is radiolucent. Tantalum powder must be mixed with the agent to provide radiopacity. Failure to mix the EVOH-DMSO-tantalum preparation constantly results in sedimentation of the tantalum from the mixture with subsequently variable opacification. This may result in suboptimal visualization of the embolysate during the injection.

Although long-term data are lacking, EVOH is, like NBCA, for all intents and purposes, a permanent agent. Jahan et al. (23) reported no recanalization in a small number of patients imaged up to 20 months after embolization. Murayama et al. (38) demonstrated no recanalization in swine after 6 months of follow-up.

ETOH

On the basis of their success using ethanol to eradicate peripheral vascular malformations, Yakes et al. (54) advocated the use of undiluted absolute ethyl alcohol (98% dehydrated alcohol injection US Pharmacopeia) for the embolization of central nervous system AVMs. They reported their initial results in a series of 17 patients (54). They were able to cure seven patients with ETOH alone; three additional patients were cured after surgery and another one after radiotherapy. Despite this impressive cure rate, it is important to note that two patients with partially treated lesions died and eight patients experienced complications related to the therapy. No other similar case series describing the application of ethanol has been reported to date.

ETOH is a sclerosant, functioning to dehydrate and denude the endothelium, creating fractures within the vessel wall that extend to the level of the internal elastic lamina. These changes result in acute thrombosis of the vessel (54).

ETOH causes significant brain edema, necessitating treatment with high doses of steroids immediately before and for 2 weeks after the procedure. In some cases, brain edema and increases in intracranial pressure necessitate mannitol therapy (47). In high doses, ETOH also has been found to induce pulmonary precapillary vasospasm, which can lead to cardiopulmonary collapse. This effect has been reported in humans after the embolization of peripheral AVMs with ETOH. It is critical that the appropriate anesthesia and critical care resources are alerted to this possibility. Given these risks, the high level of experience required to perform ETOH embolization safely, and the relatively widespread experience and comfort level with the cyanoacrylates, there has been a general reluctance among most endovascular neurointerventionalists to use ETOH for the embolization of brain AVMs.

Particles

Many different particulate embolysates have been used for AVM embolization. These initially included silk sutures and microfibrillar collagen material, evolving to more refined materials, including PVA and embolization microspheres.

PVA/Embospheres

Embolization with particulate agents is fundamentally different on a technical level than embolization with NBCA. To perform particulate embolization, a microcatheter with an internal diameter large enough to accept the particulate agent without clumping and clogging must be used. These catheters are of higher profile and are considerably less flexible than the smaller internal diameter flow-directed catheters. Correspondingly, an over-the-wire technique must be used to negotiate the microcatheter into the region of the AVM nidus. These technical factors make superselective catheterization of pedicles feeding the nidus more labor intensive and more hazardous with a greater potential for vascular perforation (46). After a pedicle has been catheterized, the size of the particles chosen is dependent on the operator's interpretation of the superselective angiogram. If superselective angiography demonstrates that any large shunts must be used, these must first be occluded with coils to avoid direct arteriovenous shunting of the particles into the pulmonary circulation. Then, the particles must be injected through the catheter gradually to occlude the vessels supplying the nidus with intermittent control angiography to assess flow. Unfortunately, the vessels coursing to the nidus are not infrequently of different sizes with differing degrees of shunting, making the selection of the optimally sized particles challenging. In addition, multiple injections are typically required with occlusion of the pedicle developing over minutes—rather than seconds, as for NBCA. In addition to the increased procedural time, there is the theoretical concern of temporarily pressurizing the nidus, as the higher flow, lower pressure fistulous components become preferentially occluded, thus theoretically raising the potential for intraprocedural hemorrhage.

In addition to these factors, the particulate agents have been reported to be more prone to recanalization than the cyanoacrylates. Sorimachi et al. (41) reported a 43% rate of nidal recanalization after particulate embolization with PVA. Mathis et al. (36) reported a 12% recanalization rate for AVMs embolized with PVA in preparation for radiosurgery when portions of the AVM were not included in the radiation field. With the exception of preoperative embolization in anticipation of a prompt and complete resection to follow, particulate agents are relatively contraindicated given the availability of more permanent embolysates.

Wallace et al. (51) reported a retrospective comparison of outcomes for 65 patients with AVMs embolized with either PVA or NBCA. These authors reported a lower complication rate after NBCA attributable to a lower surgical complication rate. In a larger, prospectively randomized trial, NBCA and PVA were subsequently compared. This study demonstrated equivalency of the two agents with similar degrees of nidal reduction and

number of vessels embolized, surgical resection times, transfusions, fluid replacement, and Glasgow Outcome Scale scores. A significant difference was identified only with respect to the rate of postsurgical hematoma, which was greater in the PVA group (two out of 42) after NBCA versus eight out of 45 after PVA (46).

Coils

Coils, both detachable (e.g., Guglielmi detachable coils) and injectable (Berenstein liquid coils), are very useful for the occlusion of arteriovenous fistulae within the AVM nidus. Detachable coils are most useful for the initial embolization of large fistulae. For the first coil, we usually select a complex three-dimensional geometry or a fibered 0.018-inch detachable coil, depending on the size of the artery to be embolized. The coil is selected on the basis of the size of the feeding artery as estimated on superselective angiography, or guiding catheter angiography if the volume of shunting precludes complete opacification of the vessel after a microcatheter injection. We oversize the coil by 1 to 2 mm and choose the longest available coil that satisfies the diameter requirements. This coil can be manipulated within the feeding artery to achieve optimal positioning. Visualization of the nondetached coil under fluoroscopy can provide some indication of its stability within the artery. After detachment, a second coil is immediately introduced. We typically choose a soft coil of a diameter similar to the artery in the greatest length available for the second coil. After several coils have been introduced and a stable basket has been created, one or more liquid coils (0.010 Berenstein liquid coils) may be deployed. Finally, after the coil pack has adequately slowed the flow through the fistula, the pedicle may be occluded definitively with an injection of NBCA. Frequently, it is useful to induce hypotension (systolic blood pressure $<$90 mmHg) for the NBCA injection to reduce the risk of NBCA passing through the fistula and into the venous system.

When detachable coils are used, the over-the-wire manipulation of a microcatheter with two distal markers into the pedicle is necessary, introducing the potential for vascular perforation. The introduction of coils into the friable arterial feeders of an AVM also presents a risk of perforation. For this reason, it is useful to have an appropriate ethiodized oil-to-NBCA (2:1) mixture prepared for use before cannulization of the pedicle to be coiled. Finally, if the coils are improperly sized, there is the potential for embolization through the fistula and into the venous system.

If the arterial pedicle supplying the fistula is small enough, embolization with injectable or small 0.010-inch pushable coils can be performed primarily. Liquid coils may be introduced through the smaller internal diameter, flexible, flow-directed microcatheters, eliminating the need for an exclusively over-the-wire catheterization. After the introduction of the coils sufficiently slows the transit through the fistula, occlusion can be achieved safely with NBCA.

PREOPERATIVE EMBOLIZATION TECHNIQUE

Goals of Embolization

Before initiating the neuroendovascular portion of AVM therapy, it is critical that the interventionist have a complete understanding of the overall plan, as well as the goals, for the embolization. This understanding is predicated on maintaining open lines of communication with the vascular neurosurgeon who will be performing the resection (or radiosurgical treatment). The risks of microsurgical resection, as defined by the Spetzler-Martin category of the lesion, should be clear before the procedure. It is important to weigh these risks with those involved with each catheterization and each embolization. For example, if embolizing a Grade II AVM in a noneloquent region, it is critical that the risks of each embolization be minimized to avoid complicating an otherwise straightforward resection.

Imaging Assessment

Magnetic Resonance Imaging

The anatomical location of the lesion is best defined on magnetic resonance imaging (MRI) scans. The size and location of the nidus and its proximity to regions of eloquence are well demonstrated on MRI scans. In addition, the major venous drainage pathways can frequently be identified accurately. The definition of these characteristics frequently allows the confident assignment of a Spetzler-Martin grade before conventional angiography. In addition, MRI data provide important information about the status of the brain parenchyma surrounding the lesion, indicating regions of encephalomalacia or hemorrhage (recent or remote).

Conventional Angiography

AVMs are highly complex anatomical lesions, often with numerous tortuous arterial feeders winding around a nidus and rapidly flowing into one or more enlarged draining veins. As such, the preprocedural assessment of AVM architecture on conventional angiography can be quite challenging.

In many cases, the specific arterial branches supplying the lesion (i.e., the targets for embolization) can be difficult to identify before superselective angiography. However, the vascular distributions involved and the approximate number and size of the feeding arterial vessels to be addressed can generally be ascertained. This information is usually sufficient to estimate the number of stages that will be required for adequate presurgical embolization.

The angiographic images should be evaluated carefully for the presence of aneurysms. Flow-related aneurysms proximal to the nidus (feeding vessel or circle of Willis) and nidal aneurysms should generally be addressed before the remainder of the lesion. The true size of the AVM nidus is sometimes better evaluated on conventional angiography, particularly if it has a diffuse component in which the small vessels are not well depicted on MRI scans.

The venous phase images represent a critical component of pre-embolization evaluation. The number, size, and location of all draining veins should be well understood before embolization. The visualization of draining veins can vary with the parent vessel injected because different parts of the nidus are opacified and are associated with patterns of contrast washout. The operator should be aware of the expected venous drainage pathways that should be visualized from any given vascular injection. The presence of any preexisting venous stenoses should also be noted. The inadvertent occlusion of venous efflux from the AVM nidus during embolization represents one of the most dangerous complications that can be encountered. Control angiography should be performed after each pedicle embolization to reassess flow through the AVM, and, in particular, to verify continued patency of venous efflux.

Staging

The number of embolizations that can be performed during a single session varies with the preference of the interventionist and the anatomy of the lesion. One potential risk of overembolization of a large lesion is hemorrhage related to normal perfusion pressure breakthrough—the sequelae of an abrupt reduction in arteriovenous shunting and sudden increase in the perfusion pressure of the adjacent normal brain parenchyma that has impaired autoregulatory capacity (*Fig. 6*).

In a patient with a large AVM scheduled for surgical resection on the next morning, we routinely perform between five and seven NBCA embolysate infusions during a single session. Given the much larger volume of Onyx that can be injected from a single catheter position, the number of pedicles catheterized and the volume of embolisate injected is much more variable and is assessed on a case-by-case basis. If multiple vascular distributions provide sup-

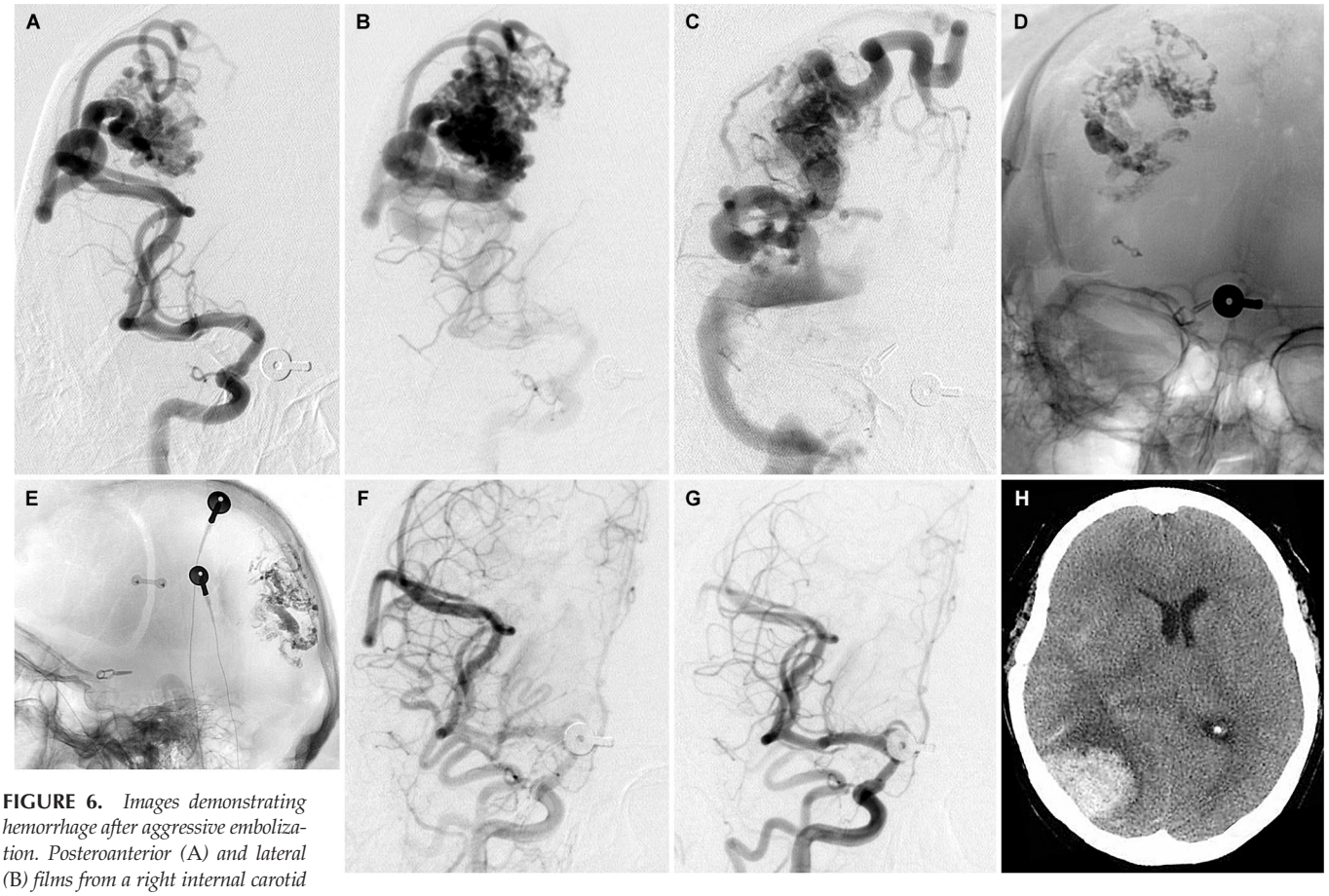

FIGURE 6. *Images demonstrating hemorrhage after aggressive embolization. Posteroanterior (*A*) and lateral (*B*) films from a right internal carotid angiogram demonstrating a large arteriovenous malformation involving the right temporal and parietal lobes in a 42-year-old woman with a seizure disorder undergoing preoperative embolization. After a single session of embolization, unsubtracted posteroanterior (*C*) and lateral (*D*) angiograms depict an extensive NBCA cast within the nidus.* E *and* F*, postembolization angiograms depicting stasis within several of the embolized arterial branches coursing into the region of the AVM nidus. Only minimal residual flow into the nidus was evident at the conclusion of the embolization (not depicted). There was no evidence of venous outflow restriction. The patient emerged from general anesthesia neurologically intact. She experienced a progressive headache and left hemianopsia 48 hours after the embolization.* G*, computed tomographic scan, performed emergently, demonstrating a left parietal lobe hematoma.* H*, computed tomographic examination, performed emergently, demonstrating a left parietal lobe hematoma.*

ply to the lesion (e.g., right internal carotid and vertebrobasilar arteries) and multiple sessions are to be performed, it is our preference to embolize within only one vascular distribution during any given session. In general, for AVMs larger than 3 cm, it is preferable to have at least two sessions of embolization scheduled (*Fig. 7*).

Technique

Although there has been extensive debate over the issue, we perform all of our AVM embolizations under general anesthesia. We forgo the potential advantage of Amytal testing and continuous neurological monitoring of the conscious patient for the practical advantage of complete paralysis and the eradication of all motion during embolysate infusion. At the Barrow Neurological Institute, all embolizations are performed with neuroelectrophysiological monitoring (both somatosensory evoked potentials and electroencephalography). Before the introduction of Onyx, NBCA was the primary agent used for AVM embolization at our institutions. We describe the techniques used with both agents.

Regardless of the agent used, access is achieved through the common femoral artery with placement of a 6-French sheath. Patients with unruptured AVMs are heparinized with a targeted activated coagulation time of between 200 and 250 seconds maintained throughout the procedure. Anticoagulation decisions during the treatment of patients with ruptured AVMs are made on a case-by-case basis. Access into the cervical segment of the artery targeted for embolization is achieved with a 90-cm, 6-French guiding catheter (Envoy guiding catheter; Cordis Endovascular, Miami Lakes, FL).

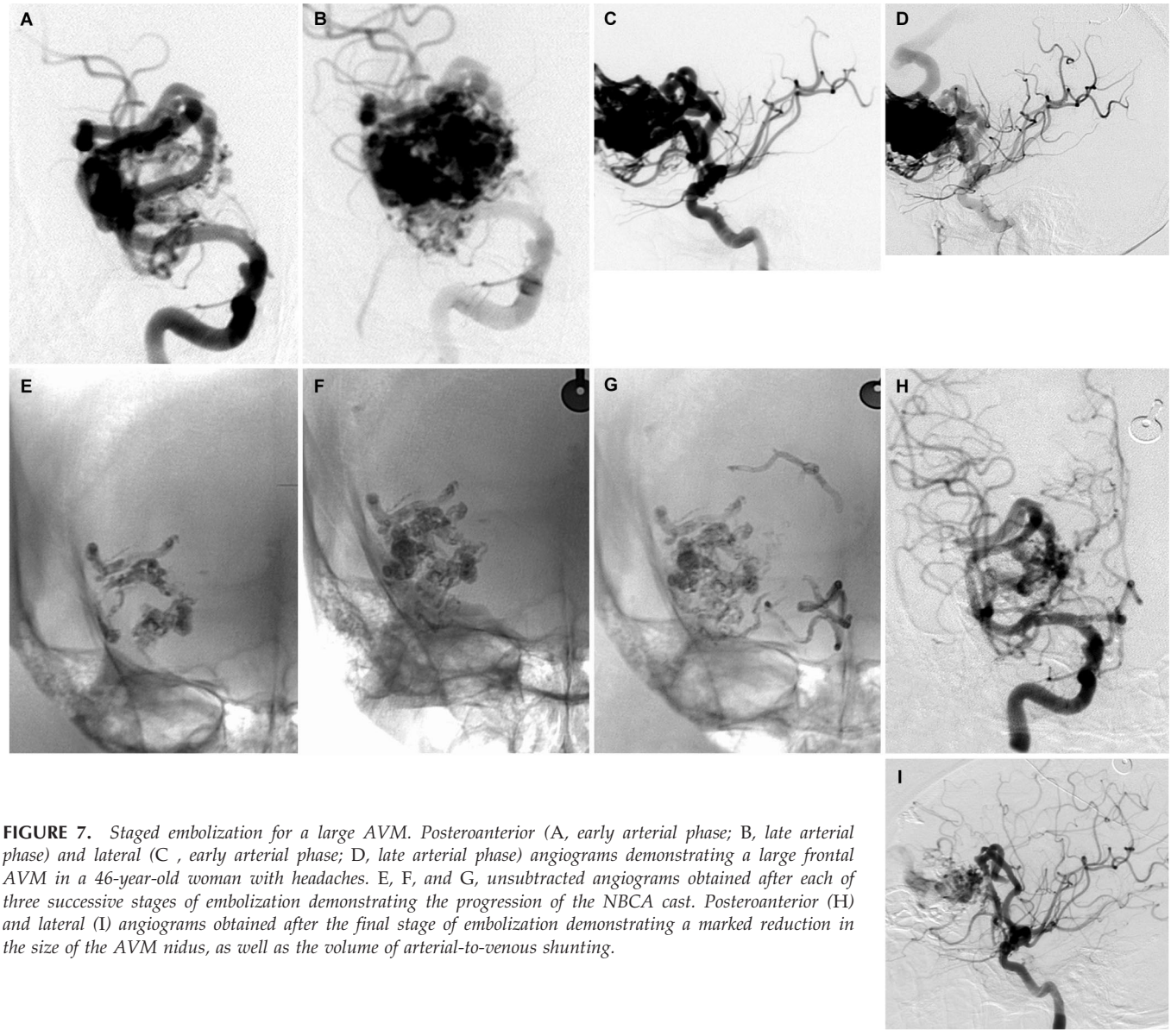

FIGURE 7. *Staged embolization for a large AVM. Posteroanterior (*A, *early arterial phase;* B, *late arterial phase) and lateral (*C , *early arterial phase;* D, *late arterial phase) angiograms demonstrating a large frontal AVM in a 46-year-old woman with headaches.* E, F, *and* G, *unsubtracted angiograms obtained after each of three successive stages of embolization demonstrating the progression of the NBCA cast. Posteroanterior (*H*) and lateral (*I*) angiograms obtained after the final stage of embolization demonstrating a marked reduction in the size of the AVM nidus, as well as the volume of arterial-to-venous shunting.*

Pedicles targeted for embolization are identified on the initial angiographic images. If NBCA is to be used, the vast majority of catheterizations are performed using the Elite microcatheter (Boston Scientific) over a 0.008-inch Mirage (EV3) microwire. If Onyx is to be used, catheterizations are performed with either a Marathon or Echelon microcatheter (EV3). The Elite microcatheters are navigated primarily using a flow-directed technique. The microwire is generally maintained within the confines of the catheter functioning to add support to the proximal aspect of the catheter as it is passed distally. Occasionally, the wire can be used to manipulate the catheter past small nontargeted branch vessels that repeatedly engage the tip of the flow-directed catheter or selectively to engage a tortuous targeted branch that cannot be selected with the microcatheter alone. The Marathon and Echelon microcatheters are applied primarily using an over-the-wire technique, typically with a 0.014-inch microwire used with the Echelon catheters and 0.010-inch Expedion or 0.008-inch Mirage microwires used with the Marathon catheter. Occasionally, the Marathon catheter can be navigated using a flow-directed technique. However, this is only feasible and safe in large, relatively straight vascular segments that typically can be captured easily with an over-the-wire technique. After the microcatheter has been successfully manipulated into a perinidal position, a gentle injection of contrast is performed on a blank roadmap. If the fluoroscopic images demonstrate catheterization of a potential pedicle for embolization, a superselective digital subtraction angiography run then is performed. A higher frame rate (5–6 French) is sometimes helpful, particularly if the pedicle courses into a region with brisk arteriovenous shunting.

The microcatheter run is then reviewed. Four primary considerations when evaluating the superselective run are: 1) the identification of any normal parenchymal branches arising from the pedicle to be embolized; 2) the anatomy of the catheterized pedicle proximal to the catheter tip and AVM nidus—specifically the identification of, and localization of the origin of, any eloquent branches arising from the targeted pedicle that could be compromised by reflux; 3) the rate of transit of contrast through the nidus; and 4) the anatomy of the draining vein that appears first.

The most important observation to be made is the identification of any parenchymal branches arising from the pedicle to be embolized. Arterial feeders range from vessels that course directly into the nidus to en passage vessels that course beside the nidus primarily to supply normal brain, but simultaneously give rise to multiple small side branches that extend into the nidus. In most cases, pedicles that give rise to parenchymal branches are not embolized. At times, if a branch supplies the nidus over a long segment of its course and then continues to normal parenchyma, the vessel can be occluded distally with coils to protect the normal parenchymal branches and then occluded proximally with NBCA—with the hope that the liquid agent is able to penetrate into the AVM nidus. This strategy is used only when there is evidence of retrograde flow (as indicated by wash out of contrast) within the distal aspect of the branch that continues on to normal brain parenchyma. In these cases, it is reasonable to assume that the branch will receive adequate leptomeningeal collateral flow to maintain the viability of any functional surrounding brain tissue in the region.

The position of the microcatheter with respect to the orientation of the pedicle and the location of the nidus are critical. In at least one view, the operator should orient the image intensifier such that the microcatheter is elongated and proximally does not overlap either the nidus or draining vein. This orientation facilitates the early visualization of NBCA or Onyx reflux, thus minimizing the risk of gluing the catheter in place (with NBCA) or occluding proximal eloquent branches because of reflux of the embolysate (either agent).

The rate of contrast transit through the AVM nidus provides data that can be helpful in the determination of the optimal composition of the NBCA-to-ethiodized oil mixture as well as the initial rate of the NBCA injection to be performed. With respect to embolization with Onyx, the rate of transit defines the concentration of agent used. Onyx-18 (6%) is used for most infusions. The more viscous Onyx-34 (8%) is available for the embolization of high-flow pedicles that lead to fistulous portions of the AVM.

Next, the later phase images are evaluated to demonstrate the location and timing of the appearance of the draining vein. The vein should be identified in both planes so that the operator immediately can recognize when the liquid embolysate has passed through the nidus and has begun to approach or enter the vein.

When the angiographic frame demonstrating the pedicle and the first appearance of the draining vein has been selected, we find it helpful to display this frame as a reference image on one of the in-room monitors so that it can be visualized periodically during the glue injection if necessary.

Before the infusion of NBCA, both physicians involved must clearly understand the desired appearance of the cast to be created. NBCA infusions are optimally performed by two experienced physician operators working in concert. Before preparing the NBCA, the neuroanesthesiologist should be informed that an NBCA infusion is imminent and the patient will need to be motionless during a prolonged (90 s) apnea. The anesthesiologist should readminister paralytics as necessary at that time. In addition, if brisk arteriovenous shunting is present, it may be helpful to reduce the blood pressure (systolic blood pressure <90 mmHg) for the infusion. After the microcatheter has been purged with a solution of 5% dextrose in water, the NBCA injection is performed with the patient apneic under blank fluoroscopic roadmap control. When the desired NBCA cast has been achieved, the physician performing the infusion gently aspirates the microcatheter and states "pull" to the second physician, who then briskly removes the microcatheter from the patient. The last image hold from the roadmap is stored. A control angiogram is then obtained to evaluate the status of the nidus, patency of the draining veins, anatomy of the remaining arterial feeders, and the presence of any complications (e.g., injury to the parent vessel, thromboembolic complication, extravasation). After an assessment of the remaining AVM nidus has been made, the operator determines if any additional pedicles are to be embolized during the session.

The technique and pace of an Onyx injection is completely different from NBCA. The injection of the agent can be performed

deliberately with the luxury of periodically being able to stop the infusion to assess the progress of the cast, the patency of the nidus and draining veins, and the status of any important vessels coming off of the pedicle more proximally. The injection is performed under blank fluoroscopic roadmap control after the dead space of the catheter has slowly been purged with the solvent DMSO (0.25 ml/90 s). The initial infusion is continued until the agent is noted to reflux around the catheter tip into the proximal aspect of the pedicle. When reflux is observed, the infusion is halted for 30 seconds to several minutes, then the blank roadmap is refreshed, and the injection is resumed. This progression continues throughout the course of a typically long, slow infusion that is paused periodically after the observation of reflux and is resumed with the goal of reestablishing antegrade flow of Onyx into the AVM nidus. The infusion can be continued until no more reflux can be tolerated because of the risk of occluding an eloquent proximal branch of the targeted pedicle or the agent has progressed into the vein and has potentially begun to interrupt the outflow of the nidus. During these injections, patience is of paramount importance. The long intermittent pauses allowed between infusions allow the proximal Onyx material to precipitate fully around the catheter, thereby increasing the odds that antegrade flow of Onyx will be reestablished when the injection is resumed (i.e., the plug-and-push technique). Using this technique, it is not uncommon that very large volume injections into the AVM nidus can be achieved. Oftentimes several milliliters of Onyx can be infused into the nidus from a single catheter position.

After the injection is completed, the syringe is aspirated gently and then slow, gentle traction is applied to remove the microcatheter. Depending on the tortuosity of the targeted pedicle, the length of the injection, and the amount of refluxed Onyx surrounding the microcatheter, variable degrees of resistance can be experienced during catheter removal. It is not uncommon for the Onyx cast to demonstrate significant deflection while traction is being applied to the microcatheter. In these cases, slow constant traction should be maintained on the catheter and incrementally should be increased over several minutes. Again, patience is critical, because it is not unusual to maintain tension on the catheter for more than 5 to 10 minutes before freeing it from the Onyx cast. If the catheter cannot be retracted without placing undue stress on the cast or cerebrovasculature, the microcatheter can be left in place and cut off at the groin sheath.

POSTOPERATIVE CARE

Most of our AVM embolizations are completed in a single session with surgical resection to be performed the following morning. Larger lesions are occasionally embolized over multiple sessions.

In most cases, heparinization is reversed at the conclusion of the procedure. In adult patients, the arterial sheath is frequently left in place in anticipation of intraoperative angiography to be performed the next day after resection. Occasionally, heparinization is not reversed or the patient is administered a heparin drip if the venous outflow appears to be sluggish on the postembolization angiogram or if an important component of the venous outflow obviously has been compromised. This is often the case when a large AVM nidus with associated venous varices is nearly totally obliterated. In these cases, sluggish flow in the varices can lead to preoperative venous thrombosis with subsequent hemorrhage from the remaining nidus.

After embolization, particularly if large AV shunts or a large volume of the nidus has been occluded, the theoretical possibility of normal perfusion pressure breakthrough hemorrhage exists. For this reason, we attempt to maintain a low systolic blood pressure (<100–120 mmHg) after the procedure with the level determined empirically by the amount of shunting that has been reduced, the patient's baseline blood pressure, and the presence of any additional vascular lesions (e.g., flow-related stenoses, carotid atheromatous stenoses, etc.). We prefer a nicardipine or nitroprusside drip for this purpose supplemented by intravenous medications as needed.

If a very large AVM has been nearly completely embolized during a single session, we pursue this hypotensive strategy even more aggressively, maintaining a systolic blood pressure of less than 90 mmHg. Previously, we maintained the patient under continuous general anesthesia (usually using an agent such as propofol) or carry out the hypotensive strategy after the procedure. More recently, we have been able to achieve adequate postembolization sedation and blood pressure using dextromedetomidine (Precedex; Hospira, Lake Forest, IL). The advantage of using Precedex is that the patient can be extubated immediately after the procedure and a neurological examination can be performed and followed up. These conditions are typically maintained through the time of surgical resection on the next day. When patients are maintained under general anesthesia, a head computed tomographic scan is performed immediately after the completion of the embolization and 4 hours later. Any increases in blood pressure that occur during the postembolization period represent a potential harbinger of intracranial hemorrhage and also require immediate evaluation by computed tomography. We have found these strategies to be effective when inadvertent venous occlusion occurs early in the stage of the embolization of a large lesion (*Fig. 8*). If surgical resection cannot be carried out on the same day after completion of the embolization, we proceed to embolize all accessible arterial feeders during the same session and then maintain the patient in this aggressive hypotensive state through the time of resection the next day.

COMPLICATIONS

Our experience with AVM embolization at the Barrow Neurological Institute is similar to that reported in the literature. From 1995 through 2003, we performed 262 NBCA embolizations in 178 patients with 10 ischemic complications (one major, three quadrantanopsia, six temporary deficits with full recovery) and seven hemorrhages (one death, two major morbidity), overall per patient yielding an 8.9% rate of neurological morbidity (3.4% permanent) and a 0.6% death rate.

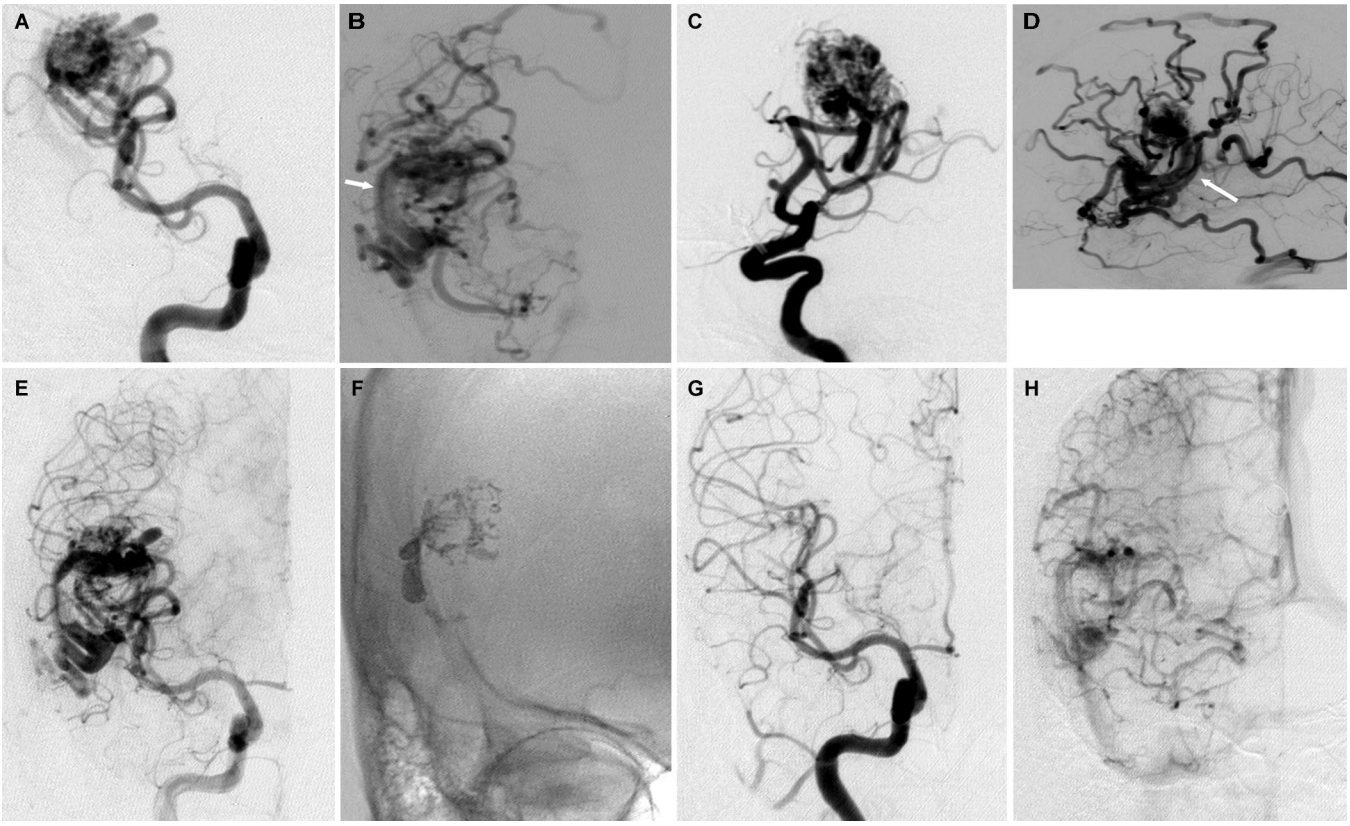

FIGURE 8. *Inadvertent venous compromise during embolization.* A–D, *cerebral angiograms obtained from a 57-year-old woman with headaches demonstrating a Grade III AVM of the right frontal lobe. The late arterial phase images (*B *and* D; arrows*) demonstrating shunting into a large curvilinear venous pouch that subsequently supplies multiple additional tributaries that efflux over the right cerebral convexity. Subtracted* (E) *and unsubtracted (*F*) angiograms from control angiography after the first NBCA infusion demonstrating a large collection of NBCA within the dominant draining vein. Later phase images depicted a change in the flow dynamics through the AVM with more persistent opacification of the nidus and slow outflow into the venous system. Because of the venous outflow compromise produced by the initial NBCA injection, the initial plan to proceed with a staged embolization was abandoned and a more aggressive embolization was pursued with urgent surgical resection to be performed the following morning.* G *and* H, *four additional pedicles were embolized, resulting in near complete obliteration of the AVM nidus. The patient was maintained under general anesthesia after the procedure with the systolic blood pressure maintained at less than 90 mmHg. Surgical resection performed the next day was uneventful, and the patient emerged from the procedures neurologically intact.*

Taylor et al. (45) reported a 2% death rate and 9% permanent neurological deficit rate in 201 patients undergoing 339 embolization procedures during an 11-year period. In this series, embolization procedures were performed using polyvinyl alcohol particles, NBCA, detachable coils, and/or the liquid polymer Onyx. Debrun et al. (8) reported a 5.6% rate of neurological morbidity and two deaths (3.7%) in 54 patients undergoing NBCA embolization. Viñuela et al. (49) reported a morbidity rate of 13% and a single death in a series of 101 patients. In Gobin et al.'s (13) series of 125 patients, permanent complications occurred in 12.8% (minor deficits in 5.6%, moderate deficits in 4.8%, major deficits in 2.4%) and there were two deaths (1.6% mortality rate). In the initial study by Wallace et al. (51) comparing NBCA with PVA, four out of the 22 patients who underwent particle embolization had ischemic neurological complications (one of which was major), whereas four out of 23 patients who underwent acrylic embolization experienced minor neurological deficits. In a subsequent trial, the NBCA investigators reported an overall death rate of 3.9% in 101 patients undergoing either NBCA or PVA embolization. Jahan et al. (23) reported four adverse events and no deaths in a series of 23 patients undergoing embolization with Onyx. Of the adverse events, only one resulted in permanent morbidity (4%). Hartmann et al. (18) reported a 14% rate of new deficits, a 2% rate of permanent disability, and a 1% death rate in 233 patients undergoing 545 sessions of embolization.

Frizzel and Fisher (12) compiled data from the medical literature available from 1969 through 1993 and calculated a 10% rate of temporary morbidity, 8% permanent morbidity, and 1% death rate in 1246 patients with brain AVMs undergoing embolization. The authors found no significant difference in morbidity or mortality when comparing series published before 1990 with those reported after 1990.

It is unclear how the introduction of Onyx will affect the complication rate associated with embolization. Although the

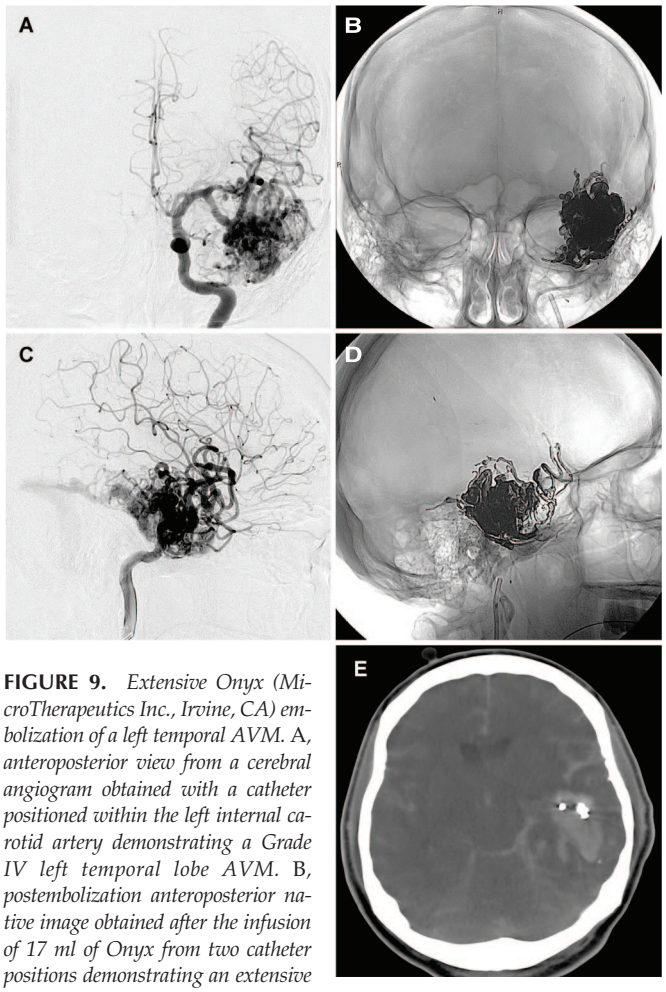

FIGURE 9. *Extensive Onyx (MicroTherapeutics Inc., Irvine, CA) embolization of a left temporal AVM.* A, *anteroposterior view from a cerebral angiogram obtained with a catheter positioned within the left internal carotid artery demonstrating a Grade IV left temporal lobe AVM.* B, *postembolization anteroposterior native image obtained after the infusion of 17 ml of Onyx from two catheter positions demonstrating an extensive Onyx cast corresponding to the entire distribution of the AVM nidus opacified on the initial angiogram. Lateral pre-embolization angiogram* (C) *and postembolization native image* (D) *demonstrating a similar correlation, with the Onyx cast encompassing the entire anatomic distribution of the AVM. Postembolization angiography demonstrated no residual filling of the nidus or arteriovenous shunting.* E, *head computed tomographic scan obtained after embolization demonstrating a large parenchymal hematoma surrounding the Onyx cast. The patient was taken for surgical resection of the AVM despite the apparent angiographic cure. At the time of surgery, a small amount of residual active AVM was identified.*

agent has significantly superior handling properties that typically allow a much more aggressive embolization of the AVM nidus, it is likely that some portion of the risk previously carried by the surgical resection may be transferred to the embolization procedure (*Fig. 9*).

CONCLUSION

Neuroendovascular embolization continues to be a critical component of the multidisciplinary, multimethod management of cerebral AVMs. Safe and effective embolization may be performed only in the context of a well-designed, rational treatment plan that is fundamentally based on a clear understanding of the natural history of the lesion, as well as the cumulative risks of multimethod treatment.

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TARGETING CEREBRAL ARTERIOVENOUS MALFORMATIONS FOR MINIMALLY INVASIVE THERAPY

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OBJECTIVE: Cerebral arteriovenous malformation (AVM) embolization has been performed for nearly 40 years to reduce the risk of hemorrhage, to reduce symptomatic arteriovenous shunting, and to pretreat patients for surgical excision or radiosurgery. In some cases, embolization alone may be able to angiographically cure an AVM, although this is a small percentage of all AVMs.

METHODS: This report reviews the current limitations of embolic therapy of cerebral AVMs from the standpoint of AVM angioarchitecture and the physical limitations of current embolic materials. In addition, it seeks to identify the areas in which embolization therapy may make advancements both as a pretreatment and as a sole therapy.

RESULTS: Currently, liquid embolic agents, ethylene vinyl alcohol, and *n*-butylcyanoacrylate seem to provide the greatest resistance to recanalization in AVM embolization. These agents, however, elicit only a weak, nonspecific, bioactive inflammatory response by histopathology.

CONCLUSION: The further evaluation and understanding of the vascular biology of AVM vessels and the endothelium cell wall biology will help us devise more bioactive material solutions to AVM nidus obliteration. Targeting specific receptors in AVMs with the embolic material delivered may additionally enhance the effects of radiosurgery in these patients.

KEY WORDS: Cerebral arteriovenous malformation, Embolization, Vascular endothelial growth factor, Vascular markers

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The prevalence of cerebral arteriovenous malformations (AVMs) in the population has been estimated between 0.14 and 0.52% of adults (20, 22). Patients may present with cerebral hemorrhage (subarachnoid, intraventricular, intraparenchymal, or subdural), seizures, headaches, or progressive neurological deficit from ischemia seen in vascular steal created by arteriovenous shunting. Patients may also have an incidental diagnosis.

The options for cerebral AVM management include medical management only, surgical excision, radiosurgery, and embolization therapy. For large or complex AVMs or for AVMs with associated cerebral aneurysms, a multidisciplinary approach is often the best strategy (5). In the early 1960s, Luessenhop and Presper (18) and Luessenhop and Spence (19) at Georgetown University first reported the transcatheter embolization of cerebral AVMs, which were thought to be inoperable, in efforts to reduce arteriovenous shunting and cerebrovascular steal. Although the microcatheter tools and techniques have advanced considerably since then, there are still technical limitations to transarterial embolization and other minimally invasive technology, such as stereotactic radiosurgery. Our growing understanding of the biology of AVMs is also evolving with the analysis of the developmental characteristics and cytokine interactions distinct for these vascular malformations (1, 4). This report evaluates the current targeting strategies for minimally invasive therapy of cerebral AVMs and speculates on advances for future therapies.

EMBOLIZATION STRATEGY

The strategy for cerebral AVM embolization is based on the goal of the embolization.

For select small AVMs with few feeding pedicles, complete angiographic obliteration of the AVM by embolization may be the goal (*Fig. 1*). In our experience, this represents fewer than 10% of cases referred at our institution. Others have reported higher angiographic cure rates of approximately 40% with more aggressive techniques (8, 30, 31). More aggressive embolization, however, may result in higher neurological complication rates. Do et al. (8) and Yakes et al. (31) reported a 47% overall neurological complication rate in a series of patients embolized via a transarterial route with absolute alcohol. Some interventionalists have advocated the use of coils to segmentally occlude a feeding artery pedicle distal to *en passage* feeders to subsequently embolize the branch with *n*-butylcyanoacrylate (NBCA). Curiously, others have proposed transvenous embolization. The long-term follow-up period in these series is lacking, bringing into question whether or not the angiographic obliteration at the time of embolization represents a long-term cure.

Embolization may be performed in preparation for surgical excision. Depending on the size of the AVM, this may require multiple sessions. Embolization of larger AVMs is usually staged because aggressive embolization of a large AVM in a single session is thought to have a higher periprocedural bleed rate. The goals of presurgical embolization may be to generally reduce the degree of arteriovenous shunting and total blood flow through the nidus, in efforts to reduce blood loss during surgical excision. Or, the goal may be more directed, such as embolizing the deep feeders to obliterate the more difficult section of the AVM to resect. A gradual change in the hemodynamics in and around an AVM are less likely to result in hemorrhage secondary to the embolization procedure itself.

For deep AVMs, embolization can help reduce the target size of the nidus for radiosurgery or radiotherapy. In such cases, we prefer liquid polymer embolization compared with polyvinyl alcohol particles (PVA) because the former is more durable, and the latter may have recanalization (28) (*Table 1*) in the 2-year period of optimal radiosurgery effect.

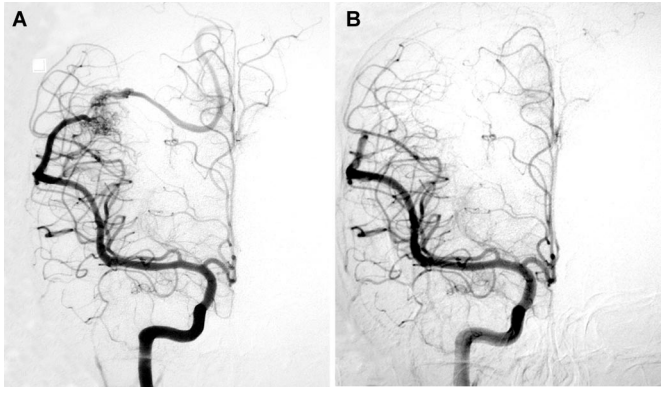

FIGURE 1. *Pre- and postembolization anteroposterior angiograms of a small parietal AVM in a 15-year-old child who presented with a hemorrhage. Two separate branches off of the posterior parietal middle cerebral artery trunk were embolized with n-butylcyanoacrylate, resulting in angiographic obliteration of the AVM.*

Palliative treatment of cerebral AVMs may be a goal in some patients, particularly those with very large AVMs, in whom subsequent surgery or radiosurgery is not planned. In these patients, headaches or ischemic symptoms may be ameliorated by decreasing the degree of arteriovenous shunting, particularly if there is a fistulous component to the AVM. Flow-related headaches seen most prominently in the parietal-occipital region seem to respond well to embolization. It is unclear from the literature whether or not palliative embolization changes the risk of AVM hemorrhage. Valavanis and Yaşargil (30) have suggested that appropriately targeted AVM embolization in otherwise untreatable AVMs may actually reduce the risk of hemorrhage, particularly if nidal aneurysms are embolized.

Limitations of Current Embolic Agents

Liquid Polymers

Liquid polymers have the advantage of being injected through small, flow-guided microcatheters, which may be positioned directly adjacent to or within cerebral AVMs. By injecting a quickly polymerizing agent directly into the nidus, a section of the nidus may be obliterated, even if there are multiple feeders to that segment. Two liquid embolic agents are currently approved by the Food and Drug Administration for AVM embolization: TruFill NBCA (Cordis Neurovascular, Miami, FL) and Onyx ethylene vinyl alcohol (EVOH) (EV3 Neurovascular, Irvine, CA).

The limitation of polymer embolization is that *en passage* feeders from a normal cortical artery cannot be effectively accessed for embolization without occluding the main artery, which may supply eloquent cortex. Likewise, feeder arteries less than 1.5–French (0.5 mm in diameter) generally cannot be accessed, and that portion of the AVM is left untreated. Similarly, if the NBCA or EVOH does not polymerize at the desired rate, it may occlude the feeding pedicle too proximally, resulting in no nidus penetration, or too distally, resulting in venous phase polymerization, compromised venous drainage from the AVM, or pulmonary emboli.

The introduction of Onyx EVOH for AVM embolization has allowed for more prolonged embolization injections and, therefore, better nidus penetration of the liquid embolic agent compared with TruFill NBCA. However, the dimethyl sulfoxide-compatible microcatheters necessary for EVOH embolization are currently stiffer and less trackable than traditional flow-guided microcatheters.

Particle Embolization

Embolization of AVMs with PVAs (Contour Embolization Particles; Boston Scientific, Cork, Ireland) of preset sizes emulates the original embolization strategy of Luessenhop, who used varying sizes of diameter beads or pellets to occlude feeding artery pedicles (18, 19). Before the availability of Food and Drug Administration-approved liquid polymer embolics, PVA was the primary embolic agent for cerebral AVMs (23). Its advantages included ease of manipulation at surgery, con-

TABLE 1. Properties of embolic agents for cerebral arteriovenous malformations[a]

Embolic agent	Ability to penetrate cerebral arteriovenous malformation nidus	Resistance to recanalization	Bioactivity
NBCA (23)	++	+++	+
EVOH (12)	+++	+++	+
PVA particles (28)	+++	+	+
Embospheres (17)	+++	+	+
Silk suture (27)	+	++	+++

[a] NBCA, *n*-butylcyanoacrylate; EVOH, ethylene vinyl alcohol; PVA, polyvinyl alcohol particles. Qualitative evaluation of embolic material properties: +, mild; ++, moderate; +++, strong.

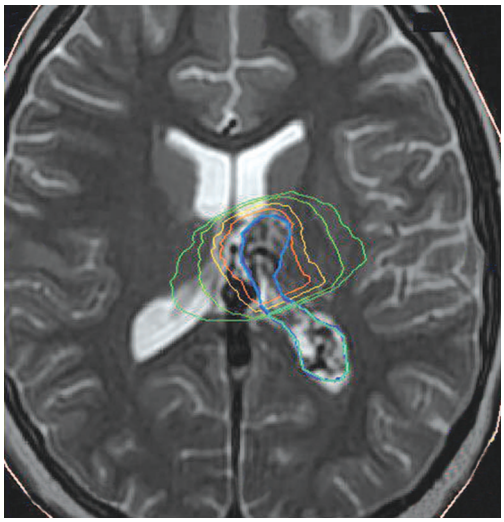

FIGURE 2. *Planning magnetic resonance imaging scan for stereotactic radiosurgery of a 13-year-old girl who presented with intraventicular hemorrhage. Note that the 1500-cGy isodose line extends significantly into the thalamus despite conformal target planning with multileaf collimators, primarily because of the irregular shape of the AVM.*

trolled embolization of a pedicle without worrying about inadvertently gluing the delivery microcatheter in place, and variety of particle sizes. Long-term evaluation of particle embolization, however, has brought into question the durability of the embolization because long-term recanalizations have been reported (28). Therefore, in its current form, PVA is used primarily as a preoperative embolic agent.

Embospheres (EmboGold Microspheres; BioSphere Medical, Inc., Rockland, MA) work on the same principle as PVA embolization in that various sizes of embospheres may be used to occlude differently sized branches. No significant documentation is available on any bioactive component of Embospheres.

Other Agents

Silk sutures may be used to embolize larger branch feeders to cerebral AVMs. Typically 6–0 silk sutures are cut in lengths measuring 1 to 3 cm and delivered through the microcatheter (27). Braided silk is a highly thrombotic agent and also elicits an inflammatory response. Because the ability of silk suture to penetrate the small vessels deep in the nidus is limited, and the silk has nearly nonexistent radiopacity, it has practical use limitations. However, from the standpoint of bioactivity, it has one of the most bioactive profiles of the embolic agents currently available.

LIMITATIONS OF RADIOSURGERY

The primary method of AVM treatment by radiosurgery is radiation-induced intimal injury or radiation arteritis, which results in vessel thrombosis. Regardless of the type of unit and radiation source used (gamma knife, linear accelerator, proton beam), radiosurgery is limited in cerebral AVMs by size criteria. In general, AVMs less than 10 cm^3 have a 2-year cure rate of 65 to 80% at the 2-year follow-up examination (10, 25, 32). Additionally, irregularly shaped AVMs may pose a targeting problem for radiosurgery because of "hot spots" in the surrounding parenchyma or undesirable extension of high-isodose lines in eloquent areas (*Fig. 2*).

Linear accelerator modality stereotactic radiosurgery uses noncoplanar beams constricted by micromultileaf collimators to conform to the AVM target. However, even with the benefit of jaws to focus on an irregularly shaped target, the isodose lines for planned treatment demonstrate higher radiation doses to the surrounding brain in irregularly shaped AVM targets. Therefore, the ability to reduce the target dose with the aid of radiation sensitizers would potentially help reduce the incidence of edema and radiation necrosis seen adjacent to the treated AVM. AVM embolization before stereotactic radiosurgery may help reduce the target volume for more effective radiation-dose planning; however, this is true only if specific anatomic compartments of the AVM nidus can be obliterated with embolization. Occluding the feeder arteries proximally or embolizing the nidus diffusely does not reduce the volume of the radiosurgery target.

FUTURE APPLICATIONS

Bioactive Materials

The ideal embolic agent would be an agent that could penetrate the AVM nidus; in the event that the AVM was not obliterated by the embolization itself, the embolic agent would have incorporated a bioactive or radiosensitive compound, which would induce a controlled cell-mediated or thrombotic response in the residual AVM and would not affect surround brain parenchyma or microvasculature. The restriction on this

technology is that differentiation between normal and pathological arteries may be difficult to achieve unless a differential expression of endothelial receptors, such as vascular endothelial growth factor (VEGF) or angiogenesis factors, are demonstrated in the AVM. A nonselective inflammatory reaction to the embolic material would also cause potentially harmful inflammation in the surrounding brain parenchyma.

NBCA promotes a mild inflammatory reaction within AVM vessels. The embolization of AVM vessels is usually durable, with improved long-term results compared with isobutyl cyanoacrylate. Delayed giant cell reactions have already been seen in cyanoacrylate embolization, particularly with the use of adjunctive tantalum powder (9). The combined effects of NBCA embolization and radiation have brought into question an increased risk of cerebral edema in sequential therapies during a short period of time. Therefore, we will normally delay the radiosurgery therapy for a short while (a few weeks) after embolization therapy to avoid an increase of periprocedural edema.

EVOH copolymer is typically delivered in dimethyl sulfoxide diluant and mixed with tantalum for radiopacity. Histological studies of this embolic combination in humans (12) show that blood vessels 80 μm to 1 mm may be filled and occluded. No associated infiltrate or reaction is seen in the vessels if the AVM is resected the same day as the embolization. At 1 day after embolization, a mild inflammatory reaction with polymorphonuclear leukocytes is seen, but little angionecrosis is observed. By a few days after embolization with EVOH, angionecrosis can be seen, with loss and fragmentation of nuclei of cells in the vessel walls, particularly smooth muscle cells. No significant evidence of recanalization has been seen.

Calcium alginate is a gel that has been evaluated in an animal model of cerebral arteriovenous malformations. Alginate and the reactive component calcium chloride are injected concomitantly. Both acute and 6-month follow-up evaluations have shown that the calcium alginate can penetrate the AVM nidus and have shown persistent occlusion in embolized vessels. In the swine rete mirabile model, histological evaluation has shown a minor bioactive response to the embolic material. Evidence of a reactive encapsulation with fibrinous tissue surrounding the alginate polymer promotes stability of the embolic material, deterring recanalization (2, 3).

Unfortunately, the bioactivity of all of the agents described is a nonspecific inflammatory response. Uncontrolled, this cellular response could lead to increased edema in surrounding brain parenchyma after embolization. The use of targeted bioactive therapy based on differential AVM markers would focus the therapeutic effect on the AVM itself and potentially minimize any harmful bystander effect to the surrounding brain parenchyma.

AVM Markers

Cerebral AVMs have abnormal vessels, angioarchitecture, and flow hemodynamics. To target these vessels for treatment via immunological, cellular, chemotherapeutic, or radiation therapies, differences in surface receptors and cellular cytokine expression may be exploited for future embolic therapies. Therefore, understanding the cellular biology of the endothelium and other cell populations of AVMs may help guide us in embolic agent development. The basic studies detailed below are summarized in *Table 2*.

Hatva et al. (11) have analyzed surgically resected AVMs by in situ hybridization and immunohistochemistry and have found that AVM endothelium and surrounding brain cells demonstrate significantly elevated levels of Tie messenger ribonucleic acid protein as well as VEGF messenger ribonucleic acid protein, whereas normal brain demonstrated little or no Tie or VEGF expression. Tie is a tyrosine kinase-dependent VEGF receptor. This suggested ongoing angiogenesis or AVM maintenance functions.

Kılıc et al. (14) evaluated 34 surgically resected AVMs, 10 cavernous malformations, and two venous angiomas, and also found increased expression of VEGF within the endothelium and subendothelium of AVMs and cavernous malformations. Transforming growth factor α elevations were also seen in the endothelial and perivascular layers. These elevations were not seen in normal brain specimens or venous angiomas. Unlike the AVMs, surrounding glial cells adjacent to cavernous malformations did not demonstrate elevated levels of VEGF, suggesting the cavernous malformations do not demonstrate all

TABLE 2. Receptors/markers for vascular pathologies[a]

Tissue type	VEGF (11, 14, 15, 29)	Tie (11)	bFGF (14, 24)	Laminin (24)	Fibronectin (24)	TGFα (14)
Cerebral arteriovenous malformation	+	+	−/+	−/+	−	+
Brain surrounding cerebral arteriovenous malformation	+	+	ND	−	−	ND
Cavernous malformation	+	ND	+	−	+	+
Brain surrounding cavernous malformation	−	ND	−	−	−	−
Venous angioma	−	−	−	ND	ND	−
Brain parenchyma	−	−	−	−	−	−

[a] VEGF, vascular endothelial growth factor; TGFα, transforming growth factor α; bFGF, basic fibroblastic growth factor; ND, no data. Qualitative immunohistochemical analysis: −, no significant elevation in expression; −/+, demonstrated in some cases, but absent in others; +, expression seen in the majority of specimens.

of the same angiogenic factors as AVMs. Likewise, in this study, AVMs did not demonstrate upregulation of basic fibroblastic growth factor, but cavernous malformations did.

In contrast, Rothbart et al. (24) showed faint expression of basic fibroblastic growth factor in four out of seven AVMs analyzed. However, both this study and the Kılıc study concur that AVMs show increased laminin expression not seen in cavernous malformations, and cavernous malformations showed increased fibronectin expression. Collagen Type 4 and α smooth muscle actin were seen both in AVMs and cavernous malformations.

Koizumi et al. (15) specifically analyzed the VEGF subtypes (VEGF-A–D) and their receptors (Flt-1, Flk-1, and Flt-4) on 31 resected AVMs and found that VEGF-A expression was the most universal in the samples (96.8%), with lesser expression of VEGF-C (54.5%), VEGF-D (51.6%), and VEGF-B (9.7%). Immunohistochemistry studies of the VEGF receptors showed equivalent positivities for Flt-1 and Flt-4 (61.3% each), with lesser expression of Flk-1 (19.4%). Interestingly, the nidus size and age of the patient did show differential expression, indicating that AVM angiogenesis is an evolving process with patient age and is not restricted to development in utero. This correlates to our previous report of a de novo AVM in a patient with angiographic documentation of no previous AVM (1) and also with previous reports of recurrent AVMs, particularly in children, who have complete angiographic resection of their AVMs.

Sure et al. (29) have implied that presurgical AVM embolization itself may promote neoangiogenesis by eliciting regional hypoxia. In their series, 17 out of 22 (77%) of the AVMs demonstrated high VEGF expression, but only two out of eight (25%) patients without preoperative embolization demonstrated elevated VEGF in their AVMs. They did perform immunohistochemical analysis that demonstrated proliferative and growth signals evident in these AVMs. Positive endothelial staining for proliferating cell nuclear antigen (87%) and MIB-1 (20%) was seen in these specimens.

Radiosensitizers

The use of radiation sensitizers in the treatment of cerebral tumors has achieved a higher dose distribution in select tumors based on sensitizer uptake. This principle also has potential applications in the AVM population. The incorporation of a radiation sensitizer in embolic material for AVM embolization is attractive because it might make the combined therapy of embolization and radiosurgery more effective. The potential deficit of this technology's application to AVMs compared with cerebral tumors is that the sensitizers would most likely be concentrated in areas of embolization, with perhaps no enhanced radiation to nonembolized sectors of the AVM nidus—the areas of the AVM that would need it the most.

In tumors, certain drugs act as adjuvants to radiotherapy or photodynamic therapy by selectively sensitizing hypoxic cells in areas of tumor that have outgrown their vascular supply or by selectively protecting well-oxygenated cells (6). The use of radiation sensitizers to selectively target deoxyribonucleic acid (DNA) and non-DNA targets seen in aberrant tumor cells has been evaluated (16). By using select DNA targeting in the radiation sensitizer, drug toxicity factors may be reduced as well (7). Finally, targeting tumor angiogenesis has proven to be an innovative strategy (13) because tumor angiogenesis differs from normal angiogenesis in that tumor vessels are generally more tortuous and hyperpermeable than normal vessels. Neovascularization and angiogenesis can also be targeted for photodynamic therapy using benzoporphyrin derivatives to enhance laser therapy (26) or hematoporphyrin esters to sensitize for photodynamic therapy in a time-dependent fashion (21).

In contrast to radiation sensitizers for tumors, however, the use of these agents for AVM therapy must take different approaches. We cannot target AVMs on the basis of hypoxia or hyperemia because normal brain-surrounding AVMs may represent either of these conditions. With current available knowledge, it would be difficult to target DNA aberrations in AVMs because these may not be as definable as in tumors. However, inroads may be made by targeting angiogenic growth factors, protein or ribonucleic acid profiles, and vascular endothelium or subendothelium receptor expression. Microcatheter delivery of liganded compounds directed to bind with these upregulated vascular receptors directly in the AVM nidus may help provide the basis for radiation sensitization in targeted radiosurgery.

Alternatively, it has been speculated that radiation-bearing microspheres may be used to directly deliver a prescribed radiation dose to the AVM directly via catheter-directed therapy. Lee and Reece (17) calculated virtual doses of radiation based on a putative model of 142 Pr-enhanced microspheres within an AVM model. Although not currently used, it is another example of targeting cerebral AVMs nonspecifically or specifically with catheter-directed therapy.

CONCLUSION

The progress of AVM therapy by embolization or combined therapies is based on an understanding of the cellular and vascular biology of the AVM vessels, particularly the arterial endothelium. By understanding the endothelial receptor characteristics, sheer stress effects, and biological differences of the AVM vessels, we can target our therapies in a more effective manner.

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THE MANAGEMENT OF VEIN OF GALEN ANEURYSMAL MALFORMATIONS

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OBJECTIVE: The vein of Galen aneurysmal malformation (VGAM) is a choroidal type of arteriovenous malformation involving the vein of Galen forerunner. This is distinct from an arteriovenous malformation with venous drainage into a dilated, but already formed, vein of Galen. Reports of endovascular treatment of VGAM in the literature approach the disease from a purely technical viewpoint and often fail to provide satisfactory midterm results. To focus the therapeutic challenge to a strictly morphological goal overlooks the fundamental aspects of neonatal and infant anatomy and fluid physiology. During the past 20 years, our approach to VGAM has remained the same. Our experience, based on 317 patients with VGAM who were studied in Hospital Bicêtre between October 1981 and October 2002, allows us to describe the angioarchitecture, natural history, and management of VGAM in neonates, infants, and children.

METHODS: Of our cohort of 317 patients, 233 patients were treated with endovascular embolization; of these, 216 patients were treated in our hospital. The treatment method of choice was a transfemoral arterial approach to deliver glue at the fistulous zone.

RESULTS: Of 216 patients, 23 died despite or because of the embolization (10.6%). Twenty out of the 193 (10.4%) surviving patients were severely retarded, 30 (15.6%) were moderately retarded, and 143 (74%) were neurologically normal on follow-up.

CONCLUSION: Our data demonstrate that most treated children survive and undergo normal neurological development; an understanding of the clinical, anatomical, and pathophysiological features of VGAM has, therefore, reversed the former poor prognosis. Our level of understanding about the lesion allows us to predict most situations and remedy them by applying a strict evaluation protocol and working within an optimal therapeutic window. Patient selection and timing remain the keys in the management of this condition. It is more important to restore normal growth conditions than a normal morphological appearance, with the primary therapeutic objective being normal development in a child without neurological deficit.

KEY WORDS: Cardiac failure, Clinical outcome, Glue, Hydrovenous disorders, Transarterial embolization, Vein of Galen malformation

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During the past 20 years, written contributions on cerebral arteriovenous malformations (AVMs) in children have evolved from anecdotal case reports to short series, offering a better understanding of the disease, the therapeutic strategies, and results of various managements. Historical contributions from the neurosurgical point of view have demonstrated limitations in the management of these difficult lesions and relinquished them to interventional neuroradiology.

The vein of Galen aneurysmal malformation (VGAM) is an AVM of the choroidal system draining into the vein of Galen forerunner. This is distinct from an AVM with venous drainage into a dilated, but already formed, vein of Galen. The first description of a possible VGAM was reported by Steinhel in 1895, cited by Dandy (8); this was, in fact, a cerebral AVM of the diencephalon draining into a dilated vein of Galen. Today, it would be described as a false vein of Galen malformation (18). The first therapeutic attempts were recorded at the beginning of this century and describe an infant with intracranial hypertension who subsequently underwent bilateral

internal carotid ligation. In 1946, Jeager reported bilateral arteriovenous (AV) communications draining into an aneurysmally dilated vein of Galen (15). Boldrey et al. (2) treated two similar patients with arterial ligation in 1949. Only the last patient seems to correspond to a VGAM. Most subsequent authors used the same generic name, VGAM, for very different entities. Failure to recognize the true nature of the lesion resulted in imprecise anatomical and natural history descriptions.

Raybaud et al. (23) were the first to recognize that the ectatic vein in VGAM was, in fact, the median vein of the prosencephalon, the embryonic precursor of the vein of Galen itself. A complete pathological specimen of a neonatal case of true VGAM was analyzed and illustrated by Landrieu in the late 1980s (15), supporting the findings of Raybaud et al. We appreciated the dural sinus abnormalities (17) and persistent alternative embryonic routes of the deep venous drainage in this condition (16). From then on, the vein of Galen malformation was recognized as an embryonic choroid plexus vascular malformation.

Reports of endovascular treatment of VGAM in the literature, although emphasizing technical solutions, often failed to provide satisfactory midterm results (7, 9, 14, 20); mental retardation in these patients was seldom mentioned or tested. Unnecessary premature interventions have also interfered with the quality of the results. Instead of dealing with the difficulty of establishing satisfactory patient selection criteria, these reports merely approached the disease from a purely technical viewpoint. In certain reports, anatomic exclusion of lesions was considered a technical success, even when the child died shortly after treatment. To focus the therapeutic challenge on a strictly morphological goal overlooks the fundamental aspects of neonatal and infant anatomy and fluid physiology (1, 12, 26).

During the past 20 years, our approach to VGAM has been a different one, which we outline in this article and which is based on our experience with 317 patients with VGAM who were studied in the Bicêtre Hospital between October 1981 and October 2002 (*Table 1*). Of these, a total of 233 patients were treated with endovascular embolization; 216 patients were treated in Bicêtre, whereas 17 were embolized elsewhere by other teams after consultation (*Table 2*). The decision for therapeutic abstention was made in 67 patients for a variety of reasons (*Table 3*). We consider our group of patients to be homogeneous because the neuroradiological assessment, technical principles, and perioperative clinical management have been similar during the past 20 years and were carried out by the same group of physicians. Our primary therapeutic objective is to preserve normal development without neurological deficit. To achieve these clinical objectives, we have chosen, since 1981, transarterial embolization using glue (*n*-butylcyanoacrylate) as the embolic agent. The following observations were derived from this experience.

TABLE 1. Characteristics of patients with vein of Galen aneurysmal malformation, 1981–2002

Age	At diagnosis (mo)	At first consultation (mo)
Fetus	93 (29.3%)	18 (5.7%)
Neonates (<1 mo)	119 (37.5%)	122 (38.5%)
Infants (>1 mo and <2 yr)	82 (25.9%)	125 (39.4%)
Children (2–16 yr)	23 (7.3%)	52 (16.4%)
Total	317	317

TABLE 2. Therapeutic decision and proposed treatment for patients with vein of Galen aneurysmal malformation

	Embolization	Abstention	Lost to follow-up	Total
Neonates	88 (5)	45	7	140
Infants	103 (8)	16	6	125
Children	42 (4)	6	4	52
Total	233 (17) 73.5%	67 (21.1%)	17 (5.4%)	317

ANGIOARCHITECTURE OF VGAM

The VGAM involves the choroidal fissure and extends from the interventricular foramen rostrally to the atrium laterally (18). The arterial supply involves the choroidal arteries; it may also receive a significant contribution from the subependymal network originating from the posterior circle of Willis. These arteries should be differentiated from transmesencephalic ones (their involvement, in fact, would exclude the diagnosis

TABLE 3. Reasons for therapeutic abstention

Reason	No. (%)
Neonates	
Therapeutic abstention	45
Encephalomalacia	25 (56%)
Neonatal score <8[a]	17 (38%)
Therapeutic interruption of pregnancy	3 (6%)
Infants	
Therapeutic abstention	16
Encephalomalacia	9 (56%)
Technical failure	1 (6%)
Spontaneous occlusion	6 (38%)
Children	
Therapeutic abstention	6
Bicêtre admission Score 1	3 (50%)
Surgery	1 (17%)
Spontaneous occlusion	2 (33%)

Score 8, four patients; Score 7, six patients; Score 6, three patients; Score 5, four patients. For further description of the neonatal score, refer to *Table 4*.

of VGAM and indicate a tectal AVM). Very rarely, thalamoperforating arteries are recruited. Subependymal and transcerebral contributions are accessory in the supply to the shunt, possibly created by the sump effect of the venous drainage. They usually disappear after occlusion of the most prominent shunts. The persistent limbic arterial arch, which bridges the cortical branch of the anterior choroidal artery initially and the posterior cerebral artery secondarily with the pericallosal artery, is seen in nearly half of the neonatal patients (*Fig. 1*). The limbic arterial arch on each side can anastomose and may fuse on the midline in the supracallosal region. The circle regresses after obliteration of the VGAM by embolization.

The nidus of the lesion is located in the midline and often receives a bilateral, and usually symmetrical, supply. In general terms, two types of angioarchitecture are encountered: choroidal and mural. The former corresponds to a very primitive condition, with contribution from all the choroidal arteries and an interposed network before opening into the large venous pouch (*Fig. 2*). This type is encountered in most neonates with low clinical scores. The latter type corresponds to direct AV fistulas within the wall of the median vein of the prosencephalon (*Fig. 3*). These fistulas can be single or, more often, multiple. The mural form is better tolerated, is, therefore, encountered more often in infants who do not experience cardiac symptoms and who feature higher clinical scores, as outlined below.

The venous drainage of the VGAM is toward the dilated median vein of the prosencephalon. No communication exists with the deep venous system. Thalamostriate veins open into the posterior and inferior thalamic veins, as occurs normally during the third month in utero. They secondarily join either the anterior confluence or, more often, a subtemporal vein or lateral mesencephalic vein, demonstrating a typical ε-shape on the lateral angiogram (*Fig. 4*). The straight sinus is absent in almost all patients. Falcine dural channels drain the pouch toward the posterior third of the superior sagittal sinus, which also happens to be where granulations are expected to appear first. Other embryonic sinuses persist, such as the occipital and marginal sinuses. The appearance of the remainder of the venous system is difficult to predict. The torcular is often dilated in relation to the flow and turbulence exiting from the falcine or straight sinus. A few months after birth, the cavernous sinus matures and captures the sylvian veins to offer the brain a potential route of drainage through the orbit, pterygoid plexus, or inferior petrosal sinus (*Fig. 5*). Drainage of the cerebral veins into unusual channels may take place, apparently without significant functional implications. The plasticity of the venous system in these instances is remarkable. It changes with the spontaneous modification of the hemodynamics and the influence on growth and maturation induced by the disease, and, eventually, treatment undertaken. It is clear that the timing of interference with the anatomic continuum is as important as the extent of the corrections proposed in the treatment of these lesions (22).

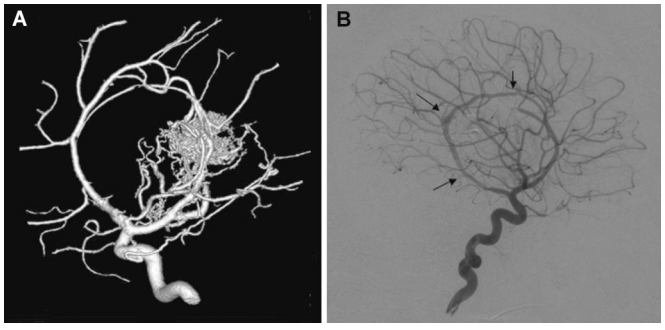

FIGURE 1. *Persistent limbic arch.* A, *three-dimensional aspect of a persistent limbic arch in a lateral and slightly anterior oblique view. Note the choroidal and subependymal feeders of the VGAM.* B, *carotid injection lateral projection after complete exclusion using glue embolization. The limbic arch can be well perceived with a communication between the posterior cerebral artery and the anterior cerebral artery via the pericallosal artery* (arrows).

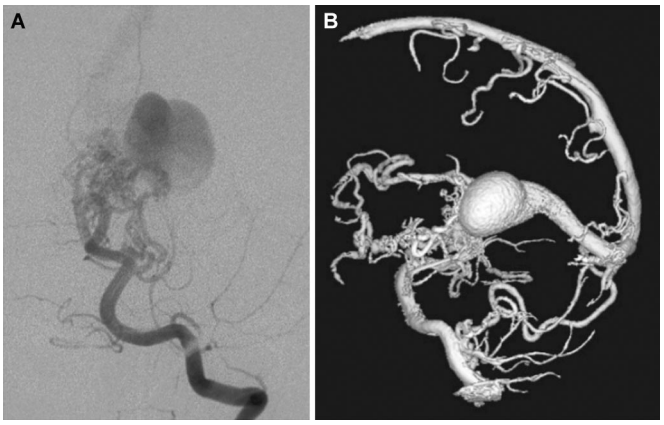

FIGURE 2. *Choroidal VGAM. Vertebral injection in frontal projection* (A) *and three-dimensional reconstructed image* (B) *demonstrating multiple choroidal feeders forming a nidus anterior to the venous pouch. This venous pouch corresponds to the dilated median vein of the prosencephalon, which is the precursor of the vein of Galen.*

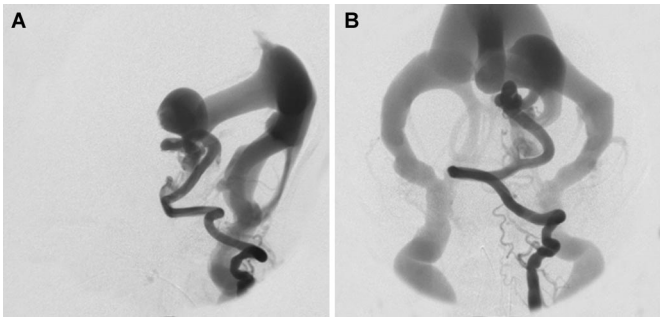

FIGURE 3. *Mural VGAM. Vertebral injections in lateral* (A) *and frontal* (B) *projections. In comparison with choroidal VGAMs, there is a direct arteriovenous fistula within the wall of the venous pouch.*

NATURAL HISTORY OF VGAM

The natural history of VGAM is difficult to discern from reports documented in the literature (13). Much of the so-

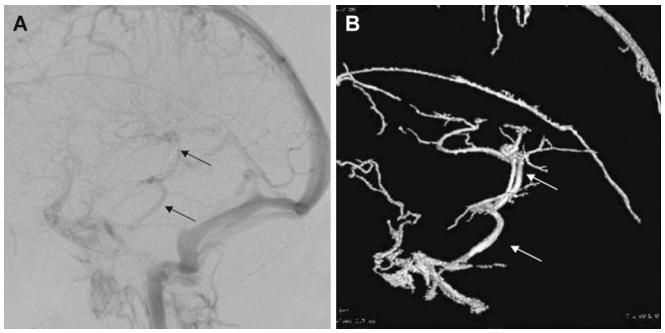

FIGURE 4. *Late venous phase of vertebral angiogram (*A*) and three-dimensional angiographic (*B*) aspect demonstrating the ε-shaped deep venous drainage into the superior petrosal sinus (*arrows*). Because there is no vein of Galen, the deep venous system has to find an alternate route to drain. Thalamostriate veins open into the posterior and inferior thalamic veins, which secondarily join a subtemporal or lateral mesencephalic vein, which then join the superior petrosal sinus, demonstrating a typical epsilon shape on the lateral angiogram.*

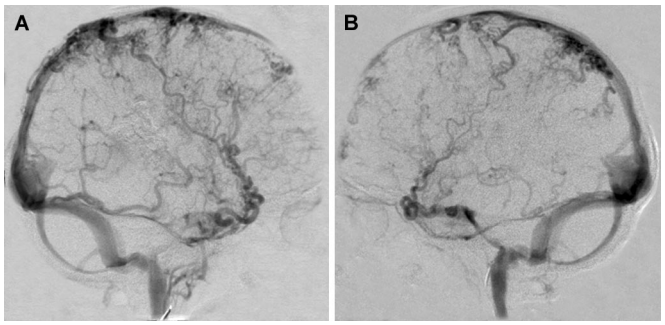

FIGURE 5. A *and* B*, angiograms showing bilateral carotid injections in the lateral projection. There is bilateral cavernous sinus drainage and a phlebitic aspect of the cortical veins, despite complete exclusion of the VGAM.*

called natural history of surviving children comes from case series that include patients who had undergone shunting procedures. The onset of seizures traditionally described in the late phase of VGAM reflects this evolution in babies who underwent shunting. Most neurological symptoms and hemorrhages reported in the literature were mistakenly diagnosed VGAM or are the result of changes in angioarchitecture, which, in turn, altered the consequences of the initial lesion. Endovascular management of this population has given us a chance to observe the anatomical and clinical evolution under nonsurgical circumstances.

Through our management of VGAM patients, the predictability of certain evolutions and the various clinical tools developed over the years have helped us to determine the optimal timing for treatment (therapeutic window). We have chosen a diagrammatic presentation of the natural history of VGAM to highlight the path followed by each individual (*Fig. 6*). As soon as previous stages have been identified, the subsequent ones are more easily anticipated. The therapeutic window outlines the optimal moment for the endovascular approach. It has become the objective of our decision regarding therapeutic timing and points to the therapeutic goals to be achieved. To achieve normal cerebral development does not require, in all cases, rapid morphological disappearance of the AV shunt or rapid shrinkage of the ectasia. To reach our objectives, we chose transarterial embolization using the femoral approach with glue (*n*-butylcyanoacrylate) as the primary embolic agent. This method has proven to offer reliable and predictable results. In the following paragraphs, we first focus on the management of VGAM in the neonate, followed by the management of this disease in infants and children, because the specific complications are different for these age groups, as outlined below.

MANAGEMENT OF VGAM

Neonates

Antenatal diagnosis is not, by itself, an indication for termination of pregnancy, early delivery, or Caesarian delivery at term. There are only two antenatal manifestations that have shown prognostic value and represent an indication for abortion: in utero cardiac failure and cerebral damage. These findings are associated with severe, irreversible multiorgan failure at birth (11, 24).

The idea that a neonate with severe multiorgan failure would do well if the VGAM was to be excluded is wrong; there is evidence in the literature that, in neonates who have undergone properly performed emergency embolization, the neurological outcome was disastrous despite apparently normal pretherapeutic brain imaging. This emphasizes the importance of a thorough analysis to best predict the degree of cerebral tissue impairment not evident on imaging. We are aware of the difficulty in making these decisions, and this represents the basis and purpose of our VGAM neonatal score (*Table 4*).

When the diagnosis of VGAM is suspected clinically, a pretherapeutic evaluation should include the following information: 1) clinical evaluation of the baby, including the weight and head circumference; 2) evaluation of renal and liver function; 3) transfontanellar ultrasound to evaluate for encephalomalacia; 4) cardiac ultrasound to assess cardiac tolerance and any associated cardiac malformation that may require specific treatment; 5) magnetic resonance imaging to provide information on lesion morphological features (the diagnosis of a cerebral AVM at this age would have completely different therapeutic consequences) and the status of myelination; and 6) electroencephalogram only if the baby is in an intensive care unit (ICU), intubated, and sedated. Angiography in the neonatal workup is not indicated. Only if embolization is contemplated should angiography be performed at the same time. Management decisions follow a strict protocol based on the neonatal score derived from the above information. The specific neonatal score documents the significant nonneurological manifestations in this age group in addition to assessing the gross neurological status. According to our experience, a score

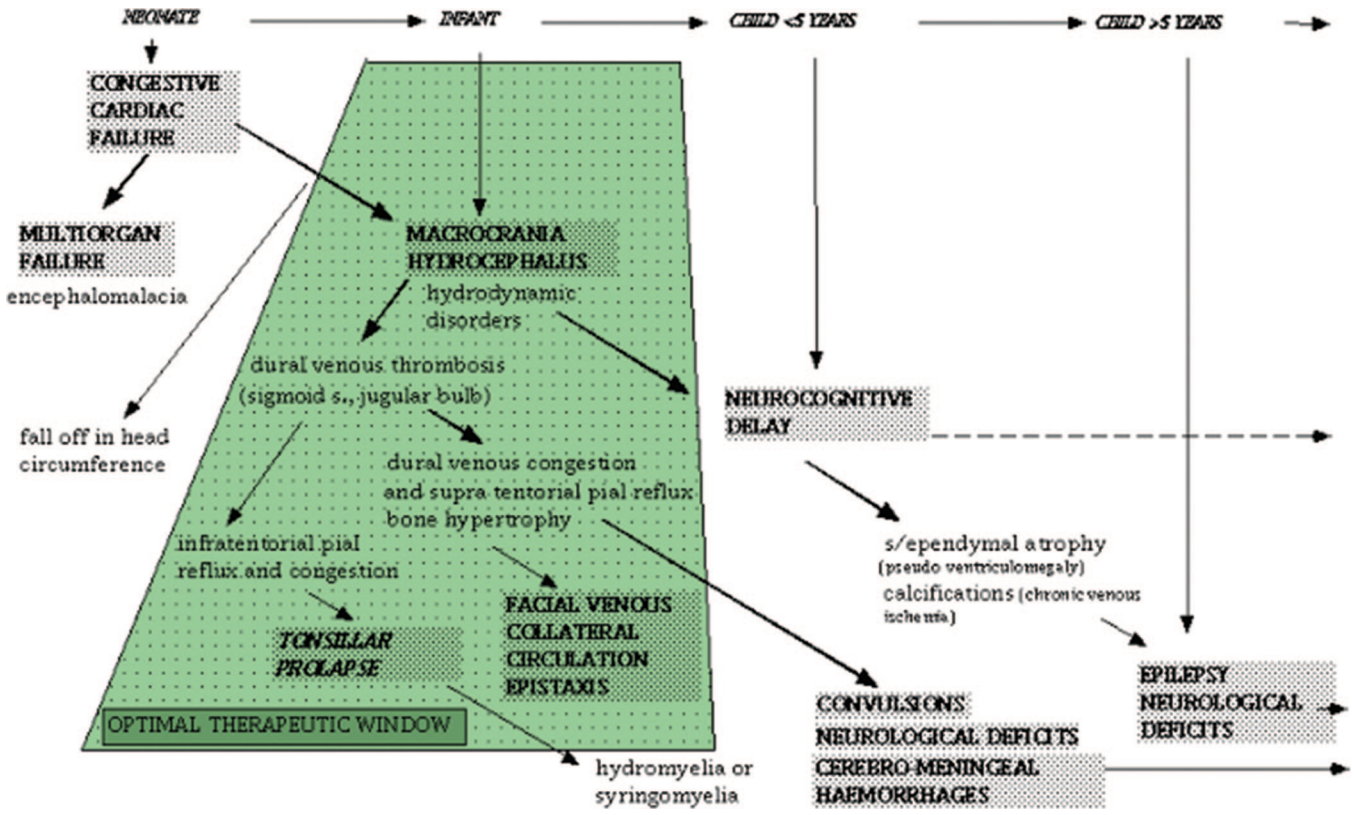

FIGURE 6. *Diagram illustrating the natural history of VGAMs over time. Note that the optimal therapeutic window is in infancy, typically at approximately 5 months of age (*from, *Lasjaunias P: Vascular diseases in neonates, infants and children. Interventional Neuroradiology Management. Berlin, Springer, 1997 [15]).*

of less than eight out of 21 results in a decision not to treat; a score of between eight and 12 out of 21 entails emergency endovascular intervention; a score of more than 12 out of 21 leads to the decision for medical management until the child is at least 5 months of age, providing there is no failure to thrive. At such a time, a decision is made to proceed with endovascular treatment no matter what the symptoms are. In our experience, angiography and treatment at 5 months has proven to balance best the maximum efficacy of embolization against the minimum risk of cerebral maturation delay.

In neonates, the immediate goal is not only to restore a satisfactory systemic physiology and to gain time, but also to recreate the conditions enabling further maturation of the vascular systems. It is apparent that the score used during the first few days of life varies from one day to the next, depending on the response to medical treatment. Failure to observe a response to ICU management (or stagnation) leads to early embolization at neonatal age. The end point of partial embolization is usually the reduction of one-third to half of the AV shunt to expect a significant systemic impact. The role of the pediatric intensive care physician is crucial at the neonatal age in the management of VGAM. We rely heavily on their analysis of the clinical situation and their therapeutic choices.

Infants and Children

In infants and children, the immediate goal is to preserve the hydrovenous equilibrium, as will be outlined later, to preserve the normal brain development, and to exclude the lesion. Our concern in patients of this age is to anticipate the natural history to avoid ventricular shunting. Premature attempts to exclude an asymptomatic lesion or taking significant technical risks to exclude, in one session, a VGAM that presents no immediate cerebral danger should not be encouraged. Conversely, a decision not to treat on the assumption that an asymptomatic lesion is well tolerated is dangerous. In children referred late with already impaired functions or severe retardation, we have attempted to improve their quality of life. Under these circumstances, endovascular treatment has proven to achieve satisfactory results, even with incomplete exclusion of the lesion. Endovascular end points are directed to the draining pattern of the brain.

Spontaneous thrombosis of the VGAM, although often referred to by those who oppose interventional treatment, is, in fact, rare. In our series, eight out of 317 patients (2.5%) experienced spontaneous thrombosis, but only half of them were neurologically normal. This is below what proper treatment can now accomplish. In addition, thrombosis is mostly unpredictable and tends to occur late, when cerebral damage may

TABLE 4. Bicêtre neonatal evaluation score[a]

Points	Cardiac function	Cerebral function	Respiratory function	Hepatic function	Renal function
5	Normal	Normal	Normal	—	—
4	Overload, no medical treatment	Subclinical, isolated EEG abnormalities	Tachypnea, finishes bottle	—	—
3	Failure; stable with medical treatment	Nonconvulsive intermittent neurologic signs	Tachypnea, does not finish bottle	No hepatomegaly, normal hepatic function	Normal
2	Failure; not stable with medical treatment	Isolated convulsion	Assisted ventilation, normal saturation $FIO_2 < 25\%$	Hepatomegaly, normal hepatic function	Transient anuria
1	Ventilation necessary	Seizures	Assisted ventilation, normal saturation $FIO_2 > 25\%$	Moderate or transient hepatic insufficiency	Unstable diuresis with treatment
0	Resistant to medical therapy	Permanent neurological signs	Assisted ventilation, desaturation	Abnormal coagulation, elevated enzymes	Anuria

[a] EEG, electroencephalogram; FIO_2, fractional inspired oxygen. Maximal score = 5 (cardiac) + 5 (cerebral) + 5 (respiratory) + 3 (hepatic) + 3 (renal) = 21.

already be irreversible. Spontaneous thrombosis should not be considered a favorable outcome. Expecting it to occur does not represent a therapeutic strategy and now constitutes an unacceptable choice.

Developmental delay is part of the natural history of untreated VGAM. Careful evaluation of neurocognitive performances shows that most children with macrocrania present some degree of mental retardation. In view of the poor prognosis of the disease, specialists and parents tend to accept as normal a child with mild retardation (up to 20% of normal for the chronological age). Such delay allows the child to attend a normal school, albeit with support. To measure the neurocognitive status during the follow-up period, the pediatric neurologists in Bicêtre have recommended the Denver test and the Brunet-Lezine test, which are easy to perform and are reproducible (10). However, one should interpret the developmental status of a child at one point in time with caution. It is more important to look at the rate of development over time and to interpret the results together with what is known about the child's background.

The specific evaluation score in neonates cannot be used for clinical follow-up in infants. We have chosen a more global clinical initial outcome assessment (*Table 5*). Although this score may lack certain details, it has been sufficient to observe the evolution in a given child. With this score, we have been able to rationalize and compare our decisions and to verify their stability over the past 20 years.

PROBLEMS IN THE MANAGEMENT OF VGAM

Cardiac Manifestations

Cardiac manifestations have been reviewed for neonates (11) and antenatally diagnosed VGAM (24). In contrast to the cardiac failure observed in large hemangiomas, where they occur at infancy at the proliferative stage of the disease, the congestive cardiac failure (CCF) in VGAM can be present during the neonatal period.

In most cases, there is a brief period of stabilization, after which the CCF worsens during the first 3 days of life, then stabilizes again and improves with appropriate medical management. Severe CCF in neonates requiring mechanical ventilation usually is associated with poor outcome (6). None of the babies referred to us developed de novo cardiac failure after the third week of life. However, cardiac function can decom-

TABLE 5. Bicêtre admission and outcome score[a]

Score	Condition
5	Normal (N)
4	Minimal nonneurological symptoms, not treated (MS), and/or asymptomatic enlargement of the cardiac silhouette
3	Transient neurological symptoms, not treated (TNS), and/or asymptomatic cardiac overload under treatment
2	Permanent minor neurological symptoms, mental retardation of up to 20%, nonpermanent neurological symptoms under treatment (MNS), normal school with support, and/or cardiac failure stabilized with treatment
1	Severe neurological symptoms, mental retardation of more than 20% (SNS), specialized school and/or cardiac failure unstable despite treatment
0	Death (D)

[a] Does not apply to neonates.

pensate at 3 weeks or can recur later after lung infections or other concurrent diseases. CCF never constitutes the presenting symptom in infants, nor does it worsen at that age if already present. The degree of failure is variable from one child to another, but seems to be independent of the characteristics of the shunt. Some high-flow lesions are well tolerated, whereas apparently small shunts may lead to multiorgan failure.

Renal and hepatic damage may aggravate CCF further, and their function can be impaired transiently or can become rapidly unstable despite intensive medical care. Severe forms of CCF are associated with persistence of the fetal type of circulation. Septal defects and patent ductus arteriosus often are noted during cardiac ultrasound; they should not be considered associated cardiac malformations. Like most of the disorders encountered under these circumstances, they usually resolve spontaneously or after endovascular management of the AV shunt itself. They should be followed with special attention if embolization is not performed early, because they may induce a failure to thrive condition. Coagulation disorders have not been noted unless there is associated hepatic failure.

Macrocrania and Hydrocephalus

After CCF, the next phase in the evolution of the disease is marked by hydrovenous disorders. As opposed to CCF, hydrodynamic disorders can manifest themselves in fetuses, neonates, and infants. They constitute the primary revealing factor at infant age if the diagnosis has not been made previously. They result from the abnormal hemodynamic conditions present at the torcular venous sinus confluence, the posterior convergence of the venous drainage of the brain, and the immaturity of the granulation system (25). Hydrocephalus and intracranial hypertension occur. During infancy, persistence of the situation leads to clinical manifestations including irritability, alteration of the conscious level and neurological status, stagnation of the head circumference, decrease in brain volume, and developmental delay.

For many years and even now, the mechanical compression of the mesencephalic aqueduct was and is sometimes still considered to be the primary cause of the hydrodynamic disorders at this age. In reality, the aqueduct is patent in almost all patients (26). The water dysfunction combines an intracerebral (intrinsic) retention with an increase in the cerebrospinal fluid (extrinsic) volume. In VGAM, the venous pressure is often very high. Mickle and Quisling (20) reported that pressures were more than 30 ml H_2O, and Quisling and Mickle (21) reported that pressures were more than 50 ml H_2O with a 1:5 ratio between the intraventricular pressure and superior sagittal sinus pressure. This explains the difficulty of the cerebrospinal fluid in entering the dural sinus compartment from the subarachnoid space. Ventricular shunting does not deal with the problem, but only transiently resolves an emergency situation at the ventricular level. It creates a cerebripetal flow along the medullary veins opposite the natural and necessary cerebrifugal one. Deficits, seizures, or hemorrhages after ventricular shunting have been well documented.

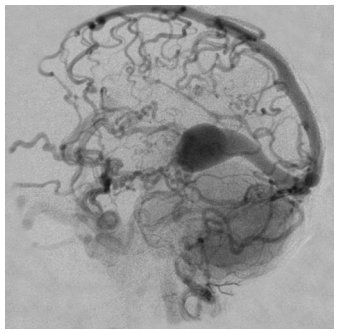

FIGURE 7. *Angiogram showing vertebral injection in the venous phase. There is reflux into the superior sagittal sinus and extensive pial venous reflux.*

Endovascular management of the same situations today has shown that, even with partial treatment of the AV shunt, these hydrovenous disorders do not occur unless additional factors intervene to change the angioarchitecture of the lesion. At the infant stage, we recommend careful clinical assessment for the development of macrocrania before endovascular treatment. If the increase in head circumference seems too rapid, if the clinical follow-up period demonstrates a significant developmental delay, or if there is preclinical magnetic resonance imaging evidence of intraventricular hyperpressure, urgent embolization should be carried out and ventricular shunting should be avoided. If, however, the child is referred too late with clinically detectable increased intracranial pressure and ventricular enlargement, clinical improvement after emergency embolization is usually insufficient even if the hemodynamic result is excellent, and surgical ventricular drainage may have to be performed. With such a treatment sequence, morbidity from the shunting procedure is lower. In our experience, after additional embolization and clamp tests, the ventricular drain can often be removed after a few months. Today, endoscopic ventriculostomy offers an acceptable alternative to ventricular drainage after embolization in patients with symptomatic hydrodynamic disorders. The reversed strategy, shunting followed by embolization is, without doubt, the worst option, unless endovascular treatment is not available.

Dural Sinus Occlusion and Supratentorial and Infratentorial Pial Reflux

Dural sinus occlusion and supratentorial and infratentorial pial reflux correspond to a dysmaturation of the jugular bulbs. With persistence of the occipital and marginal sinuses in VGAM, most of the efferent torcular flow is directed medially and does not trigger development of the sigmoid sinuses, which remain distally thin. When the embryonic sinuses finally disappear, the sigmoid sinuses will have occluded fully distally, even though the extracranial jugular veins are still patent and receive the inferior petrosal sinuses.

Thrombosis is usually progressive and may develop without symptoms over a long period. The development of jugular bulb stenosis protects the heart, but exposes the brain. Not only does it interfere with water resorption, it also creates congestion within the cerebral veins. Symptoms will depend on the timing between the upstream effects of the stenosis and the capture of the sylvian veins by the cavernous sinus. The overall prognosis of an untreated VGAM is, therefore, largely

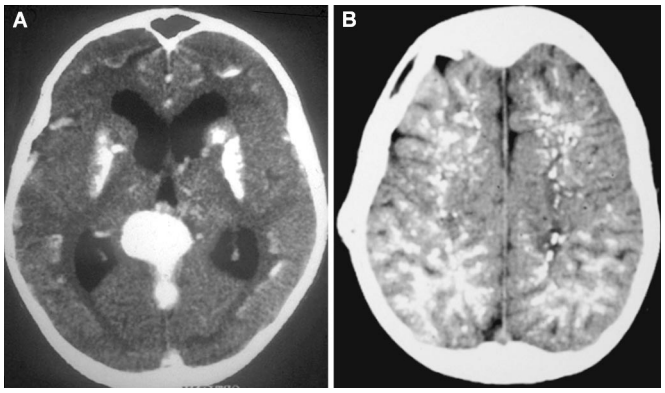

FIGURE 8. A *and* B, *axial computed tomographic scans showing diffuse intracranial calcifications in two patients with VGAM who were referred late for treatment. These calcifications are the results of a longstanding hydrovenous disorder.*

dependent on the patency of the jugular bulbs. The situation is particularly unstable if the stenosis is complete and bilateral. The risk of hemorrhage and venous infarction is high because there is significant pial reflux and the VGAM has become an AVM draining into the pial venous system (*Fig. 7*). Under these circumstances, emergency endovascular management should aim to balance the flow of the AV shunt to the capacity of the posterior outlets and functionally to disconnect the VGAM drainage from the normal cerebral one.

The infratentorial consequence of dural sinus occlusion is tonsillar prolapse. It develops secondary to congestion of the cerebellar pial veins and does not occur in the neonate. It may disappear with correction of the AV shunt, provided that the prolapse has not existed for a long time. The prolapse is not related to global intracranial hypertension. Therefore, its presence does not call for emergency ventricular shunting, but rather embolization to diminish the drainage of the VGAM into the overall venous pathways.

Late Sequelae

Seizures and mental retardation are the main symptoms seen if the correction of the AV shunt was not carried out in time, and they often occur in children who were referred late or after ventricular shunting. Cerebral morphological sequelae include calcifications (*Fig. 8*), subependymal atrophy (pseudoventriculomegaly), and the stigmata of previous acute accidents with cortical and subcortical atrophy. It should be noted that in VGAM with patent sinuses, as opposed to cerebral AVMs, local or regional melting-brain phenomena are not encountered, because pial and, therefore, subpial reflux does not occur (15). The insult to the brain is, therefore, a slow and permanent one, as testified by the calcifications. The calcifications, however, do not have a predictive value for neurological outcome in a treated VGAM. They rarely produce abnormal movement disorders that are seen most often with more posteriorly located damage. There is no real link between the images and the clinical evolution of the child. This highlights the inability of imaging methods to appreciate the true substrate of neurological handicap in all instances.

It is important to note that the clinical outcome of children with patent sinuses is relatively good compared with those with secondarily occluded sinuses. This is probably the single most clinically relevant observation to be derived from angioarchitectural analysis at infant age.

TABLE 6. Technical aspects of vein of Galen aneurysmal malformation embolization at Bicêtre

General anesthesia
Femoral puncture with 20-gauge Teflon needle; 4-French sheath
6 ml/kg contrast (diluted at 50% for fluoroscopic control)
4-French diagnostic catheters
One to three angiographic runs in neonates, 3 ml/s, total 6 ml (vertebral Towne's projection or biplane if possible), followed by bilateral internal carotid artery lateral projection. If one posterior cerebral artery is not seen on the first run, choose the corresponding internal carotid artery side as second run, and the opposite one for expected cerebral venous information.
Microcatheters: Baltaci P. 1.8 (Balt, Montmorency, France); if slow flow feeders, Magic 1.8 (Balt, Montmorency, France)
Guidewires (if necessary): 0.012 (Terumo, Tokyo, Japan); Mirage 0.008 (MTI, Irvine, CA)
Pure *n*-butylcyanoacrylate + Tantalum powder + Lipiodol (in slow flow shunts)
Intraoperative blood pressure: 70 mm Hg systolic if possible during high flow fistula embolization
No additional arterial line
No heparin
Alternate side for femoral puncture at each session
Usual length of procedure, 45 min; maximum length of procedure, 2 h
Bladder evacuation (if necessary) after the procedure before removing the sheath
Recovery room after procedure (few h)
Pediatric neurology ward (after recovery room)
Pediatric intensive care unit (24 h asleep) if occlusion complete or almost complete (secondary thrombosis expected)
No low blood pressure in intensive care unit, but controlled blood pressure

TABLE 7. Therapeutic results in the embolized group, 1981–2002[a]

	Neonates	Infants	Children	Total
Neurologically normal (BOS 3–5)	36.4% (4/11)	78.9% (112/142)	67.5% (27/40)	74% (143/193)
Moderate retardation (BOS 2)	54.5% (6/11)	11.3% (16/142)	20% (8/40)	15.6% (30/193)
Severe retardation (BOS 1)	9.1% (1/11)	9.8% (14/142)	12.5% (5/40)	10.4% (20/193)
Death despite or because of embolization	52% (12/23)	7.2% (11/153)	0% (0/40)	10.6% (23/216)

[a] BOS, Bicêtre outcome score. Total of 216 patients, 193 surviving. Note that nearly 50% of neonates referred for management died. Many of these represent earlier cases that today would be scored below eight and, thus, would fall into the nontreatment group.

TABLE 8. Complications of embolization procedures, 1981–2002

Complication	No. of complications/total[a] (%)
Transient neurological disability	3/193 (1.6%)
Permanent neurological disability	4/193 (2.1%)
Nonneurological complication (nondisabling)	13/193 (6.7%)
Death related to embolization[b]	3/196 (1.5%)
Hemorrhage[c]	11/196 (5.6%)

[a] One hundred ninety-three surviving patients.
[b] Three out of 196 patients.
[c] During or within 2 weeks after embolization. Clinical eloquence included.

RESULTS

Technical Remarks

The technical aspects of VGAM embolization at Bicêtre are outlined in *Table 6*. We use the transarterial femoral approach to deliver glue in situ as the first treatment method in every case. In rare cases, we have had to perform femoral puncture with the aid of Doppler ultrasound. The smallest baby who was embolized weighed 2.3 kg. No surgical exposure of the femoral artery or umbilical vein approach has been necessary in our experience. We try to obtain complete exclusion in the fewest numbers of sessions, but this goal is primarily guided by the clinical stability observed in the infant and the angioarchitecture of the cerebral vasculature.

In our series of embolized patients, with a total of 502 sessions (an average of 2.4 sessions per child, ranging from one to five sessions), the venous route was used in only eight patients when it became impossible to achieve effective embolization by the arterial route, or specifically to disconnect a sinus reflux to protect the brain. In each case, the children were in a clinical condition that necessitated immediate treatment; no attempt was made to exclude the VGAM completely considering the hemorrhagic risk related to the sudden congestion of nonvisualized subependymal anastomoses.

Whenever the occlusion of the VGAM is complete or almost complete, neonates and infants are kept under general anesthesia for the next 24 hours in the ICU. This protocol has been followed since the beginning of our experience to avoid the unnecessary agitation of a baby awakening in the immediate postembolization period. Heparin and steroids are not used, and blood pressure is kept normal while the child is asleep in the ICU. Endovascular treatment sessions are arranged every 3 to 6 months, depending on the clinical status and response to the embolization.

Follow-up

We have not observed revascularization at later follow-up when angiographic evaluation results at 6 months to 1 year were completely normal. When slight hyperemia is demonstrated at 6 months, even without evidence of AV shunting, additional control angiograms are obtained 1 and 2 years later.

Total or nearly total obliteration (90–100% occlusion) of the lesion has been obtained in 55% of the children who were embolized in our series and a 50 to 90% occlusion rate has been obtained in 38.5% of patients, whereas only 6.2% of patients had an occlusion rate of less than 50%. In many instances, complete disappearance of the shunt is not achieved at the end of embolization. Some slow flow can still be demonstrated, but the remaining shunt represents less of a risk in comparison with the technical difficulty in completely obliterating it. We have not seen rupture of the VGAM under these circumstances.

During the follow-up period, all children are evaluated clinically by the referring physicians or the pediatric neurologists. Clinical assessment is based on neurocognitive examination using the Denver and Brunet-Leizine test. After treatment is completed, children are followed up with a clinical examination every year and magnetic resonance imaging every 2 years, because we have created a population of children who did not exist 20 years ago. This ongoing clinical follow-up period is mandatory in the pediatric population, because therapeutic success can be evaluated truly only when brain maturation is complete and functionally evaluated over time.

Clinical Results

In our series, 143 out of 193 surviving patients (74%) were neurologically normal on follow-up after embolization (*Table 7*). There were non-neurological complications related to the embolization procedure and the technical difficulty of injecting pure bucrylate glue in 13 out of 193 patients (6.7%). In this same group of treated patients, 2.1% experienced permanent neurological disability (*Table 8*).

Two children treated by the transvenous route after failure to achieve further embolization by the transarterial approach

sustained an intracerebral hemorrhage within a few hours after embolization. In both patients, occlusion of the venous outlet was complete and the remaining flow into the VGAM was reduced insufficiently. From the literature and in our own limited experience with the transtorcular approach, hemorrhage occurred in more than 10% of patients during the venous approach after coil deposition.

The mortality rate in our group of children was 10.6% (23 out of 216 patients). Many of these, especially the neonates, represent earlier cases that today would be scored below eight and, thus, would fall into the nontreatment group.

OTHER TECHNIQUES

Transvenous treatment of VGAM has been described (19). Reduction in arteriovenous shunting is achieved by packing the venous pouch with a variety of materials, including coils, balloons (19), and nylon (3). Transvenous dural sinus angioplasty and stenting have also been performed (4) in patients with progressive sigmoid sinus-jugular occlusion. The long-term results of these anecdotal dural sinus stenting procedures are unknown at this point. Transvenous occlusion of the venous pouch carries the risk of venous infarction and hemorrhage. Consumptive coagulopathy after transvenous treatment has also been reported (5). A number of centers use a combination of both transarterial and transvenous approaches, tailoring the technique according to the angioarchitecture of the lesion and response to previous treatment attempts.

Stereotactic radiotherapy has a limited role in the treatment of VGAM. The effectiveness is uncertain and the time required to achieve results is unacceptably long for the developing brain.

Arterial coiling has been performed in some rare favorable cases with single high-flow mural types. The fistulous point had been reached either through arterial or venous approach retrogradely. Transarterial balloon occlusion of the fistula's feeder was also advocated in the past; however, the lack of long-term clinical results, unreported failures, and complications supported our technical choices. The introduction of large coils in the venous pouch to slow down the flow so that glue may be used has also been proposed by others. However, series and clinical outcome are still missing.

It is likely that many technical approaches are applicable in the various situations faced in VGAM management. The purpose of this review, however, is to share the features interfering with the therapeutic goals per age group, the clinical challenges, as well as the results of these clinical decisions in a large personal series.

CONCLUSION

An understanding of the clinical and the anatomical and pathophysiological features of VGAM has reversed the former poor prognosis, as was indicated by Johnston et al. in 1987 (13); our data demonstrate that a majority of treated children survive and have a normal neurological development. Our level of understanding about the lesion allows us to predict most situations and remedy them by applying a strict evaluation protocol and working within the therapeutic window. Management of the patient is best adapted to the malformation itself. In this environment, pediatricians assist us with neurological assessment in neonates and young infants, whereas the neurosurgical and ICU team provide support whenever needed.

At the present time, patient selection remains the key in the management of this condition. Clinical outcome is of paramount importance. It is more important to restore normal growth conditions than a normal appearance, with our primary therapeutic objective being normal development in a child without neurological deficit. Our purpose in this review is to share 20 years of experience in the management of VGAM in Bicêtre. The main emphasis is on the clinical decision making and results obtained with the technique we use. The technical challenges faced and choices made to overcome them are secondary in the discussion. Most likely, different technical solutions can be brought to the treatment of this disease to ensure a normally growing child.

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CLASSIFICATION AND SURGICAL MANAGEMENT OF SPINAL ARTERIOVENOUS LESIONS: ARTERIOVENOUS FISTULAE AND ARTERIOVENOUS MALFORMATIONS

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OBJECTIVE: Preexisting spinal arteriovenous malformation nomenclature can be confusing. The aim of this article is to present a modified classification system for spinal arteriovenous lesions and to discuss its implications for microsurgical strategies.

METHODS: Based on the literature review of prior classifications as well as on the experience of the senior author (RFS), the authors delineate an anatomically and pathophysiologically based classification to facilitate the description and treatment of these uncommon entities.

RESULTS: Spinal arteriovenous lesions are composed of arteriovenous fistulae and malformations. These lesions are classified as extradural, extradural-intradural, or intradural. Intradural lesions are characterized further as ventral or dorsal fistulae or as intramedullary lesions. Intramedullary lesions are characterized as compact or diffuse. A new category, conus medullaris arteriovenous malformations, is described as a distinct entity.

CONCLUSION: This updated classification system eliminates confusion related to older nomenclature and is based on the anatomical and pathophysiological features of these lesions. When treating these lesions, the neurovascular team must collaborate closely with their microsurgical and endovascular colleagues. Finally, treatment should be individualized, depending on lesional angioarchitecture and the patient's clinical status.

KEY WORDS: Classification, Nomenclature, Spinal arteriovenous fistula, Spinal arteriovenous malformation, Surgical management

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Spinal arteriovenous lesions are a collection of disparate and diverse entities. Our understanding of their pathophysiology has evolved significantly over the past century. As a byproduct of our gradual understanding of these lesions, a cadre of nomenclature has developed over time. Unfortunately, this terminology has served mostly to confound rather than to facilitate accurate descriptions of spinal arteriovenous malformations (AVMs). Recently, anatomically based classifications that offer accurate descriptions have been developed.

In tandem with our understanding of the pathophysiology of spinal AVMs, our technical ability to treat these lesions, both microsurgically and endovascularly, has improved tremendously. This report describes the classification schemas of spinal AVMs, pointing out the recent trend toward anatomical nomenclature and the surgical strategies and techniques used in the practice of contemporary neurosurgery.

CLASSIFICATION OF ARTERIOVENOUS FISTULAE AND AVMS

Spetzler et al. (44) proposed a modified classification system for spinal arteriovenous lesions based on specific anatomical and pathophysiological factors. Descriptions are based on extradural or intradural, ventral, dorsal, or intramedullary locations of the lesions and on the presence of single or multiple feeding branches.

Extradural Arteriovenous Fistulae

Extradural arteriovenous fistulae (AVFs; *Fig. 1*), known as epidural fistulae in older nomenclature, represent an abnormal communication between an extradural arterial branch that usually arises from a branch of a radicular artery and an epidural venous plexus. This entity results in significant engorgement of the venous system, leading to subsequent com-

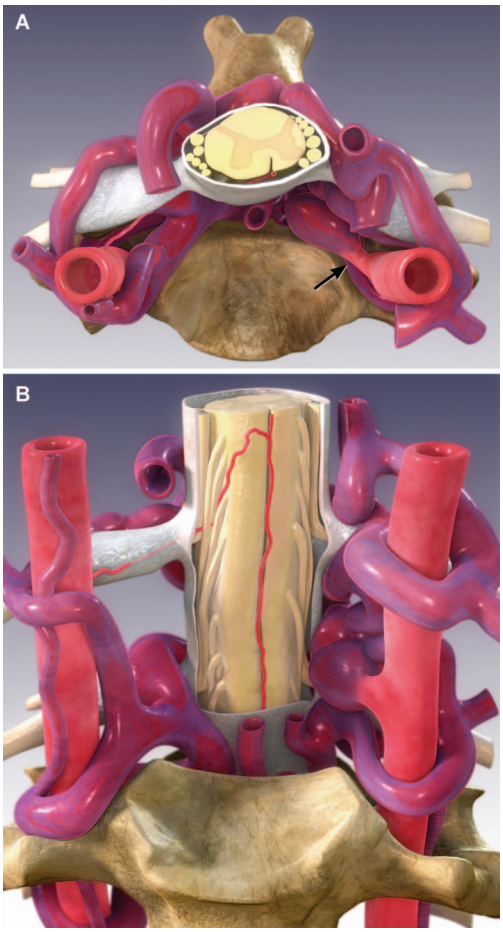

FIGURE 1. A, *axial illustration demonstrating an extradural AVF along a perforating branch of the left vertebral artery (*arrow*).* B, *illustration of the posterior view demonstrating that engorgement of epidural veins can produce symptomatic mass effect on adjacent nerve roots and spinal cord (*courtesy of *Barrow Neurological Institute, Phoenix, Arizona).*

pressive mass effect on adjacent nerve roots and spinal cord. Venous hypertension and vascular steal also may contribute to myelopathic symptoms.

Intradural Dorsal AVFs

Intradural dorsal AVFs (*Fig. 2*), which correlate with Type 1 dural AVFs, are composed of a radicular feeding artery that communicates abnormally with the venous system of the spinal cord at the dural sleeve of the nerve root. Inherent to the pathophysiology is obstruction of spinal cord venous outflow, which ostensibly contributes to the formation of the fistula. In turn, arterialization of the coronal venous plexus, venous hypertension, and myelopathy ensue.

Intradural Ventral AVF

Intradural ventral AVFs (*Fig. 3*) are ventral midline lesions located in the subarachnoid space. The fistulous site occurs between the anterior spinal artery (ASA) and an enlarged venous

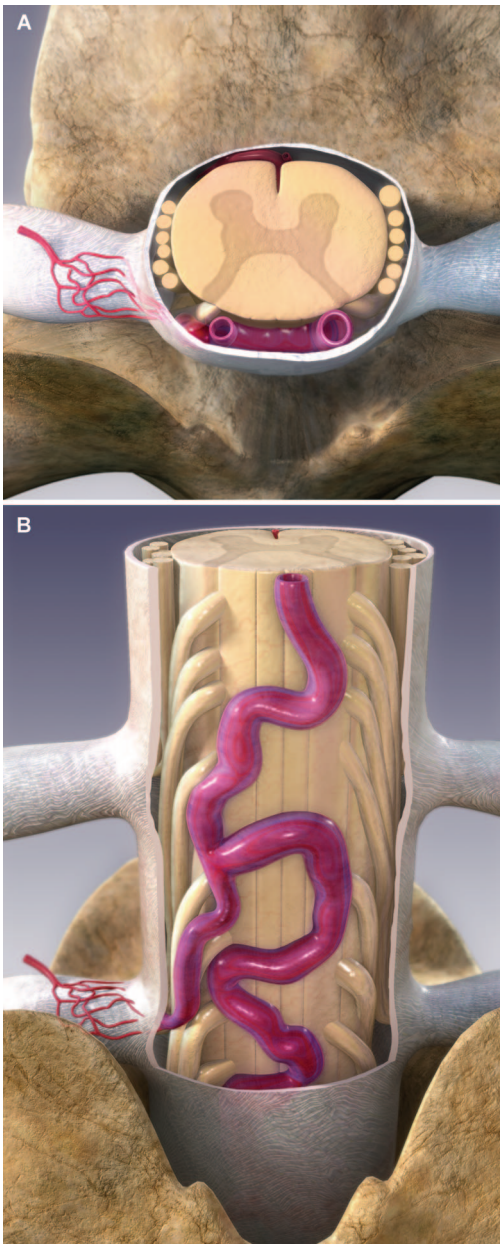

FIGURE 2. A, *axial illustration of an intradural dorsal AVF demonstrating an abnormal radicular feeding artery along the nerve root on the right. The glomerular network of tiny branches coalesces at the site of the fistula along the dural root sleeve.* B, *illustration of the posterior view demonstrating the dilatation of the coronal venous plexus. In addition to venous outflow obstruction (not shown), arterialization of these veins produces venous hypertension. Focal disruption of the point of the fistula by endovascular or microsurgical methods will obliterate the lesion (*courtesy of *Barrow Neurological Institute, Phoenix, Arizona).*

network. The lesions have been subclassified as Types A, B, and C (1). Type A intradural ventral AVFs are small and have a single feeder. The size of Type B lesions is intermediate. They have a major feeder from the ASA and minor feeders at the level of the

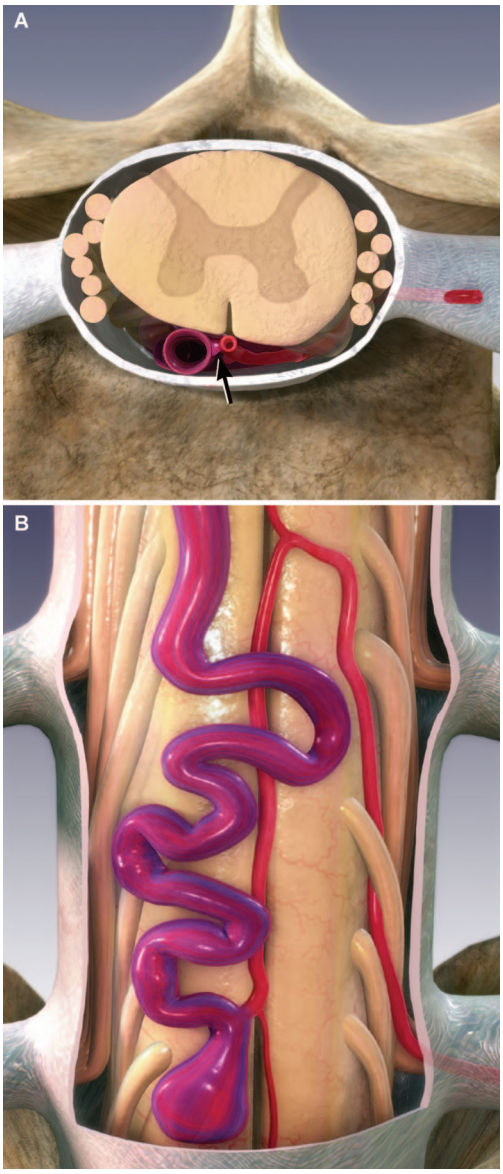

FIGURE 3. A, *axial illustration demonstrating an intradural ventral AVF, a midline lesion derived from a fistulous connection* (arrow) *between the anterior spinal artery and coronal venous plexus.* B, *illustration of the anterior view demonstrating the fistula along the anteroinferior aspect of the spinal cord. Proximal and distal to this Type A lesion, the course of the anterior spinal artery is normal* (courtesy of *Barrow Neurological Institute, Phoenix, Arizona).*

fistula. Type C lesions are giant. They are multipediculated and have massively dilated venous channels. Extraordinarily high flow through these lesions leads to the phenomenon of vascular steal from the intrinsic spinal cord arterial supply and to the sequelae of ischemic symptoms.

Extradural-Intradural AVM

Extradural-intradural AVMs (*Fig. 4*) correspond with juvenile or metameric AVMs. These formidable lesions are invested along a discrete somite level. Typically, they involve bone, muscle, skin, spinal canal, spinal cord, and nerve roots. Complete involvement of an AVM along an entire somite level has been described as Cobb's syndrome.

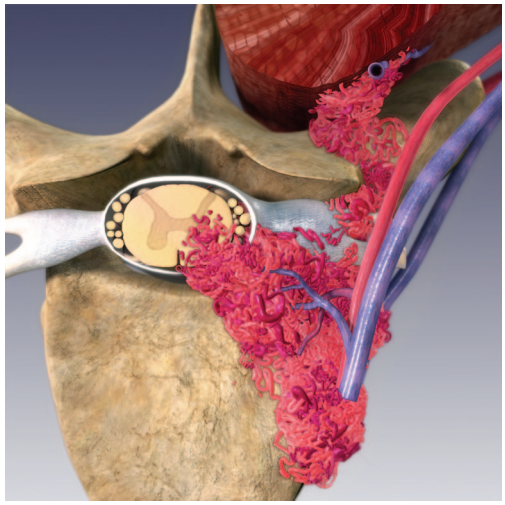

FIGURE 4. *Axial illustration demonstrating an extradural-intradural AVM. These treacherous lesions can encompass soft tissues, bone, spinal canal, spinal cord, and spinal nerve roots along an entire spinal level. Considerable involvement of multiple structures makes these entities extremely difficult to treat. Although cures have been reported, the primary goal of treatment is usually palliative* (courtesy of *Barrow Neurological Institute, Phoenix, Arizona).*

Intramedullary AVMs

Intramedullary AVMs are analogous to intracranial AVMs, located entirely in the spinal cord parenchyma. These lesions may have single or multiple feeding arteries from branches of the ASA and posterior spinal artery. They are classified further as compact or diffuse (*Figs. 5* and *6*), depending on the angioarchitecture of the nidus.

Conus Medullaris AVMs

Conus medullaris lesions (*Fig. 7*) occupy a separate category (44). Conus lesions typically exhibit multiple feeders from the ASA and posterior spinal artery with direct arteriovenous shunts and large dilated veins. The pathophysiology underlying neurological decline includes venous hypertension, ischemia, and mass effect from hugely dilated venous structures. Because the location and angioarchitecture of these lesions are unique, both upper and lower motor neuron symptoms can occur. Elimination of mass effect on descending nerve roots of the cauda equina can be associated with striking improvements.

DISCUSSION

Historical Perspective and Previous Classifications

In 1888, Gaupp (16) provided the earliest description of a spinal AVM. In 1910, Krause (25) reported the first surgically

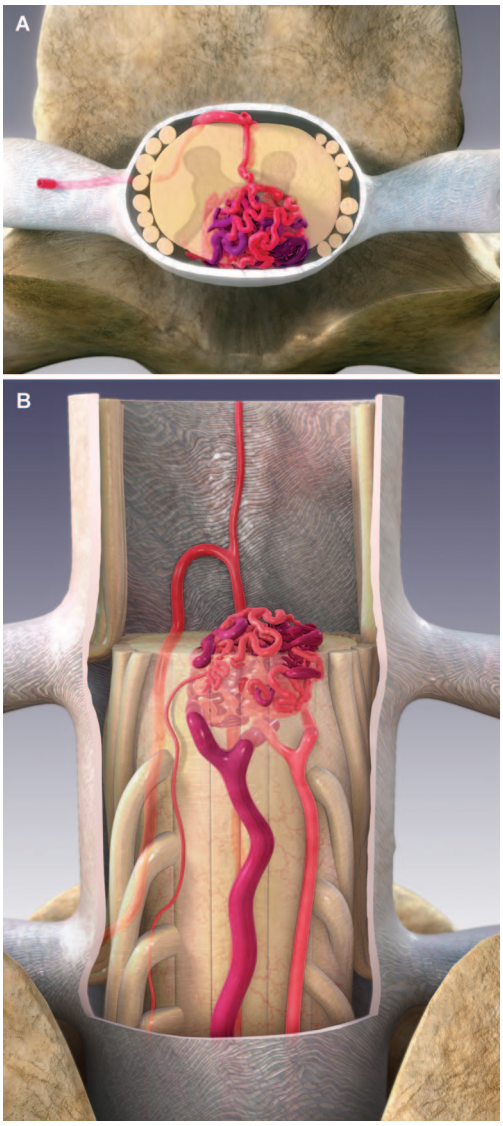

FIGURE 5. A, *axial illustration demonstrating a compact intramedullary AVM. In this figure, an arterial feeder from the anterior spinal artery is identified. Note the discrete, compact mass of the AVM.* B, *posterior view demonstrating additional feeding branches from the posterior spinal artery and reemphasizing the compact nature of this type of spinal AVM. Portions of the AVM are evident along the surface of the spinal cord. Surgical resection is the mainstay of treatment. Preoperative embolization is reserved for select cases only* (courtesy of *Barrow Neurological Institute, Phoenix, Arizona).*

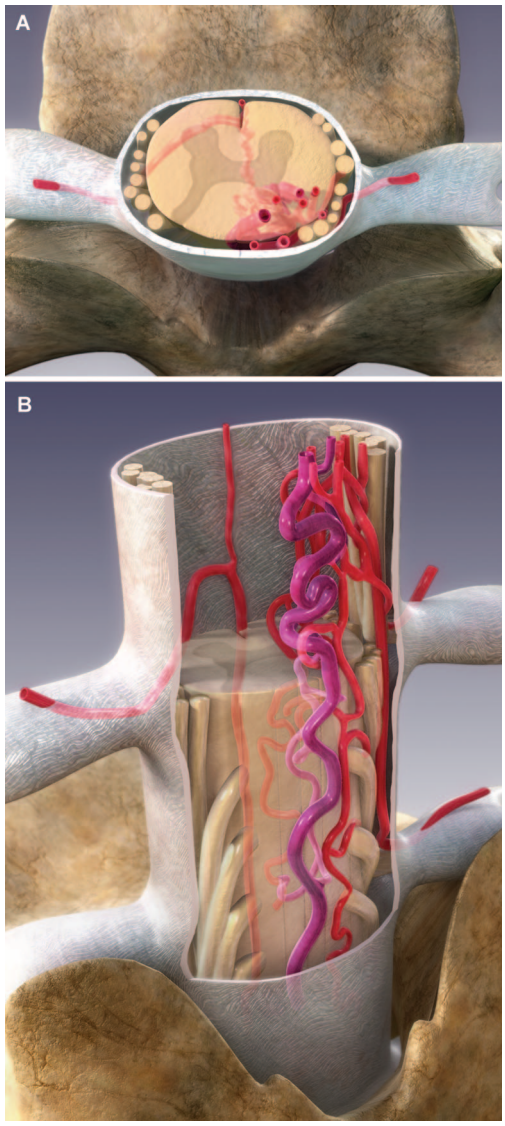

FIGURE 6. A, *axial illustration demonstrating a diffuse intramedullary AVM with areas of intervening neural tissue between the intraparenchymal loops of AVM. Portions of the AVM also course along the pial surface and subarachnoid space.* B, *illustration of the oblique posterior view demonstrating the loops of the AVM coursing in and out of the spinal cord. Normal neural tissue is evident between intraparenchymal portions of the AVM. This view accentuates the diffuse character of these lesions* (courtesy of *Barrow Neurological Institute, Phoenix, Arizona).*

treated spinal dural fistula, and in 1916, Elsberg (14) described the successful surgical treatment of a spinal epidural AVM. In 1926, Foix and Alajouanine (15) reported the syndrome of subacute necrotic myelopathy associated with rapidly progressive onset of paraplegia and subsequent death.

Subsequent investigators recognized that Foix-Alajouanine syndrome was associated with spinal AVMs after acute thrombosis of the pathological vessels (28, 39). It is now understood that the syndrome can occur after acute exacerbation of underlying venous hypertension. If treated sufficiently early, the condition can be reversed in some cases. In 1943, Wyburn-Mason (49) reported 110 spinal AVMs, which he classified histologically into arteriovenous angiomas and purely venous angiomas. The latter category accounted for more than two-thirds of all cases. Consistent with Virchow's original classification of vascular lesions, Wyburn-Mason perpetuated the older nomenclature by popularizing the terms

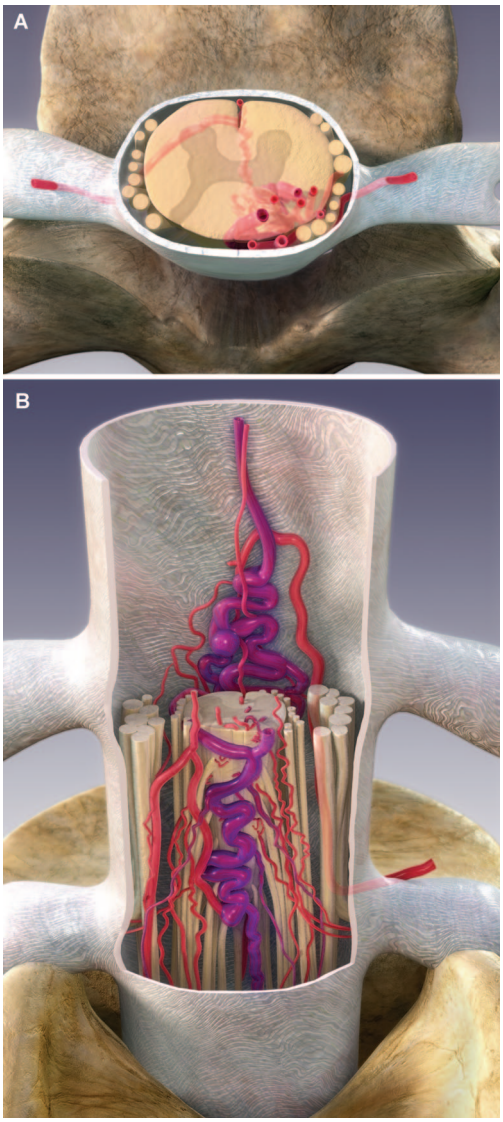

FIGURE 7. A, *axial illustration demonstrating a conus medullaris AVM and the feeding arteries and draining veins from both the anterior and posterior aspects of the spinal cord. Note the proximity of the AVM to branches of the cauda equina.* B, *illustration of the posterior view recapitulating the complexity of the angioarchitecture of these lesions. Anterior and posterior spinal arteries, radicular arteries, and anterior and posteriorly draining veins are involved simultaneously. Portions of the AVM can consist of direct AV shunts as well as regions of true AVM nidus. During endovascular treatment, surgical treatment, or both, it is crucial to identify the en passage branches of the anterior and posterior spinal arteries* (courtesy of *Barrow Neurological Institute, Phoenix, Arizona).*

for these lesions as *angioma racemosum venosum* and *angioma racemosum arteriovenosum* (49).

As spinal angiographic techniques evolved (5, 10–13), radiographic imaging of spinal AVMs afforded the opportunity to develop anatomically based classifications. The most common classification scheme for spinal AVMs uses the Type 1 to 4 grading system (11, 13, 22, 29, 37). Type 1 lesions are dural AVFs in which a dural branch from a radicular artery forms an abnormal communication with the dural veins at the nerve root sleeve. Arterialization of the perimedullary coronal venous plexus results. Type 2 refers to glomus or intramedullary lesions. Type 3 lesions are juvenile or metameric AVMs associated with both extradural and intradural extension of the spinal AVM. Type 4 spinal AVMs, as first described by Djindjian et al. (12) and categorized as Type 4 by Heros et al. (22), refer to perimedullary fistulae. These ventrally located fistula primarily receive arterial contributions from the ASA.

Borden et al. (8) described a three-point classification for both intracranial and spinal dural AVFs using the term *dural arteriovenous fistulous malformation*. Type 1 referred to extradural AVFs or epidural types, with direct drainage of the feeding artery into Batson's venous plexus. Type 2 referred to dural artery feeders draining into both epidural and intradural venous systems. Type 3 referred to what is known as intradural dorsal AVFs, or Type 1 AVMs, according to the description of Di Chiro et al. (11).

More recent spinal vascular lesion classifications are based on descriptive anatomic considerations. Niimi and Berenstein (35) divided vascular lesions of the spine into spinal vascular lesions and spinal cord vascular lesions. They subdivided spinal vascular lesions into spinal dural fistulae and extradural fistulae. Spinal cord vascular lesions are referred to as *spinal cord vascular malformations*, of which there are two types: isolated, which includes AVMs and AVFs, and multiple, which includes metameric and nonmetameric forms.

Bao and Ling (6) classified spinal cord vascular lesions as intramedullary AVMs, intradural AVFs, dural AVFs, paravertebral AVMs, and Cobb's syndrome. Intramedullary lesions include glomus and juvenile forms. Intradural AVFs are subdivided into Types 1 to 3, as the size of the lesion and degree of AVF flow increase.

Rosenblum et al. (42) differentiated spinal AVFs from AVMs based on their experience with 81 treated patients. Intradural AVMs were divided into intramedullary and direct AVFs. Intramedullary lesions included glomus and juvenile AVMs. Direct AVFs occupied either an intramedullary or extramedullary location. Intramedullary lesions were supplied by medullary arteries, and the arteriovenous shunt was located partially in the spinal cord or pia mater. Dural AVFs were supplied by a radicular branch along the dural nerve root sleeve, which drained via an AVF into the coronal venous plexus.

Our classification system represents an evolution that incorporates our enhanced understanding of these entities in recent decades (7, 27). This classification system offers several advantages. First, it includes all spinal AVFs and AVMs, including the recently proposed conus medullaris category (41, 44). Second, the system is based on the anatomic location of each lesion with its corresponding pathophysiological mechanism. Finally, it eliminates potential confusion inherent in the older nomenclature.

Treatment Strategies

Three pathophysiologic mechanisms underlying spinal AVMs can cause neurological injury: hemorrhage, mass effect, or vascular steal. Venous hypertension tends to be associated with either intradural spinal AVFs or conus medullaris-type spinal AVMs. Clinical manifestations can include pain, acute or progressive myelopathy, and radiculopathy. Magnetic resonance imaging and a thorough catheter-based angiogram provide the most important diagnostic information.

In contemporary neurosurgical settings, these lesions should be approached in a team-oriented fashion. Optimal patient care depends on direct collaboration between open vascular and endovascular neurosurgeons. The role of each half of this neurovascular team depends on the lesion, and treatment must be individualized to the specifics of each situation. The following surgical strategies and technical consideration serve only as a guide.

At our institution, monitoring somatosensory and motor evoked potentials has become a routine part of spinal AVM surgery. Intraoperative angiography should be used in selected cases when residual AVM may remain. When intraoperative angiography is unwarranted or indeterminate, immediate postoperative, as well as long-term, follow-up catheter-based angiography is the mainstay of our treatment paradigm.

Surgical Management

Extradural AVFs are treated primarily by endovascular techniques (3, 18, 21, 32, 35, 43). In our experience, the purely extradural fistula is an extremely uncommon lesion. The role of surgery in treating these lesions is limited to patients requiring reduction of local compression.

In 1977, Kendall and Logue (24) accurately redefined the pathophysiology of intradural dorsal AVFs. They recognized that the fistulous point occurred at the level of the dural root sleeve rather than along the dilated coronal venous plexus, which can be striking in such patients. Earlier, it was common to perform vein stripping procedures with no benefit or even worsening of symptoms (26) and with no effect on obliteration of the fistula itself. It is worth reiterating that successful surgical management of these lesions requires a careful and thorough catheter-based spinal angiogram to identify the arterial feeder(s) and artery of Adamkiewicz. Although angiographic visualization is paramount, angiographically occult lesions in patients under high clinical suspicion for intradural dorsal fistulae have been associated with successful surgical exploration and fistula disruption (36). These rare instances stress the importance of recognizing the clinical manifestations of these fistulae.

As soon as the appropriate spinal level has been identified, the surgical strategy involves its posterior exposure. We favor a posterior approach and laminoplasty. High-powered magnification and illumination with the operating microscope are used to perform intradural dissection along the appropriate nerve root. Typically, an arterialized vein is identified along the nerve root and can be dissected sharply to its exit point at the margin of the dural root sleeve. Nonstick bipolar cauterization and microscissors are used to interrupt the fistula. The advantage of surgical disruption is the relative ease of exposure and direct visualization of the vascular anatomy (2, 33, 36, 38, 42, 46).

Small intradural ventral AVFs (Subtypes A and B) are managed surgically (1, 17, 20, 40). These lesions may require an anterior or anterolateral approach for adequate exposure; however, posterolateral approaches are feasible for ventrolateral lesions (23, 30). Therefore, a thorough understanding of complex spinal approaches is essential for both the operative approach and spinal stabilization. Key to surgical success is preservation of the ASA branches during obliteration of the fistula. Giant (Subtype C) lesions, however, are best treated with endovascular embolization techniques because of their complex angioarchitecture and multipedicled feeders (1, 19, 22, 31, 34, 40).

Extradural-intradural AVMs are formidable lesions involving neural structures, bone, and soft tissue along the affected spinal level. They are treated primarily with endovascular embolization; surgery is reserved for decompression of mass effect along the nerve roots and spinal cord (22, 29, 30, 35, 38, 45). Although treatment cures have been reported (30, 45, 47), the realistic goal in most cases is reduction of mass effect, venous hypertension, and vascular steal to ameliorate the patient's neurological deficits.

Intradural-intramedullary AVMs have been treated successfully with embolization procedures (4). However, the mainstay of treatment remains surgical extirpation (9, 44). We recommend preoperative embolization in selected cases, particularly for patients with complex, multipedicled lesions. Typically, a posterior or posterolateral approach is suitable, but an anterior approach may be warranted in selected cases (9, 30, 48). For diffuse lesions (*Fig. 6*) situated superficially on the spinal cord, it is prudent to avoid chasing vascular loops of AVM that may invaginate into the spinal cord parenchyma. Because the pathophysiology of this lesion defines it as a superficial entity, it is best to truncate vessels embedded in the parenchyma at the pial surface. This strategy minimizes trauma to the tissue that could lead to inadvertent neurological injury yet still permits complete obliteration of the lesion. We have achieved gross total resection of 92% of the intramedullary AVMs that we have treated (44).

Conus medullaris AVMs are treated with a combined endovascular and microsurgical approach. Careful identification of ASA and posterior spinal artery branches separate from the lesion is crucial. Because the venous structures associated with conus AVMs are so hugely dilated, surgical decompression of adjacent spinal cord and nerve roots can relieve neurological symptoms significantly. Conus AVMs are usually easily accessible from a posterior approach. Our continuing experience with these entities has demonstrated that aggressive combined treatment can result in good outcomes (44).

CONCLUSION

Our ability to identify and treat spinal AVMs has advanced tremendously in the past several decades. This article describes a modified classification system of spinal arterio-

venous lesions based on this current anatomic and pathophysiological understanding. Further advances in the treatment of spinal AVMs mandate an integrated approach with microvascular and endovascular neurosurgeons.

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ENDOVASCULAR TREATMENT OF SPINAL CORD ARTERIOVENOUS MALFORMATIONS

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SPINAL CORD ARTERIOVENOUS malformations are rare lesions that represent one-tenth of the brain arteriovenous malformations. Depending on their location and relationship to the dura, these lesions are divided into four categories. Their clinical manifestations may vary from mild symptoms to severe motor deficits. Spinal angiography remains the "gold standard" for diagnosing spinal cord vascular lesions. Although the type of shunting remains difficult to determine by the magnetic resonance imaging, it is well analyzed by spinal angiography. The cure of the shunting is not by itself a therapeutic goal, but the objective is the creation of a new hemodynamic equilibrium between the lesion and the spinal cord to decrease the risk of hemorrhage and prevent the progression of the spinal cord ischemia. The endovascular tools seem to be a reasonable therapeutic option for the treatment of the majority of the spinal cord arteriovenous malformations.

KEY WORDS: Arteriovenous malformation, Embolization, Endovascular, Spinal cord

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Spinal arteriovenous malformations are rare and still under-diagnosed entities. Without proper treatment, they can typically lead to severe spinal cord symptoms and myelopathy. These malformations can be symptomatic as a result of mass effect by venous congestion, "steal phenomenon" with ischemia, or hemorrhage. Their evolution is marked by acute or progressive neurological deficit, and can sometimes lead to nonspecific neurological symptoms, which can delay proper diagnosis.

Surgical treatment of these malformations still carries a high risk of morbidity. During the last decade, endovascular treatment has established itself as the procedure of choice and the "gold standard" for the treatment of spinal arteriovenous malformations, and many series in the literature show that embolization is a safe and efficient way to treat these lesions.

At our institution embolization is the treatment of choice, regardless of the type of shunting present inside the vascular malformation.

VASCULAR ANATOMY

A thorough knowledge of the vascular anatomy of the spinal cord is key to understanding the architecture of spinal arteriovenous malformations. The spinal cord is supplied by two systems of vessels: anterior and posterior spinal arteries. The anterior spinal artery courses in the anterior median fissure and supplies the anterior system, supplying the anterior two-thirds of the spinal cord (19). The anterior spinal artery is formed from the two branches of the vertebral artery at the foramen magnum and descends to the conus medullaris. The anterior spinal artery is joined by radicular arteries, which form a plexus connecting the anterior and posterior systems. The anterior spinal artery is smallest in the thoracic spinal cord and largest in the conus (19). The anterior spinal artery supplies the anterior horn cells, corticospinal tract, and the spinothalamic tract. Two additional longitudinal arteries coursing from the foramen magnum to the conus are the posterior spinal arteries. At six to ten spinal levels paired radiculomedullary arteries join the anterior spinal arteries, while radicular arteries persist at each segmental level (13, 19, 23). In the cervical spine, the radiculomedullary arteries are more numerous and are derived from the vertebral and subclavian arteries (via the costocervical trunk); in the thoracic and lumbar region, these are derived from the aorta and

the iliac arteries (13, 19). The most important of these branches is the artery of Adamkiewicz, providing most of the blood supply to the spinal cord below T6 and arising from the left between T8-L2 (75% from T9-T12) (27). This artery is also referred to as the artery of the lumbar enlargement. The configuration of these radiculomedullary vessels changes from a Y-shape at the cervical region to a classical "hairpin" bend at the thoracolumbar level. Therefore, the spinal cord watershed is in the upper thoracic cord. Sulcal arteries arising from the anterior spinal artery penetrate the spinal cord to supply the central gray and white matter not supplied by the leptomeningeal collaterals of the lateral plexus. Blood supply to the nerve roots occurs from proximal branching of the radiculomedullary arteries and the dural arteries supply the dural root sleeve at each segmental level (19).

The spinal cord veins extend both intra- and extradurally. The intradural veins are subdivided into intramedullary veins and pial veins, while the epidural veins include veins of the spinal column and Batson's plexus. The intradural spinal cord veins are comprised of an anterior median, sulcal, and radial veins (13, 19). Blood traveling from the center of the spinal cord drains into deep sulcal veins located in the anterior median fissure, specifically draining the anterior median portion of the spinal cord. Adjacent sulcal veins drain into the anterior median vein while the lateral and posterior portions of the spinal cord are drained into the anterior medullary veins and posterior medullary veins, respectively (13). These two veins comprise the major draining pattern for the spinal cord and drain into the intervertebral vein, where they converge. Extradural spinal cord veins are comprised of a plexus of veins known as the internal or external plexus depending on its position inside or outside the spinal column (13). Communication exists between this system and the occipital, sigmoid sinuses, and the basilar plexus (13, 19, 23).

DIAGNOSTIC IMAGING

Spinal angiography remains the gold standard for diagnosing spinal cord vascular lesions. Spinal angiography provides the exact location and size of the lesion and provides valuable information regarding feeding and draining vessels. Magnetic resonance imaging (MRI) and now computed tomographic (CT) scan angiography have increasingly been used as valuable tools in diagnosis. MRI, in particular, allows visualization of thrombosed veins and visualization of the spinal cord. At our institution, all spinal angiography is performed under general anesthesia. This not only allows comfort for the patient but also improves the quality of the imaging in allowing the patient to undergo apnea to reduce motion artifact while performing a run. A Foley catheter is also helpful in maintaining an upopacified bladder during sacral runs.

A 6-French intravascular sheath is placed in the common femoral artery, and depending on the location, an aortogram is usually helpful in localizing a lesion. A 5-French pigtail catheter is placed typically at T5 for thoracolumbar spine surveillance. Full strength contrast is administered at an injection rate of 8 to 10 ml/sec for a total of 30 to 40 ml. The anesthetist is instructed to induce apnea at the onset of the run. Individual intercostal or lumbar segmental arteries are selectively studied based on the findings of the aortogram. For lesions involving the cervical cord, both vertebral arteries should be catheterized as well as the ascending and deep cervical arteries. Arterial phase should be studied for arteriovenous shunting as well as delayed runs to ascertain the venous drainage. The pattern of venous drainage should be noted and taken into account as a baseline for future embolization.

Several specialized catheters are useful for spinal angiography. They include HS1, HS2, Simmons I and II SoS, and Michelson catheters (*Fig. 1*).

CLASSIFICATION AND TREATMENT

Type 1

Spinal arteriovenous malformations (AVM) can be subdivided into four general categories (*Table 1*).

Type 1 refers to a dural arteriovenous fistula (DAVF) and is not a true AVM. These are typically found in the dorsal aspect of the low thoracic cord and the conus, and usually consist of a single arterial transdural feeder that drains into an intradural vein. The majority occur spontaneously but up to 40% may be traumatic (27). Subdural arteriovenous fistulas (SDAVF) usually arise in the dura along a root sleeve but may also involve the dura of the spinal cord.

SDAVFs are most frequently found in men between 50 and 80 years old (5). It is thought that patients become symptomatic from chronic venous hypertension (3, 24). The local venous hypertension, which has been reported to approach 75% of the arterial pressure, has been postulated to decrease medullary arterial perfusion to as low as 25% of normal (17). The result is a progressive sensorimotor myelopathy.

Magnetic resonance imaging reveals increased signal intensity on T2-weighted images throughout the central area of the cord, particularly in the conus, and is accompanied by decreased signal intensity on T1-weighted images. Prominent signal voids are frequently present in the surrounding subarachnoid space. These are the result of flow in the veins.

Angiographically, SDAVFs have a small nidus of arteriovenous shunting, usually located on the lateral aspect of the spinal canal near the intervertebral foramen. The supply is usually from the radiculoradial artery. A single draining vein usually emerges from the nidus and drains intradurally. These may be congested over several levels, so it is critical to assess delayed venous phases (*Fig. 2*).

The lesion should be evaluated at two levels above and below to establish possible collateral supply.

Treatment of this malformation is readily achieved with surgery (16). When a spinal cord artery shares the same pedicle as the feeder of the SDAVF, surgery should be the first choice. For more complex lesions where identification of the

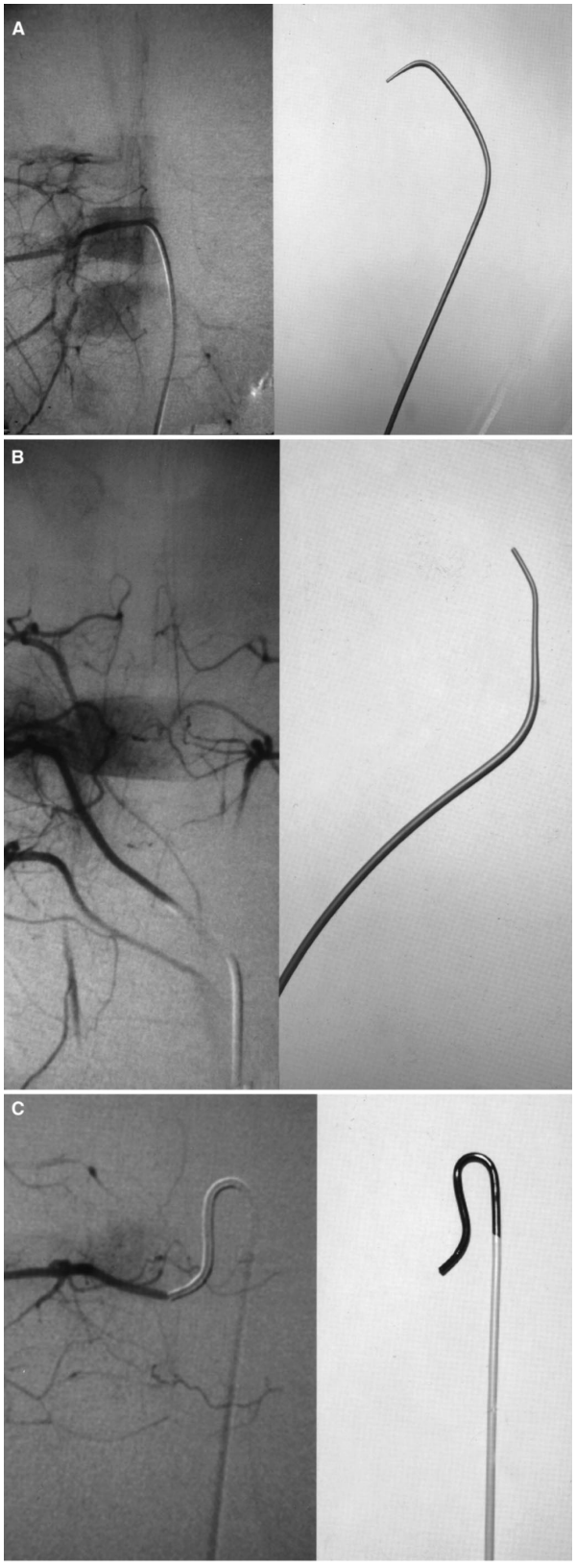

TABLE 1. Categories of spinal arteriovenous malformations

Type 1	Dural Arteriovenous fistula
Type 2	Glomus malformations
Type 3	Juvenile type
Type 4	Intradural extramedullary cavernous malformations

fistula and draining veins is more difficult, embolization may represent a better option (31).

Three conditions should be met prior to attempted embolization of SDAVFs. First, the dural artery supplying the shunt should not originate from branches supplying the spinal cord (25). Second, selective catheterization of the pedicle must be achievable. Third, the surgeon should be familiar with the use of liquid polymerizing agents. The use of polyvinyl alcohol (PVA) and coils has been documented to result in very poor long-term results (11, 15).

Complications related to embolization of SDAVFs are usually related to inadvertent embolization of normal spinal cord arteries. It has also been reported that delayed symptoms can be related to formation of thrombus within the perimedullary veins (22, 31). The mainstay of treatment for this is usually anticoagulation.

The successful treatment of SDAVFs is dependent on permanent obliteration of the arterial venous shunt. Outcomes are generally directly related to the severity and duration of neurological deficit pretreatment. In adequately treated patients, neurological improvement may be seen in up to 80% of patients.

Type 2

Type 2 spinal cord AVMs are also referred to as glomus malformations and are found intramedullary. These lesions usually present in younger patients with acute neurological deterioration secondary to their location (1, 2, 20). They are usually supplied by multiple feeders from the anterior and posterior spinal arteries and are more commonly found in the dorsal cervicomedullary region. For this reason, all patients at our institution who present with an angiogram negative subarachnoid hemorrhage undergo an MRI for evaluation of the cervical spine. Less commonly, progressive myelopathy may occur as the result of mechanical compression or medullary venous compression (6, 14) (*Fig. 3*).

The mortality rate related to SCAVMs is reported at 17.6% (14). After initial hemorrhage, the rebleed rate is 10% within the first month and 40% within the first year.

Type 3

Type 3 SCAVMs are also referred to as juvenile type or metameric vascular malformations. These lesions are typically

FIGURE 1. *Catheters used in spinal angiography.* A, *HS1 catheter with selective catheterization of Rt T10 intercostal artery.* B, *H1H catheter with selective catheterization of Rt T5 intercostal artery.* C, *SoS catheter with selective catheterization of Rt L3 lumbar segmental artery.*

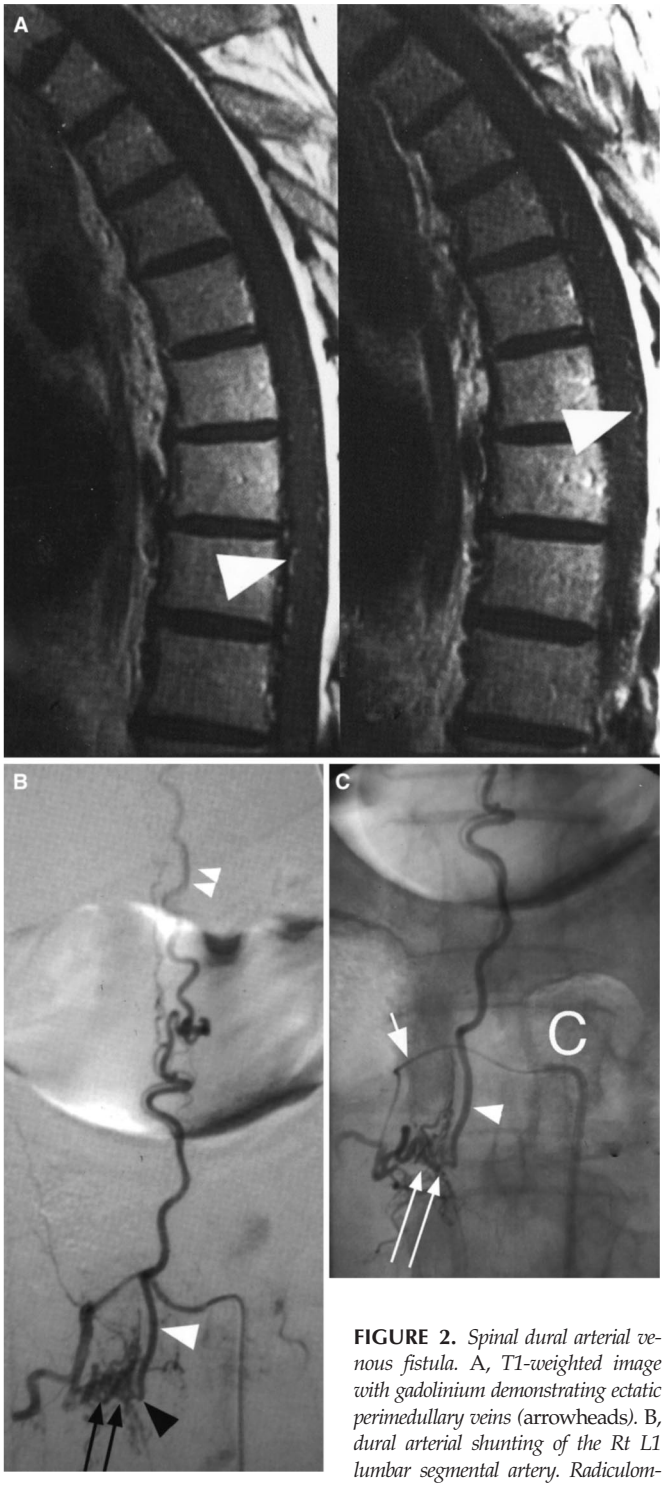

FIGURE 2. *Spinal dural arterial venous fistula.* A, *T1-weighted image with gadolinium demonstrating ectatic perimedullary veins* (arrowheads). B, *dural arterial shunting of the Rt L1 lumbar segmental artery. Radiculomenengial arteries form a network* (double arrows) *that supply the dural fistula* (black arrowhead). *Radicular vein draining shunt* (white arrowhead), *congested perimedullary veins* (double arrowheads). C, *common branch of the Rt L1 lumbar segmental artery* (short white arrow), *illustrating the dural network* (double arrows) *and fistula. Draining radicular vein* (white arrowhead). C, *Catheter tip.*

found in young adults and children. They commonly have an intramedullary component when they present with spinal cord symptoms. They may also have extensive extramedullary and even extraspinal extension. Multiple feeders over several vertebral levels are common.

The extensive nature of these lesions usually limits treatment options to embolization. The goal of treatment is to reduce venous hypertension, but is usually palliative (12, 21, 30, 32).

Type 4

Type 4 SCAVMs are intradural extramedullary fistulas, resulting from a direct communication between a spinal artery and a spinal vein without an interposed vascular network (14, 29) (*Fig. 4*). They are commonly found near the conus in an anterior location and fed by the anterior spinal artery. They are usually seen in patients between the ages of 30 and 60 years. Like, DAVFs they often present with progressive neurological symptoms (5). Flow-related aneurysms arising from the feeding arteries and venous ectasias are often present (8). The venous drainage is usually complex and includes perimedullary veins over the anterior and posterior surfaces of the spinal cord. These are often found extending over multiple levels.

Magnetic resonance imaging provides very good detail of the topography of SCAVMs. Multiple perimedullary signal voids are often evident. Hematomyelia, myelomalacia, edema, and thrombosis can help identify an intramedullary component.

Spinal angiography provides the necessary information for both diagnosis and treatment options of SCAVMs. High-flow lesions will have either direct or collateral supply from either the anterior or posterior spinal arteries. It is crucial that both of these arteries are visualized both above and below the suspected malformation (1, 18). The early arterial phase should be closely examined to determine the presence of shunting and the source of arterial supply. The venous phase should likewise be examined for the type and extent of venous drainage.

Stenosis of the feeding or draining vessels should be identified. If affecting the draining veins, large dilated vessels may be evident that predispose the lesion to hemorrhage and worsening of compressive symptoms. Aneurysms, usually found on feeding arteries or in the nidus itself, should likewise be evaluated. Pseudoaneurysms are usually the result of recanalized hematoma and are found in patients with a history of hemorrhage.

Treatment options are dictated by the location of the lesion, the patient's medical condition, and the risk versus benefit ratio. The factor most important in determining the treatment option is the presence of intra- or extramedullary shunting. Malformations that are subpial in location are less likely to be cured. These are usually supplied by subcommisural branches of the anterior spinal artery. The role of partial embolization is not clear. Long-term clinical results in patients with symptomatic SCAVMs have demonstrated a lower incidence of recurrent hemorrhage and this may have a role in difficult lesions (9, 10). Lesions that are located on the surface and are supplied

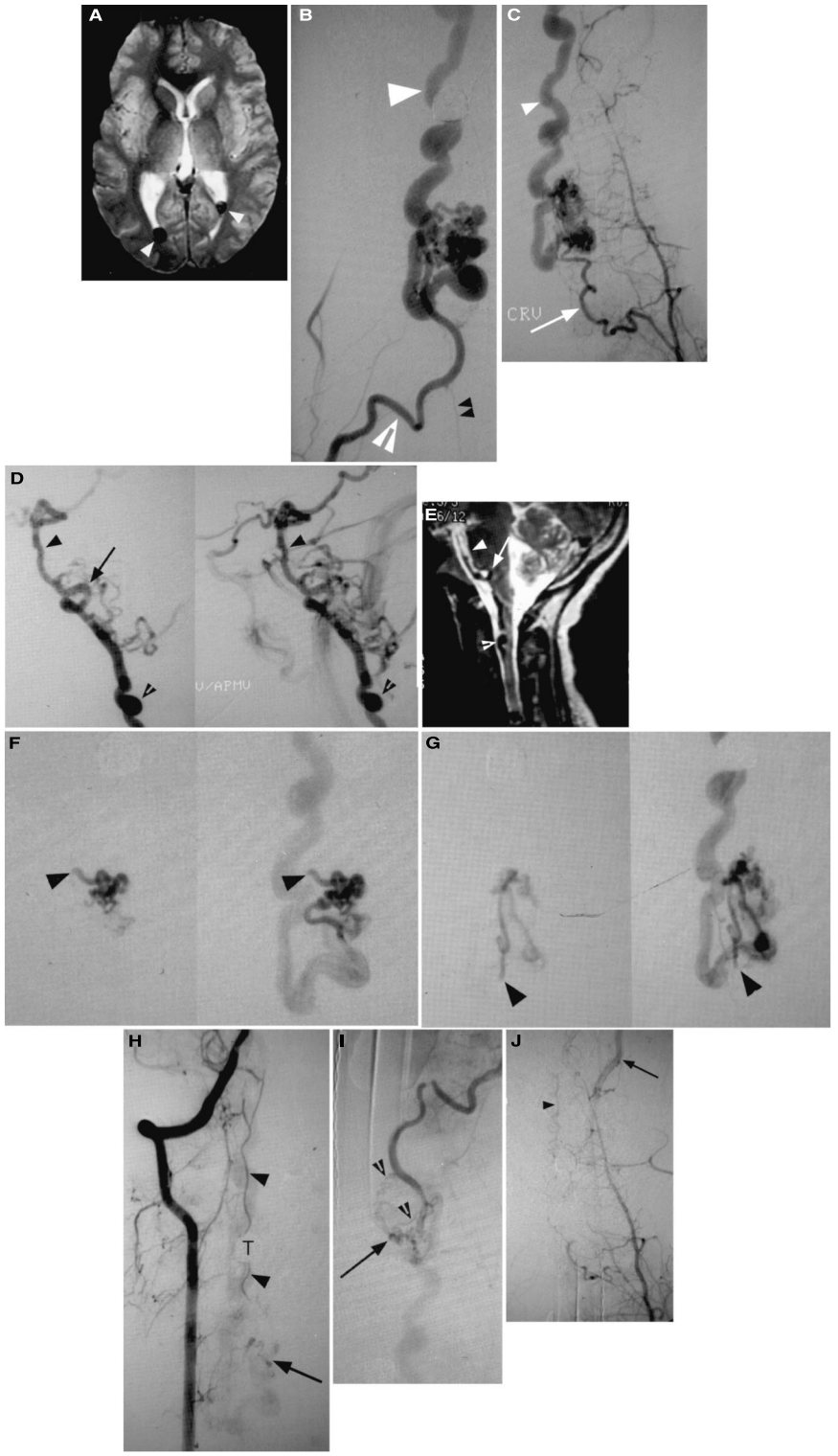

FIGURE 3. *Cervical spinal cord arterial venous malformation presenting with intraventricular hemorrhage.* A, *axial T2–weighted spin echo magnetic resonance image of the brain demonstrating intraventricular blood* (white arrowheads) *layering within the occipital horns of the lateral ventricles.* B, *cervical spinal angiographic imaging disclosed an AVM involving the C5 segment of the spinal cord. The AVM was supplied by the anterior and posterior spinal arteries. A large radiculomedullary branch* (striped white arrowhead) *of the right deep cervical artery supplied the AVM through the anterior spinal artery. Note the descending limb of the anterior spinal axis* (black double arrowheads). *The venous receptive field of the AVM involved intrinsic tributaries of anterior spinal vein* (white arrowhead) *which was grossly ectatic cephalad to the AVM.* C, *arterial phase image from digital subtraction angiography (DSA) of the left deep cervical artery demonstrating radiculopial* (white arrow) *supply to the AVM. Additional supply to the AVM was provided by the left vertebral artery through its lateral spinal branch. Note the identical drainage pattern involving an enlarged anterior spinal vein* (white arrowhead). *The anterior spinal vein was continuous into the posterior fossa with the anterior pontomesencephalic vein, ultimately emptying into the straight sinus through the basal veins.* D and E, *venous phase images (lateral projection) from DSA of the right deep cervical artery centered over the posterior fossa. Note the continuation of the anterior spinal vein* (striped black arrowheads) *with the anterior pontomesencephalic vein* (black arrowheads). *The venous drainage of the SCAVM congests the basal veins, deep sylvian veins, and cerebellar veins. A companion sagittal T2–weighted spin echo magnetic resonance image of the cervical medullary junction provides a comparison view of the vascular structures. Note the continuity of the anterior spinal vein* (striped white arrowhead) *with the anterior pontomesencephalic vein* (white arrowhead) *across the pontomedullary junction* (white arrow *in* E; black arrow *in* D). F and G, *AVM was embolized through a large sulcocommisural branch of the anterior spinal artery* (F) *and a radiculopial branch of the left deep cervical artery* (G). *The use of liquid acrylate to embolize the ASA contribution to the AVM was made possible by the superselective catheterization of the sulcocommisural branch in* (F). *The microcatheter tips are demarcated by* arrowheads *in* F *and* G, *respectively.* H to J, *embolization resulted in closure of the posterior spinal contribution to the AVM. Minor residual ASA contribution persisted, evident from the postembolization DSA of the right vertebral* (arrow *in* H) *and right deep cervical* (I) *arteries. The remaining sulcocommisural branches* (striped black arrowheads) *of the ASA supplying the SCAVM could not be embolized due to their small size. The postembolization DSA of the left deep cervical artery confirms the occlusion of posterior spinal contribution to the AVM. The posterior spinal axis above the lesion* (black arrowhead) *is visualized, supplied from the lateral spinal branch of the left vertebral artery* (black arrow).

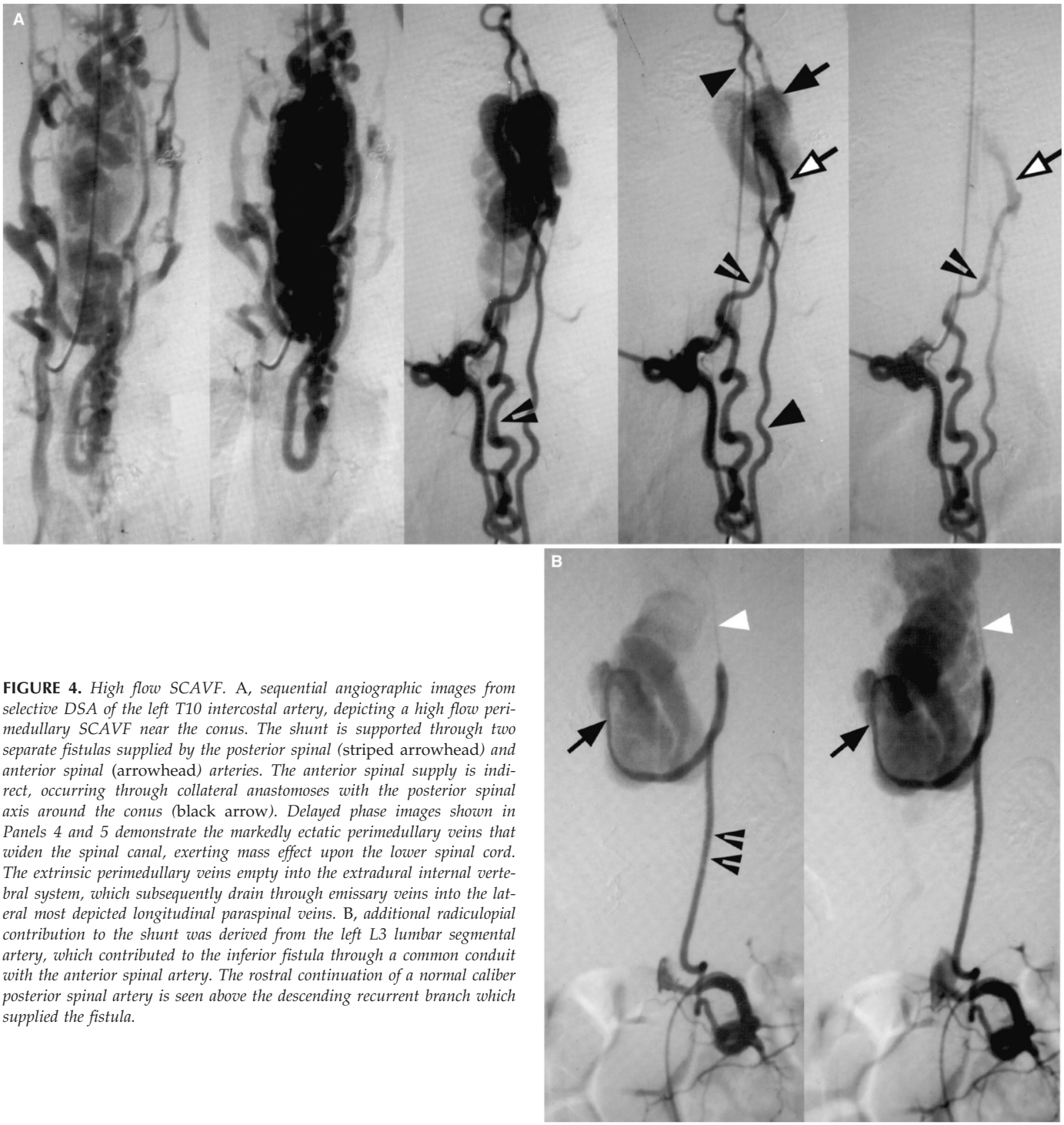

FIGURE 4. *High flow SCAVF.* A, *sequential angiographic images from selective DSA of the left T10 intercostal artery, depicting a high flow perimedullary SCAVF near the conus. The shunt is supported through two separate fistulas supplied by the posterior spinal* (striped arrowhead) *and anterior spinal* (arrowhead) *arteries. The anterior spinal supply is indirect, occurring through collateral anastomoses with the posterior spinal axis around the conus* (black arrow). *Delayed phase images shown in Panels 4 and 5 demonstrate the markedly ectatic perimedullary veins that widen the spinal canal, exerting mass effect upon the lower spinal cord. The extrinsic perimedullary veins empty into the extradural internal vertebral system, which subsequently drain through emissary veins into the lateral most depicted longitudinal paraspinal veins.* B, *additional radiculopial contribution to the shunt was derived from the left L3 lumbar segmental artery, which contributed to the inferior fistula through a common conduit with the anterior spinal artery. The rostral continuation of a normal caliber posterior spinal artery is seen above the descending recurrent branch which supplied the fistula.*

by circumferential branches of the anterior spinal artery may be treated safely by either embolization or surgery (6, 26).

The new generation of liquid embolic material and microcatheters have made interventional treatment of SCAVMs safer with better results. The goal of any intervention is elimination of the shunt. Microcatheterization is paramount to achieving effective results. Delivery of embolic material to the nidus of the lesion achieves reduction of the AVM, as well as reducing the risk of inadvertent embolization of normal vessels.

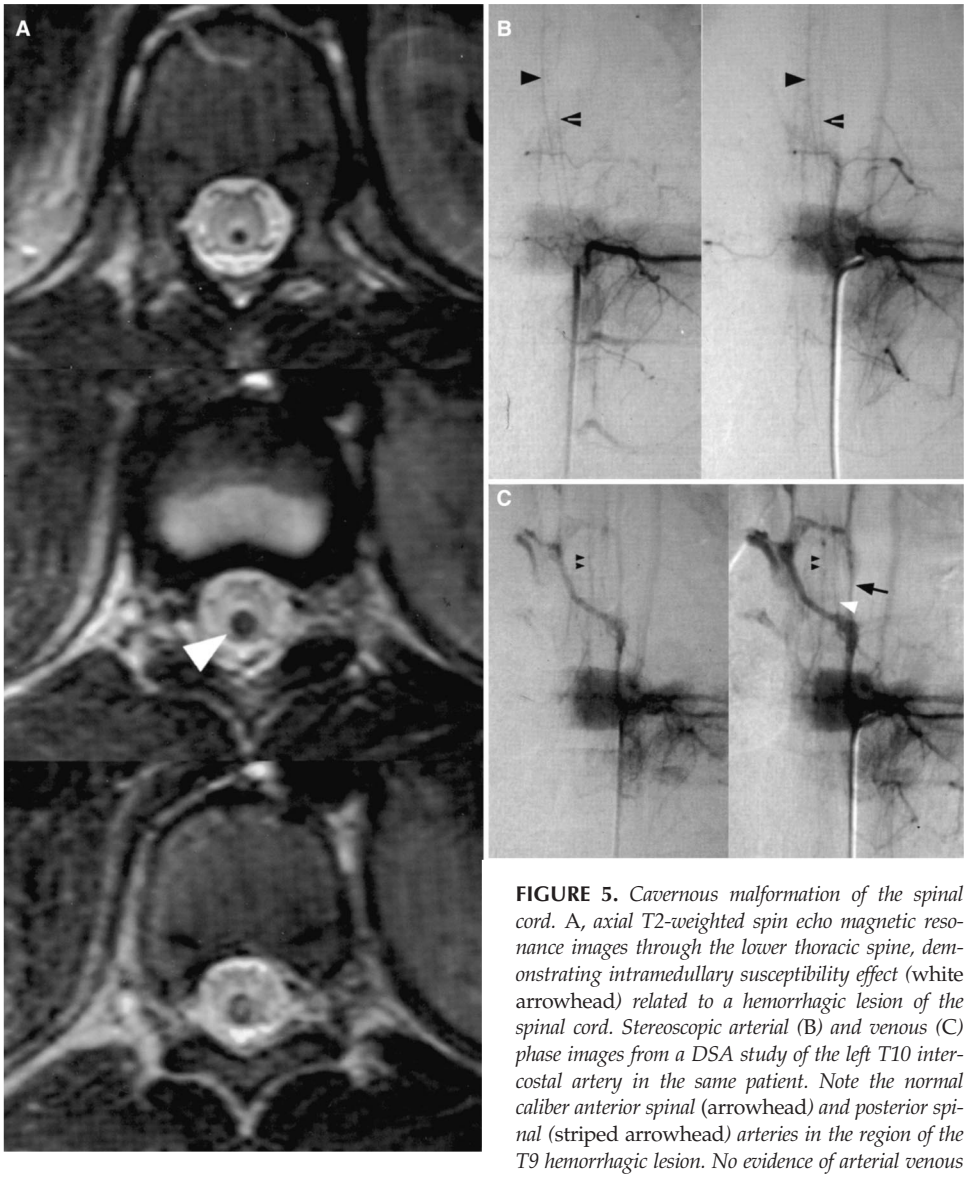

FIGURE 5. *Cavernous malformation of the spinal cord.* A, *axial T2-weighted spin echo magnetic resonance images through the lower thoracic spine, demonstrating intramedullary susceptibility effect (*white arrowhead*) related to a hemorrhagic lesion of the spinal cord. Stereoscopic arterial (*B*) and venous (*C*) phase images from a DSA study of the left T10 intercostal artery in the same patient. Note the normal caliber anterior spinal (*arrowhead*) and posterior spinal (*striped arrowhead*) arteries in the region of the T9 hemorrhagic lesion. No evidence of arterial venous shunting was noted. The posterior spinal axis on the contralateral side was also normal in caliber. Venous phase images illustrate the normal median anterior (*double arrowheads*) and posterior perimedullary veins which emptied through radicular veins (*white arrowhead*) into the epidural internal vertebral veins (*black arrow*). The lesion was subsequently excised and proved to be a cavernous malformation.*

Liquid embolic agents are the first choice for most SCAVMs, not only because they are the most likely to fill distal nidus, but they also have a low recanalization rate. The authors' agent of choice is *n*-butylcyanoacrylate (NBCA). Embolization of lesions supplied by the anterior spinal artery requires selective catheterization and deposition of embolic material. Permanent deficits resulting from embolizations in the ASA territory occur in up to 11% of patients (28).

The manipulation of viscosity of the liquid embolic helps ensure more precise deposition. Polymerization should occur in transit through the arteriovenous shunt. In higher flow lesions, pharmacologically induced hypotension is used, typically with a mean arterial pressure of 50 mmHg. With larger draining vessels, the Valsalva maneuver also helps delay transit time.

When preoperative embolization is planned, polyvinyl alcohol microparticles (PVA) are a reasonable choice of embolic material. They are also useful for embolization of Type 2 AVMs. An advantage of PVA is that embolization may be performed at a more proximal location and the size of particle can be determined depending on the size of the lesion and its collaterals. The goal of treatment with either agent is to provide distal occlusion of the nidus. Proximal occlusion results in collateral reconstitution with little hope of cure.

Regardless of choice of material used for embolization, all procedures should be performed under general anesthesia with neurophysiologic monitoring, depending on the location of the lesion. Somatosensory evoked potentials (SSEPs) are very accurate in assessing spinal cord function (7). Motor evoked potentials (MEPs) are also useful when a SCAVM is supplied by the American Society of Anesthesiologists (ASA).

CAVERNOUS MALFORMATIONS

Cavernous malformations (CMs) of the spinal cord are rare lesions. They are characterized histologically as thin walled microvascular channels that are lined with endothelium and a subendothelial stroma devoid of smooth muscle layers. The lesions frequently contain hemorrhages of various ages. Most are sporadic and are found in patients who are 30 to 60 years old. There is a 2:1 female preponderance. Familial forms have also been identified and usually harbor multiple lesions. The clinical course ranges from slowly progressive to acute loss of neurological function (4)

MRI appearance is typified by a discrete mass of mixed signal intensity on T1- and T2-weighted spin echo sequences (*Fig. 5*). A rim of hypointensity on TR and gradient echo sequences localizes the typical hemosiderin ring. Spinal angiography is of little use in the diagnosis of CMs.

The natural history of CMs in the spinal cord is still not clear. Surgery at this point is restricted to symptomatic lesions only. There is no role for neurointervention to date. For incidentally found lesions, the authors perform yearly surveillance

CONCLUSION

When a spinal vascular malformation is suspected, MRI should be the first diagnostic modality, followed by a spinal angiography, which is the gold standard for optimal analysis of the angioarchitectural features of the lesion. Embolization with a liquid embolic agent is the first treatment choice for Types 2 to 4 malformations, whereas surgery may be a better option for the Type 1 malformations. The prognosis of these lesions seems better than previously thought, especially with advances in endovascular techniques and the new embolic agents which offer a high success rate with low morbidity.

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CURRENT CONCEPTS IN THE MANAGEMENT OF INTRACRANIAL ATHEROSCLEROTIC DISEASE

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MEDICALLY REFRACTORY, SYMPTOMATIC intracranial atherosclerotic disease has a poor prognosis. Based on the results of the Warfarin-Aspirin Symptomatic Intracranial Disease study, the risk of ipsilateral stroke at 1.8 years is between 13 and 14% in patients with symptomatic intracranial atherosclerosis. Synergistic advances in intracranial angioplasty and stenting, modern neuroimaging techniques, and periprocedural and postprocedural antithrombotic regimens are creating new models for the diagnosis and successful endovascular treatment of intracranial stenosis. In this article, the most recent clinical developments and concepts for the diagnosis and endovascular treatment of intracranial atherosclerotic disease are discussed.

KEY WORDS: Intracranial atherosclerosis, Stent, Treatment

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Intracranial atherosclerosis accounts for 8 to 10% of all ischemic strokes (64, 82). Because the Extracranial-Intracranial Bypass Study demonstrated a poor clinical outcome for patients with middle cerebral artery stenosis and high rates of morbidity and mortality have been reported with posterior circulation bypass procedures, patients with symptomatic intracranial atherosclerotic disease have had, until recently, oral antithrombotic medications as the first and only line of treatment (15, 27, 28). The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) investigators compared outcomes among patients with symptomatic intracranial stenosis receiving warfarin (international normalized ratio, 2.0–3.0) and those receiving high-dose aspirin (1300 mg daily) in a randomized, double-blinded trial (9). In 569 patients at a mean follow-up period of 1.8 years, warfarin was associated with a higher rate of death, major hemorrhage, myocardial infarction or sudden death, and death from nonvascular or vascular cause. Further work by the WASID group has shown that patients with 70 to 99% stenosis, those enrolled within 17 days of their symptoms, and women are subsets at greater risk for subsequent stroke in the territory of the stenotic artery (31). At 1 year, the stroke risk for patients with 50 to 69% stenosis was 6%, compared with 19% for those with 70 to 99% stenosis. On the basis of the WASID data, the ipsilateral stroke risk at 1.8 years for patients with symptomatic intracranial stenosis is between 13 and 14% (31). With the poor outcome from warfarin therapy, WASID is a call for new treatment strategies for this challenging group of patients (9).

After the publication of the North American Symptomatic Carotid Endarterectomy Trial results (58) and early reports like that of Sundt et al. (71) of initial successful balloon angioplasty of two patients for medically refractory basilar stenosis, the intellectual framework for attempting endoluminal treatment of atherosclerotic intracranial vessels became a clinical reality. During the past decade, several investigators (12, 30, 41, 52, 66) reported technical success with angioplasty with or without stenting of the intracranial arteries. Mori et al. (52) defined an easily applicable and clinically relevant angiographic grading system to determine the risk and success of angioplasty of intracranial arteries based on plaque length, stenosis degree, and plaque eccentricity. Connors and Wojak (12) began to refine the technique with the concept of slow inflation and undersizing of balloons for angioplasty. Because flow increases by the vessel radius (4) (Poiseuille's law), small increases in luminal diameter will increase blood flow significantly, thereby alleviating hemodynamic insufficiency and changing the milieu such that an embolism is less likely to form. However, difficulty with patient selection, early angiographic restenosis, and significant morbidity and mortality rates continue to present challenges.

Experience with angioplasty and stenting of the coronary vessels continues to supplement our knowledge of the treatment of intracranial atherosclerosis in four critical aspects: 1) cor-

onary stents were, until recently, the only available devices able to be navigated and deployed in the intracranial circulation; 2) data in the cardiac literature has demonstrated lower restenosis rates with angioplasty and stenting than standalone angioplasty; 3) well-defined antithrombotic regimens and evidence of the benefits of periprocedural bolus-dose administration and postprocedural therapy with aspirin and clopidogrel have resulted in decreases in both recurrent stenosis and postprocedural neurological events; and 4) implantation of new coated and drug-eluting stents is proving to yield significantly lower restenosis rates (17, 47, 53, 65, 69, 83).

Combining the strategies of the cardiologists and neurointerventionists, a technique of submaximal angioplasty followed by delayed repeat angioplasty and, if necessary, stenting was developed for intracranial symptomatic atherosclerotic disease (37). In this staged treatment approach, the patient returned for angiography approximately 4 to 6 weeks after angioplasty. If there was evidence of in-lesion binary stenosis (50% luminal-diameter stenosis), stenting was performed. The rationale for this approach is that during the weeks of delay, neointimal proliferation and scar formation after angioplasty result in a thickened fibrous lesion (2, 73), which may incur a lower risk for plaque embolization and vessel dissection during a subsequent stenting procedure. With this strategy, the composite rate of mortality and permanent neurological morbidity for the procedure dropped to less than 5%, and between 20 and 30% of patients did not require further intervention at follow-up (38). In a review of a larger recent series of cases performed between October 2004 and October 2005, a staged treatment approach was planned for 36 patients at the State University of New York at Buffalo Neurosurgery (Institutional Review Board NSG0750605E: Stenting registry). Looking at the index cases for 30-day morbidity and mortality, six (17%) out of 36 cases needed stenting at the time of the procedure because of significant residual stenosis or plaque dissection with angioplasty alone. Complications occurred in two (6%) out of 36 patients in this series. One patient experienced a Weber's syndrome during the procedure but improved and made a remarkable recovery. In the other patient, a small cavernous-carotid fistula developed that resolved on follow-up 6 weeks later.

Recently, the Food and Drug Administration approved the Wingspan stenting system (Boston Scientific, Fremont, CA) under the Humanitarian Device Exemption (HDE) program for use in patients with symptomatic intracranial stenosis of 50% or more in severity (70). Use of this system involves submaximal inflation of an angioplasty balloon, followed by removal of the balloon and subsequent deployment of the stent. The Wingspan is a self-expanding intracranial stent composed of nitinol with similar trackability but at least twice the radial outward strength of the Neuroform III stent (Boston Scientific) (22). The HDE study involving 44 out of 45 patients treated with the Wingspan demonstrated a composite occurrence of ipsilateral stroke and death at 30 days, 6 months, and 1 year of 4.5%, 7.1%, and 9.3%, respectively (23, 70). Twenty-three lesions were located in the anterior circulation and 22 in the posterior circulation (70). Six-month follow-up angiograms available for 40 of the patients documented restenosis ($\geq$50%) in three patients (7.5%). Interestingly, 24 out of 44 patients had further reduction in stenosis as compared with the immediate postprocedure angiogram, suggesting a long-term benefit to the continued radial outward force of the self-expanding stent (70). This rate compares favorably with the more than 30% restenosis rate for intracranial vessels in the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial (66), which will be discussed later in the text.

PATIENT SELECTION

With respect to the anterior circulation, the best medical care randomization arm of the Extracranial-Intracranial Bypass Study provides the best prospective clinical data. Patients with middle cerebral artery stenosis randomized to the medical arm had a 7.8% per patient, per year risk of ipsilateral stroke (5). In a retrospective study of 52 patients with symptomatic intracranial stenosis receiving antithrombotic therapy, Thijs and Albers (75) found that 29 (56%) patients failed medical therapy, and 50% of recurrent events occurred within 36 days of the initial transient ischemic attack (TIA) or stroke. In addition to stroke-related morbidity and mortality, the risk of death resulting from ischemic heart disease is high in patients with intracranial atherosclerosis (13, 45, 55). Although the probability of disabling stroke and death is high in patients with symptomatic intracranial stenosis, endovascular treatment carries significant risk. Careful patient selection is essential to good outcomes. Modern imaging techniques, including computed tomographic (CT) perfusion, xenon-enhanced CT analysis, magnetic resonance imaging diffusion-perfusion, single-photon emission CT scanning, and positron emission tomography, can help to identify those patients with poor vascular reserve and/or hypoperfusion to a vascular territory supplied by a stenosed intracranial artery who stand most to benefit by endoluminal revascularization (3, 26, 81). Acetazolamide challenge testing augments the specificity of CT perfusion and single-photon emission CT scanning (26, 35, 59). Not all of these studies are readily available at all academic medical centers.

At our institution, CT perfusion imaging with and without acetazolamide challenge testing is used most often for evaluation of lesions located in the supratentorial vasculature, whereas single-photon emission computed tomographic scanning is reserved for the posterior circulation or for those patients who cannot tolerate a significant load of contrast material (*Fig. 1*). CT perfusion is useful for the evaluation of cerebral blood flow, cerebral blood volume, time to peak or mean transit time, and cerebral infarction volume in the setting of acute stroke. Symptomatic patients with severe reduction in vascular reserve in a poorly perfused territory are candidates for endoluminal revascularization. Symptomatic patients without perfusion abnormalities are likely experiencing embolic phenomena, and a trial of antithrombotic medication could be considered for this group. A patient previously treated by an endovascular approach occasionally will have follow-up imaging studies that identify a new, but asymptomatic, area of severely impaired vascular reserve

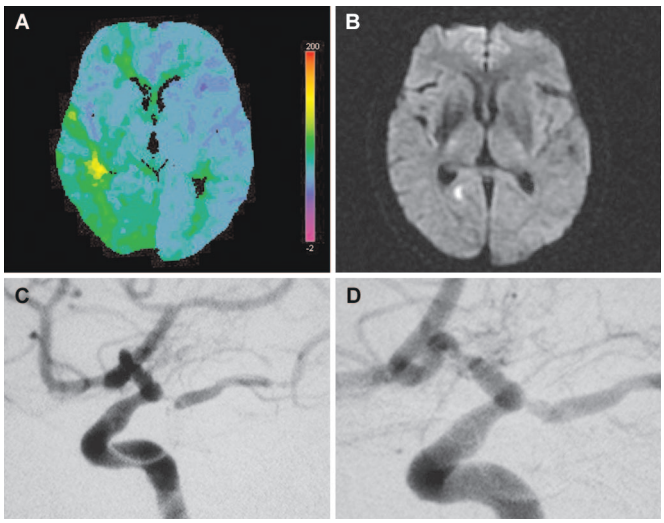

FIGURE 1. A, *computed tomographic perfusion imaging obtained from a 72-year-old woman with a history of a 5-minute episode of unresponsiveness at home demonstrating significantly increased time to peak in the right posterior cerebral territory.* B, *diffusion-weighted magnetic resonance image scan obtained from the same patient demonstrating only a small area of infarction in the right posterior cerebral territory.* C, *diagnostic cerebral angiogram demonstrating a fetal posterior cerebral artery with more than 90% stenosis.* D, *postangioplasty cerebral angiogram demonstrating significantly increased lumen size of the posterior cerebral origin.*

with the appropriate angiographic correlate of a severely stenosed artery. Such patients constitute a group of asymptomatic patients whom we have treated on the basis of neuroimaging physiology and history of refractory symptomatic disease.

CLINICAL SERIES

Between 1993 and 2000, technical and clinical success with stand-alone angioplasty was documented in 11 case series consisting of 193 patients (1, 7, 10, 24, 43, 46, 52, 56, 72, 74, 78). Good revascularization, by varying definitions, was reported for 67 to 100% of the patients, with overall complication rates ranging from 5 to 40%. The occurrence of late restenosis and data from the cardiac literature demonstrating better long-term results with angioplasty and stenting led to the performance of the combination approach in the intracranial circulation. The results of intracranial angioplasty and stenting performed between 1999 and 2002 were reported in 10 series consisting of 89 patients (19, 20, 41, 42, 50, 51, 54, 57, 61, 62). Technical success rates ranging from 64 to 100% were reported, with major complication rates ranging from 0 to 36%.

Three recent clinical series, the SSYLVIA study (66), the consecutive series of angioplasty and stenting for M1 stenoses reported by Jiang et al. (30), and the HDE study for the Wingspan (23, 70), are important additions to the literature. SSYLVIA was a safety and feasibility study designed to evaluate the Neurolink stent (Guidant Corporation, Indianapolis, IN), a flexible, stainless steel stent specifically designed for intracranial placement, in 61 symptomatic patients with intracranial stenosis (66). The stent was deployed successfully in 95% of patients. By 1 year, six strokes had occurred in 43 patients with intracranial lesions (13.9%). At 6 months, restenosis (>50% stenosis) developed in 12 out of 37 (32.4%) intracranial arteries. Overall (no distinction made between intracranial and extracranial vessels), seven (39%) of these patients were symptomatic (stroke or TIA). Among the interesting secondary findings in the intracranial stenosis group were the predictors of restenosis, including diabetes, 30% or more postprocedure residual stenosis, and the pretreatment diameter of the vessel.

In a single-center series consisting of 40 patients with 42 symptomatic M1 stenotic lesions treated with angioplasty and balloon-mounted coronary stenting, Jiang et al. (30) reported a technical success rate (≤20% residual stenosis) of 97.6%, with a 10% major complication rate. Among patients with major complications, one died of a subarachnoid hemorrhage and three experienced no major neurological injury. None of the 38 patients available for clinical follow-up evaluation (median follow-up, 10 mo) experienced stroke or recurrent TIA. Follow-up angiography was performed in only eight patients, with one case of restenosis documented. The results of both the SSYLVIA study and the series reported by Jiang et al. clearly demonstrate more than 95% accuracy for deployment of a stent in the correct intracranial location. Despite improved technical success, it remains uncertain whether or not the cardiac literature, which demonstrates that stenting in small coronary arteries leads to less restenosis than stand-alone balloon angioplasty, is applicable to the intracranial circulation (34).

A comparison of the findings of the Wingspan study with those from the SSYLVIA trial and the series reported by Jiang et al. demonstrates lower complication and restenosis rates for the self-expanding Wingspan stent (*Table 1*). As mentioned, in the SSYLVIA trial, the stroke incidence was 13.9% at 1 year, with a 32.4% restenosis rate in the intracranial arteries and more than 30% of study patients being symptomatic. Jiang et al. reported on 40 patients with 42 middle cerebral artery symptomatic stenoses. The overall morbidity and mortality was 10%, and no patient had a TIA or stroke during the 10-month follow-up period. As mentioned, restenosis occurred in one out of eight patients for whom follow-up angiography was obtained. In a population with a history of stroke in more than 90% of patients, versus 60% for SSYLVIA and WASID, the Wingspan HDE trial had ipsilateral stroke and death rates of 4.5% at 30 days and 9.3% (four out of 43 patients) at 6 months. Three (out of 40 cases; 7.5%) patients had restenosis at 6 months. Although the SSYLVIA trial and Jiang et al. demonstrate a lower complication profile compared with historical controls, no study has been reported in which staged and nonstaged self-expanding stenting has been compared. In a recent series of 36 patients with 37 symptomatic intracranial stenoses treated with angioplasty alone, Marks et al. (44) report stroke and/or death rates of 8.3% at 30 days and 10.8% at 1 year (*Table* 1) (44). The Wingspan system seems to have a better safety profile and lower restenosis rate than other systems to date (*Fig. 2*). However, the onus is on physicians involved in the treatment of intracranial atherosclerotic disease to

TABLE 1. Recent major series of treatment of symptomatic patients with intracranial atherosclerotic disease[a]

	WASID (9), warfarin versus aspirin	Jiang et al. (30), balloon-expandable stenting	SSYLVIA (66), balloon-expandable stenting	Wingspan HDE (22, 70), self-expanding stenting	Marks et al. (44), stand-alone angioplasty
No. of patients	569	40	43	45 (44 lesions)	36 (37 lesions)
Average % stenosis pretreatment	63.5	80.6	69.9[b]	74.9	84.2
Index event					
TIA (%)	39.1	72.5	39.3[b]	8.9	86
Stroke (%)	61.0	27.5	60.7[b]	91.1	14
30-d ipsilateral stroke and/or death rate (%)	N/A	10	6.6	4.5	8.3
1-yr ipsilateral stroke and/or death rate (%)	13.7%[c]	0[d]	13.9	9.3 (44 patients)	10.8
Restenosis (%)	Not applicable	12.5	32.4	7.5	Not available

[a] WASID, Warfarin-Aspirin Symptomatic Intracranial Disease; SSYLVIA, stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries; HDE, Humanitarian Device Exemption; TIA, transient ischemic attack.

[b] No breakdown provided for intracranial versus extracranial vessels.

[c] Ipsilateral stroke risk at mean follow-up of 1.8 years.

[d] Eight-month follow-up.

create studies that compare the paradigm of initial self-expanding stenting with staged angioplasty and stenting and best medical management.

ANTITHROMBOTIC AGENTS

Much of the data regarding the use of antithrombotic agents for primary treatment of patients with intracranial stenosis or for secondary prophylaxis after stent placement is obtained from the cardiac literature. By causing disruption of the intima, intracranial devices have significant thrombogenic properties and a great propensity to create platelet-fibrin deposits. For most intracranial endovascular interventions, anticoagulation with heparin to maintain an activated coagulation time between 250 and 300 seconds is essential at the beginning of the procedure. If the operator anticipates the possible use of glycoprotein (GP) IIb-IIIa agents during the procedure, maintaining the activated coagulation time in the range of approximately 200 seconds is recommended to reduce the risk of intracranial hemorrhage.

In addition to intraprocedural heparin therapy, the administration of periprocedure antiplatelet medications has become a standard of care for all extracranial and intracranial stenting procedures. Aspirin, a cyclooxygenase-1 inactivator that irreversibly inhibits platelet aggregation by blocking the conversion of arachidonic acid to thromboxane in platelets, and clopidogrel, a thienopyridine derivative that inhibits adenosine diphosphate receptor-mediated platelet activation, are workhorses in most procedures. Combining these antiplatelets agents has proved to be synergetic. A regimen consisting of both aspirin and clopidogrel, as compared with aspirin alone, has been shown to reduce the risk of vessel thrombosis (47, 83). Postprocedurally, clopidogrel routinely is continued for 4 weeks, the interval during which endothelial integrity is expected to be restored. However, there is additional data that continuing clopidogrel for up to 1 year may be beneficial, and sustained dual antithrombotic regimens may provide further protection against delayed thrombosis (67).

In addition to aspirin and clopidogrel, intravenous and extremely potent IIb-IIIa inhibitors are available. By binding the platelet GP IIb-IIIa receptor, these agents (abciximab, eptifibatide, tirofiban) are the most potent inhibitors of platelet aggregation. When used in concert with aspirin and heparin, GP IIb-IIIa inhibitors produce a maximal effect within minutes of an initial bolus injection. Abciximab, a receptor-specific antibody, prevents the binding of fibrinogen to the GP IIb-IIIa receptor. When administered intravenously, abciximab has a half-life of 10 minutes but a pharmacological action lasting for 48 hours. Eptifibatide, a cyclic peptide, is shorter acting, with platelet inhibition lasting for 2 to 4 hours. Tirofiban, a nonpeptide receptor inhibitor, has a half-life of 2 hours. The use of GP IIb-IIIa inhibitors has been advocated in high-risk patients with cardiac disease during percutaneous coronary interventions (16, 77). These agents have been used with good results during extracranial and intracranial stent placement in small, uncontrolled, nonrandomized clinical series (12, 37, 62). Another major use of GP IIb-IIIa inhibitors to date has been as a rescue drug when embolic phenomena have occurred during an endovascular procedure (33, 76). Typically, a bolus dose of the drug is administered directly into the thrombosed artery, followed by a 23-hour intravenous infusion. In patients with chronically hypoperfused brain tissue in the context of carotid stenosis and carotid angioplasty and stenting, a high rate of intracranial hemorrhage is associated with the use of GP IIb-IIIa inhibitors, likely because of a lack of autoregulation (60).

For patients with TIA or stroke who require medical treatment, the question remains as to the best regimen. Both the Management of Atherothrombosis with Clopidogrel in High-

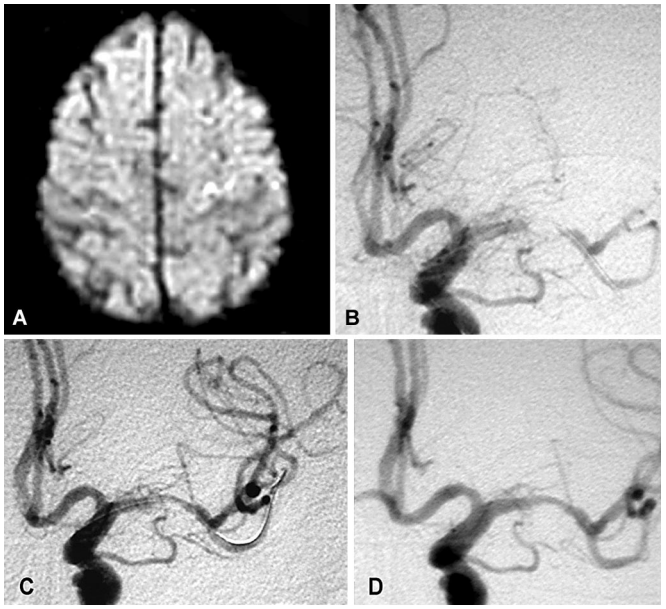

FIGURE 2. A, *diffusion-weighted magnetic resonance imaging scan showing a small watershed infarction in a 61-year-old woman with a 4-week history of progressive right hemiparesis and aphasia.* B, *cerebral angiogram showing a string of the left middle cerebral artery filling.* C, *cerebral angiogram showing excellent luminal improvement after M1 dilation with a 1.5 × 15-mm angioplasty balloon. Some haziness of the lesion can be appreciated, which is consistent with plaque disruption.* D, *cerebral angiogram showing the final result after deployment of a 2.5 × 15-mm Wingspan stent (Boston Scientific, Fremont, CA), across the stenosis. Excellent luminal reconstruction can be seen.*

risk Patients trial and the recent Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial have demonstrated no benefit for the combination of aspirin and clopidogrel and an associated increase in the risk of bleeding (4, 14). The European Stroke Prevention Study trial demonstrated the efficacy of dipyridamole plus aspirin versus aspirin alone (14). The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial demonstrated a slight benefit for clopidogrel compared with aspirin (8). Certainly, on the basis of the WASID results, warfarin is not the answer (9). Judicious use of high-dose aspirin, clopidogrel, or dipyridamole as a single agent is likely a best first choice for conservative management in the context of global risk-factor reduction, including smoking cessation, cholesterol-lowering agents, and diabetes and hypertension management.

FROM THE PAST TO THE FUTURE

In 1999, Connors and Wojak (12) published the report of their learning curve with a series of 70 patients who underwent angioplasty for intracranial atherosclerotic disease. Their technique progressed from directly sizing the balloon to the artery caliber with rapid balloon inflation to undersizing the balloon with slow inflation. The occurrence of acute vessel occlusion and dissection dropped from 75 to 14% with this technique (12). The classification scheme developed by Mori et al. (52), which is based on length of stenosis, degree of stenosis, and eccentricity of plaque, is highly predictive of outcome, with 92, 86, and 33% clinical success rates in patients with Types A, B, and C lesions, respectively: Type A, 5 mm or less in length concentric or moderately eccentric lesions less than totally occlusive; Type B, tubular 5 to 10 mm in length, extremely eccentric or totally occluded lesions, less than 3 months old; and Type C, diffuse, more than 10 mm in length, extremely angulated (>90 degrees) lesions with excessive tortuosity of the proximal segment, or totally occluded lesions, and 3 or more months old. At the 1-year follow-up evaluation, restenosis rates associated with these lesion types were 0, 33, and 100%, respectively; the risk of major stroke or death was 8% in Type A, 26% in Type B, and 87% in Type C (49). In 2002, Levy et al. (37) published a small series in which they described the concept of staged stent placement after angioplasty, reasoning that delayed stent placement gives the artery time to heal in the acute phase after angioplasty and would lead to a decrease in morbidity (*Fig. 3*). Kennedy et al. (32) and

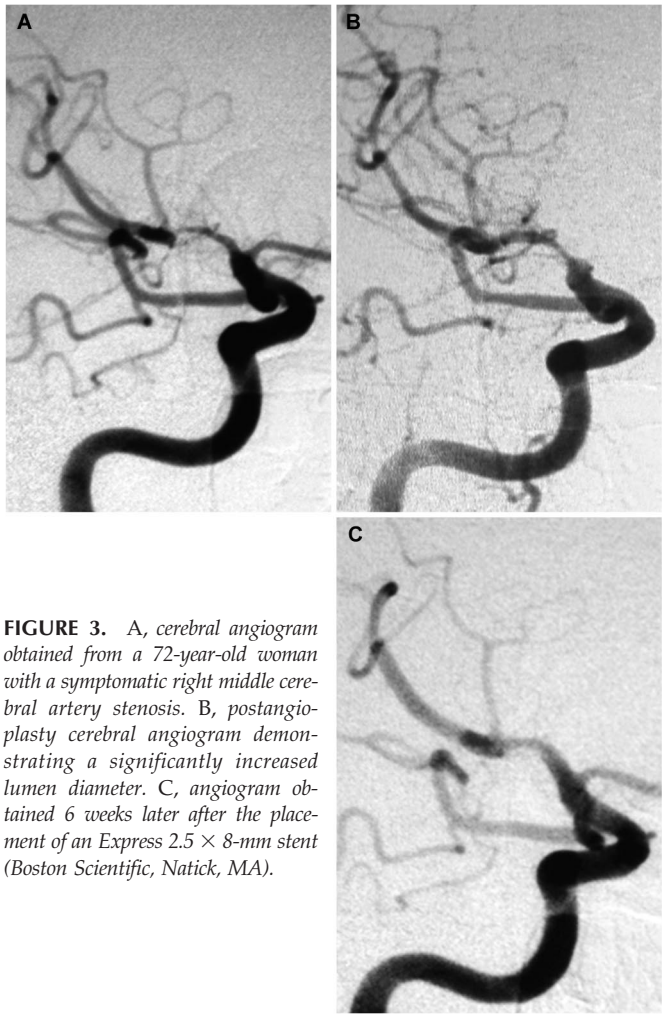

FIGURE 3. A, *cerebral angiogram obtained from a 72-year-old woman with a symptomatic right middle cerebral artery stenosis.* B, *postangioplasty cerebral angiogram demonstrating a significantly increased lumen diameter.* C, *angiogram obtained 6 weeks later after the placement of an Express 2.5 × 8-mm stent (Boston Scientific, Natick, MA).*

Wainwright et al. (80) published extensive animal data demonstrating that balloon angioplasty injures the intima, upregulating inflammatory mediators and leukocytes at the injury site. Leukocytes seem to be the major player in the cascade of events leading to both neointimal proliferation and fibrosis (80). At our practice, undersizing balloons, slow inflation, and staged stent-assisted angioplasty have led to improved outcomes in patients undergoing endovascular treatment of intracranial atherosclerosis (38). Type C lesions are high risk and should be treated only with great caution in patients with high risk for cerebral infarction. In the series reported by Jiang et al. (30), the mortality rate was 25% for the equivalent of a Mori Type C lesion and 0 for Types A and B.

Many technical issues remain. Long-term restenosis rates continue to be a concern. More stents, balloons, and delivery systems that are able to navigate the intracranial circulation easily are still needed. Drug-eluting stents that have been used with recent success in coronary vessels hold promise for lowering restenosis in intracranial vessels (39, 53, 69). An increasing number of randomized, prospective trials have demonstrated the efficacy of drug-eluting stents in the coronary circulation. The two drugs used in clinical practice have been sirolimus and paclitaxel. Sirolimus (rapamycin) is an antifungal agent that induces cell-cycle arrest and has been shown to reduce neointimal proliferation in animals. Paclitaxel, a microtubule inhibitor, also has been shown to prevent neointimal proliferation. The results of the Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent showed that sirolimus-eluting stents prevent neointimal proliferation, regardless of vessel diameter (approximately 40% of the vessels were small, i.e., <2.5 mm) (53). In a prospective, randomized, multicenter trial of 536 patients, results of the 6-month follow-up evaluation indicated that polymer-based paclitaxel-eluting stents led to reductions in neointimal propagation and restenosis rates (11).

Three studies have examined heparin- and sirolimus-coated stents in canine basilar arteries (36, 39, 40). The first study demonstrated that heparin-coated stents had an average 12% luminal stenosis at 12 weeks of follow-up versus 22% in the bare metal stent group (36). In the second study, sirolimus-coated stents, when compared with bare metal stents, tended to reduce smooth muscle cell proliferation, did not impair endothelialization, and, importantly, demonstrated no toxicity to the surrounding vessel wall or brainstem (39). The latter findings were recently confirmed by a randomized, blinded, prospective study involving bare metal stents, polymer-coated stents, and sirolimus-eluting stents (40). The data demonstrated that arterial tissue juxtaposed to the stent retained sirolimus up to 90 days and that brain and cerebrospinal fluid levels of sirolimus could not be detected after 1 week. Additionally, smooth muscle proliferation was reduced significantly in the drug-eluting arm as compared with the polymer-coated or bare metal stent arms for as long as 180 days (the duration of this investigation). Currently, there is no ideal stent for the intracranial circulation. Coronary balloon-mounted stents deploy at high pressures and are more rigid because they have been designed for more robust arteries. Interestingly, in the Stenting in Small Coronary Arteries trial, a total of 145 patients were randomized to receive angioplasty alone, or in combination with a heparin-coated stent in small (reference diameter of 2.1–3.0 mm) coronary arteries (48). In the heparin-coated stent group, event-free survival rates were higher and 6-month angiographic results were superior. This study concurred with the finding in the Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent that small-caliber vessels respond favorably to drug-eluting stents (63). An ideal stent would need to be visualized easily, to be navigable through the intracranial circulation, to be porous, to deploy reliably at low atmospheres of pressure, and to be coated with an agent to prevent restenosis and thrombosis.

Ultimately, angioplasty and stenting may not be the best treatment for symptomatic intracranial atherosclerosis. Despite elegant images provided by three-dimensional angiography, we lack real-time imaging documentation of vessel-specific anatomy and physiological parameters, such as elasticity and plaque configuration. Intravascular ultrasound and real-time magnetic resonance imaging techniques are being developed that may guide the interventional cases of the future (18, 21, 25, 79). These techniques also may be able to give direct feedback as to the elasticity and tensile strength that cerebral blood vessels can tolerate during angioplasty and stenting. In the future, tools like the SilverHawk direct atherectomy system (FoxHollow Technologies, Inc., Redwood City, CA) and cryoplasty could be miniaturized to fit the intracranial circulation without the need for stenting or angioplasty (29). Ultimately, the mechanical issues may be superseded by a noninterventional, biological treatment; the stroke reduction associated with statins administered in large clinical trials approaches 30%, and there is data suggesting an increase in cortical vessel reactivity with statin treatment (6, 68).

CONCLUSION

Intracranial stenosis is common and dangerous. Symptomatic stenosis carries a 10 to 20% 2-year risk of stroke and should be treated. Patients experiencing a single TIA and with less than 50% stenosis, no perfusion abnormality, or poor life expectancy may be treated medically with antiplatelet agents. High-dose aspirin, clopidogrel, or dipyridamole likely should be used as single agents. Warfarin has been shown to increase the risk of death and hemorrhage and no longer should be used. Asymptomatic patients should be treated medically, except those with a severe perfusion abnormality in the region of a fixed, focal lesion. Symptomatic patients, other than those mentioned above, should be considered for treatment with interventional techniques. The risk of percutaneous angioplasty and stenting has been lowered by the staged technique. With new self-expanding stents, the restenosis rate has dropped, without compromising safety.

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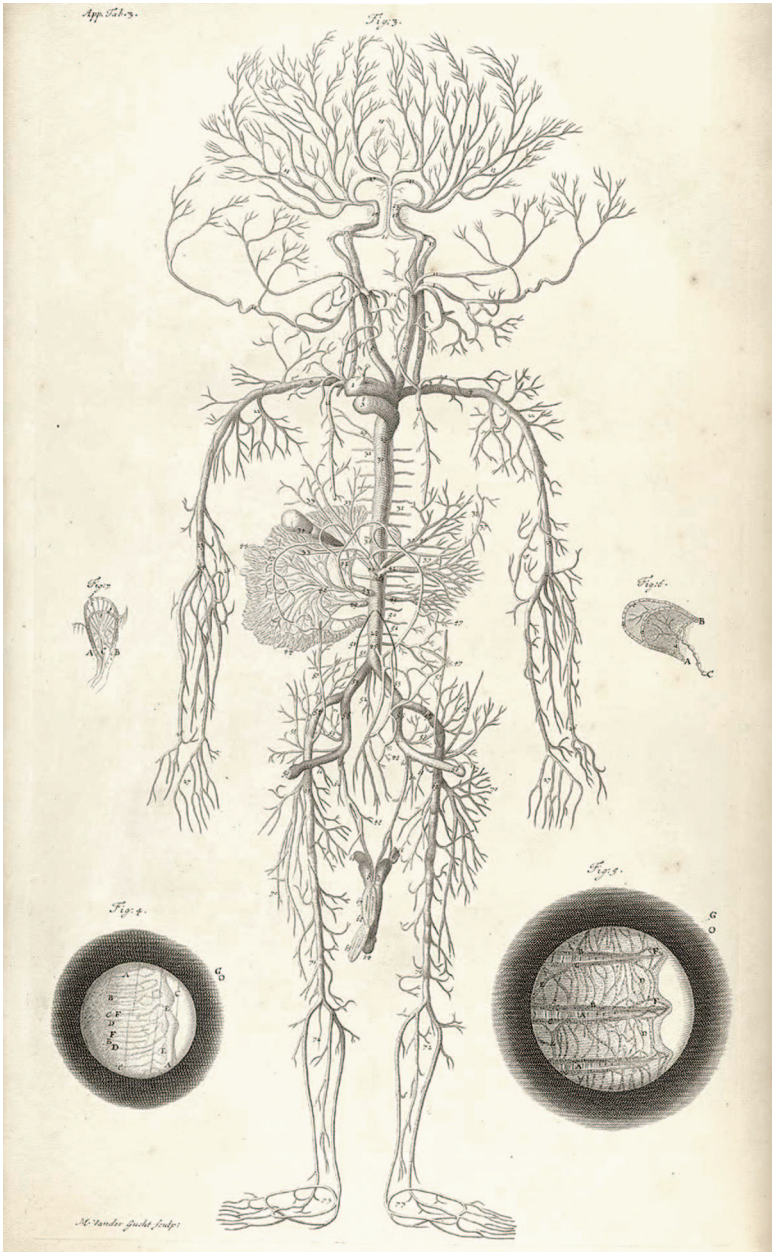

*William Cowper, 1666-1709, **The Anatomy of Humane Bodies**. Oxford: Printed at the Theater, for Sam. Smith and Benj. Walford, 1698 (courtesy of the U.S. National Library of Medicine, National Institutes of Health, Bethesda, Maryland).*

HISTOPATHOLOGY OF CAROTID ATHEROSCLEROTIC DISEASE

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STROKE IS THE third leading cause of death in the United States, constituting approximately 700,000 cases each year, of which about 500,000 are first attacks and 200,000 are recurrent attacks. Ischemic stroke accounts for the majority of all strokes (88%), followed by intracerebral hemorrhage (9%) and subarachnoid hemorrhage (3%). Patients with substantial carotid narrowing are at increased risk for major stroke; however, recent studies suggest that factors other than the degree of carotid stenosis are involved in ischemic stroke pathogenesis. Atherosclerotic plaque of the stenotic carotid artery is the underlying cause of the majority of ischemic strokes and specific plaque characteristics have been associated with ischemic brain injury. Several studies have demonstrated that the mechanisms of plaque instability in the carotid circulation are similar to those in the coronary circulation. The purpose of this review is to characterize atherosclerotic carotid disease in light of our knowledge of coronary atherosclerosis and relate carotid plaque morphology to cerebral ischemic syndromes. Histological examination of the carotid plaque specimen should provide insights into the underlying plaque morphology that is responsible for the disease and should help determine the potential treatments that are likely to be beneficial in the prevention of a subsequent event.

KEY WORDS: Atherosclerotic carotid disease, Cerebral ischemic syndromes, Stroke

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The earliest classification of atherosclerosis, although simple, had merit. Two types of lesions were described: the fatty streak and the atheromatous plaque. The fatty streak was considered a precursor lesion to the advanced atheromatous plaque. The fatty streak consists of cellular elements, including smooth muscle cells, fat-laden macrophages, and other inflammatory cells within a proteoglycan-collagenous matrix. The atheromatous or fibrofatty plaque was defined as a raised lesion having a lipid-rich necrotic core containing cholesterol and cholesterol esters with an overlying fibrous cap. The atheromatous plaque may develop into more complicated lesions, which include calcification, ulceration, thrombosis, and hemorrhage.

A more sophisticated numerical classification was put forth recently by the American Heart Association (29, 30). It implies an orderly linear pattern of progression of lesions, which may or may not be valid, and is based on the assumption that all thrombosis occurs from plaque rupture, which is not the case in the coronary arteries.

We have recently published a modification of the American Heart Association classification based on examination of more than 200 cases of sudden coronary death (34). The early lesion classification is similar to that reported by Stary et al. (30). The more advanced lesions, or fibrous cap atheromas, can be further characterized by the nature of the fibrous cap. The thin cap atheroma is thought to be a precursor lesion to plaque rupture and is characterized by a necrotic core (approximately 25% of plaque area) and has a thin fibrous cap (<65 μm), which is heavily infiltrated by macrophages. Another term for the thin cap atheroma is *vulnerable plaque*, based on the propensity of this lesion to rupture. Because plaque rupture accounts for the majority of thrombi in patients with sudden coronary death, identification of thin cap atheroma is critical. The precursor lesion for the less common type of coronary thrombosis, plaque erosion, differs from that of plaque rupture, and includes early lesions with or without a well developed necrotic core (fibroatheroma) and pathological intimal thickening. The "calcified nodule"

represents the least frequent cause of luminal thrombus accounting for 2 to 5% of coronary thrombi.

MECHANISMS OF ACUTE CORONARY SYNDROMES

In cases of sudden coronary death, at least 75 to 80% of patients dying suddenly show the presence of acute or organized thrombi, while the rest demonstrate "critical" (≥75%) cross sectional area luminal narrowing. Acute plaque rupture or erosion account for 60% of sudden deaths, and only 15% of these will show presence of myocardial infarction. Stable plaque or fibrocalcific plaques, with or without necrotic core, which lead to a luminal narrowing of 75% or more are present in up to 26% of patients dying suddenly. The mechanism of death in these patients is poorly understood.

ENDARTERECTOMY AND STROKE

In 2003, the estimated number of endarterectomy procedures performed in the United States was 117,000. Carotid endarterectomy is the most frequently performed surgical procedure to prevent stroke (33). Clinically, the patients present with ipsilateral neurological events that include amaurosis fugax, transient ischemic attacks (TIA), or stroke. Most of the symptoms originate from the internal carotid artery or the common carotid artery from underlying severe atherosclerotic disease. The diagnosis of carotid atherosclerotic disease is established via imaging techniques, such as ultrasonography with or without Doppler, angiography, computed tomographic scan, magnetic resonance imaging, and single photon-emission tomographic scanning.

In the North American Symptomatic Carotid Endarterectomy Trial, endarterectomy was efficacious in reducing the risk of stroke and death up to 2 years in patients with 70 to 99% stenosis of the ipsilateral carotid artery (23). The benefit of carotid endarterectomy is reduced for those with 50 to 69% stenosis; however, for patients with less than 50% stenosis, the failure rate was similar for endarterectomy or medical therapy (2, 3). Subsequent studies in asymptomatic carotid stenosis of 60% or more among patients who are good surgical candidates have demonstrated a reduced 5-year risk of ipsilateral stroke after carotid endarterectomy versus medical therapy (14).

CAROTID ATHEROSCLEROTIC PLAQUE PATHOLOGY

The North American Symptomatic Carotid Endarterectomy Trial study focused on luminal narrowing as a primary measure for evaluating the benefits of endarterectomy in stroke patients and currently guides the management for patients with symptomatic stenosis greater than 69%. However, the degree of stenosis does not always accurately predict those patients who will develop vulnerable lesions, as low-grade stenosis may also result in cerebrovascular events. Pathological studies suggest that other factors, such as atherosclerotic plaque composition, may represent an independent risk factor for ischemic stroke.

The earliest pathological studies described the occurrence of atherosclerosis near branch ostia, bifurcations, and bends, suggesting that flow dynamics play an important role in its induction. It has been demonstrated that laminar flow is disturbed at carotid bifurcation regions. The greatest atherosclerotic plaque accumulation typically occurs on the outer wall of the proximal segment of the sinus of the internal carotid artery, in the region of the lowest wall shear stress. The intimal thickness is the least on the flow divider side at the junction of the internal and external carotid arteries where wall stress is the highest (*Fig. 1*) (16).

Fewer pathological studies have correlated carotid and aortic plaque morphology with cerebral findings, and, as a result, the mechanisms by which carotid atherosclerosis results in cerebrovascular symptoms are less well understood than those linking coronary disease and myocardial symptoms. Several recent studies, one of which analyzed 526 symptomatic carotid plaques, have demonstrated that the pathology of symptomatic plaques is similar to that of culprit coronary plaques (25, 28). Furthermore, these studies have demonstrated that occlusive thrombus triggered by plaque rupture is one of the major determinants of ischemic stroke in patients affected by carotid atherosclerotic disease (25, 28). However, there are important differences between the coronary and carotid vascular beds. For example, unlike the myocardial circulation, the carotid vascular bed is subject to high blood flow. The majority of ischemic strokes seem to result from embolization from an atherosclerotic plaque or acute occlusion of the carotid artery and propagation of the thrombus distally rather than static occlusion (18).

A recent study by Spagnoli et al. (28) proposed that thrombosis associated with plaque rupture is one of the major determinants of ischemic stroke in patients affected by carotid atherosclerotic disease. Thrombotically active plaques were defined by the presence of an acute thrombus composed of platelets or fibrin on the plaque surface with or without interspersed red and white blood cells. A thrombotically active plaque was observed in 74% of plaques from patients with ipsilateral major stroke. Of these, 90.1% were associated with plaque rupture and 9.9% with luminal surface erosion. In contrast, 35.2% of patients with transient ischemic attack and 14.6% of asymptomatic patients were found to have thrombotically active plaque. In the group of patients with transient ischemic attack, erosion was approximately twice that of patients with stroke. Total thrombotic occlusion was found in 40.8% of cases with a thrombotically active plaque as documented by angiographic stenosis of more than 95%. These results demonstrate a major role of carotid thrombosis and inflammation in ischemic stroke in patients affected by carotid atherosclerotic disease.

Moreover, the study demonstrated the severity of clinical events correlated significantly with the degree of inflammation in ruptured plaques, suggesting that inflammatory cells

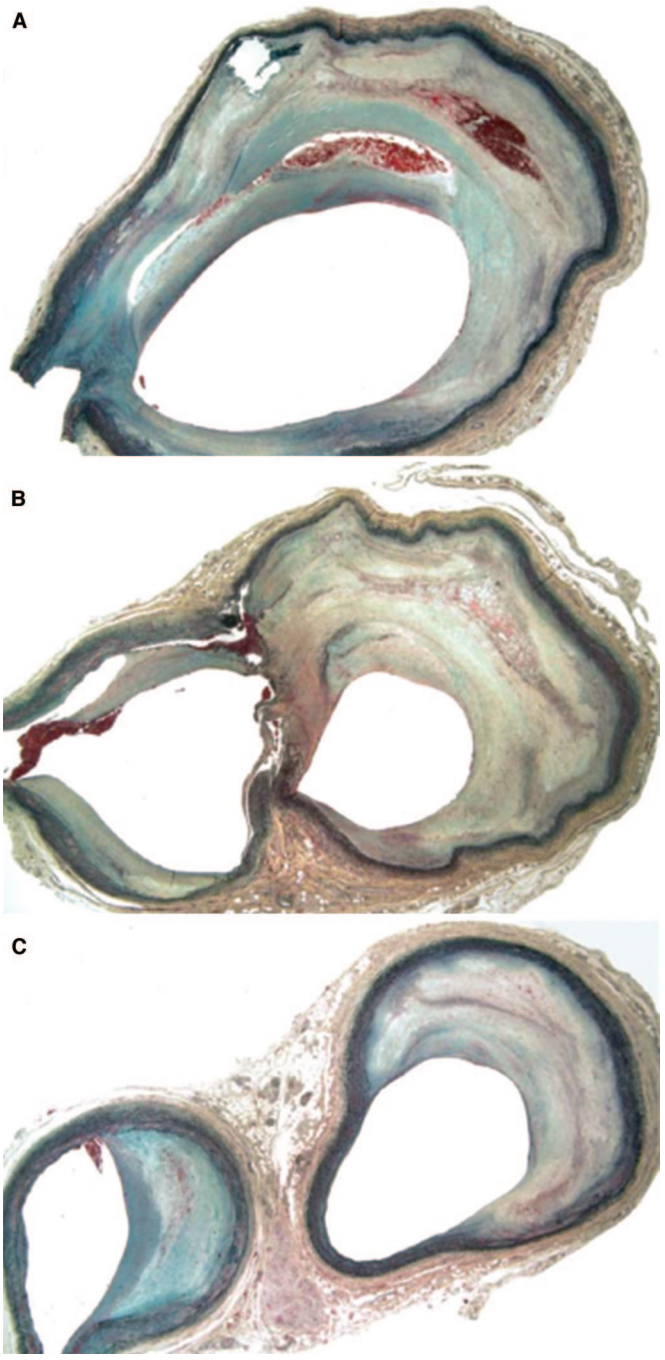

FIGURE 1. *Carotid bifurcation, atherosclerotic disease.* A *demonstrates the common carotid artery. There is moderate narrowing by atherosclerotic plaque of the common carotid artery, with two hemorrhagic necrotic cores. This layering indicates repeated surface disruption (rupture) and healing with smooth muscle cells.* B *demonstrates the bifurcation, with the flow divider illustrated in the center. Note that the flow dividers on either side are relatively devoid of plaque, indicating the high shear stress in this site is relatively protective of accumulation of atherosclerotic material.* C *shows the internal carotid artery* (right)*, with the external carotid* (left)*. Note the positive remodeling of the internal carotid artery at the site of atherosclerotic plaque.*

originating from the inflamed plaque may contribute to cell and tissue injury in ischemic brain disease.

While recent reports highlight significant differences in the frequency of plaque rupture between symptomatic and asymptomatic patients, other factors have also been associated with ischemic stroke. These include surface irregularity, plaque vascularity, ulceration, fibrous cap thinning, and infiltration of the fibrous cap by macrophages and T cells (5, 9, 18, 25).

Previously, we reviewed 44 carotid endarterectomy specimens (from 25 asymptomatic and 19 symptomatic patients). The asymptomatic and symptomatic patients had similar mean percent stenosis (77% versus 74%, respectively). Thirty-three patients were men and 11 were women, with a mean age of 74 years for asymptomatic patients and 70 years for symptomatic patients. Patients were considered symptomatic if they had experienced stroke, transient ischemic attack, or amaurosis fugax ipsilateral to the carotid lesion being studied. Other risk factors, including hypertension, diabetes mellitus, coronary artery disease, smoking history, and serum cholesterol and triglyceride levels were similar between groups. Each plaque was evaluated for the presence of a necrotic core, calcification, microscopic ulceration, plaque rupture, intraplaque hemorrhage, thrombus, infiltration of smooth muscle cells, fibrous cap thinning, infiltration of the fibrous cap with foam cells, and intraplaque fibrin. We showed that symptomatic carotid artery disease is more frequently associated with plaque rupture (74%) than is asymptomatic disease (32%) (9). Our observations suggest critical differences in plaque morphology between patients with symptomatic and asymptomatic disease.

In a study of carotid endarterectomy specimens from symptomatic high-grade stenosis lesions and asymptomatic autopsy specimens without high-grade carotid artery stenosis, Bassiouny et al. (4) showed that high-grade carotid stenotic plaques were associated with a significantly higher incidence of ulceration (53%), thrombosis (49%), and lumen irregularity (78%) compared with nonstenotic asymptomatic plaques (6, 0, and 17%, respectively; $P < 0.01$). Although these features were more prominent in symptomatic patients, they were also present in 80% of the stenotic bifurcations and did not distinguish between symptomatic endarterectomy and asymptomatic autopsy lesions.

The study by Bassiouny et al. (4) differed from our observations in that it failed to show distinct morphological differences between asymptomatic and symptomatic carotid lesions. The reason for the discrepancies between our study and that of Bassiouny et al. may be dependent on the degree of stenosis in the varying patient populations. Approximately half of symptomatic and asymptomatic patients in our study had stenosis of 80% or more, another 30 to 35% of the patients had 60 to 79% stenosis, and 21% of symptomatic versus 8% of asymptomatic patients had less than 60% stenosis. Furthermore, our patient population was older (mean age 74 yr versus 61 yr in the study by Bassiouny et al.).

In a subsequent report from the same group, examination of the proximity of the necrotic core to the lumen showed that it was twice as close to the lumen in symptomatic versus asymptomatic plaques (0.27 ± 0.3 mm versus 0.5 ± 0.5 mm, respectively; $P < 0.01$). The percent area of necrotic core or calcification was similar for both groups (22% versus 26% and 7% versus 6%, respectively). The number of macrophages infiltrating the fibrous cap was three times greater in the symptomatic plaques compared with the asymptomatic plaques (1114 ± 1104 versus 385 ± 622, respectively, $P < 0.009$) (5). Finally, disruption or ulceration of the fibrous cap was more common in the symptomatic than asymptomatic plaques.

In our laboratory, the mean fibrous cap thickness in carotid plaque rupture was nearly three times greater than coronary plaque rupture (72 ± 15 μm versus 23 ± 17 μm, respectively) (*Fig. 2*). Carotid vulnerable plaques (necrotic core with overlying thin cap and infiltration by macrophages, *Fig. 3*) have a mean cap thickness of 72 ± 24 μm, whereas the upper limit of a thin-cap fibroatheroma in the coronary artery is 65 μm or less. In addition, there are fewer macrophages in the fibrous cap of carotid plaque ruptures than coronary plaque ruptures (13.5 ± 10.9 versus 26 ± 20%, respectively). Similarly, in carotid vulnerable plaques, the number of macrophages is fewer than coronary vulnerable plaques (10 ± 1.8 versus 14 ± 10%, respectively) (34).

Plaque vascularity has been shown to correlate with intraplaque hemorrhage and the presence of symptomatic carotid disease (22). The role of vasa vasorum in precipitation of acute coronary syndromes and aortic plaque disruption is the focus of ongoing research. Imaging techniques for detection of vasa vasorum in carotid plaques may be important in future evaluation of carotid stenosis.

CAROTID VERSUS CORONARY DISEASE: DIFFERENCES IN PLAQUE MORPHOLOGY

The classification of atherosclerotic plaque devised for coronary arteries and aortas is well suited for use in the carotid circulation. There are, however, unique features of carotid plaque morphology because of the high flow rates and the shear forces caused by the bifurcation of the common carotid artery into the internal and external carotids. Most importantly, the ulcerated plaque, which is rare in the coronary artery circulation, is relatively common in the carotid and other elastic arteries. *Ulcerated plaque* is a term used when the thrombus and a portion of the plaque have embolized, leaving an excavation in the remaining lesion (*Fig. 4*). Another feature of carotid atherosclerosis is the infrequency of total occlusion relative to the coronary circulation. Occlusive carotid disease is reported in 3% of patients with posterior circulation infarcts, 14% in those with partial anterior circulation infarcts, and 29% in patients with total anterior circulation infarcts; however, in coronary circulation, the incidence of chronic total occlusion in patients dying suddenly is 40% (8, 18). The explanation for the low rate of total occlusions in carotid plaques is most likely related to high flow rates that limit thrombotic occlusions, unless there is severe luminal narrowing caused by repeated plaque ruptures.

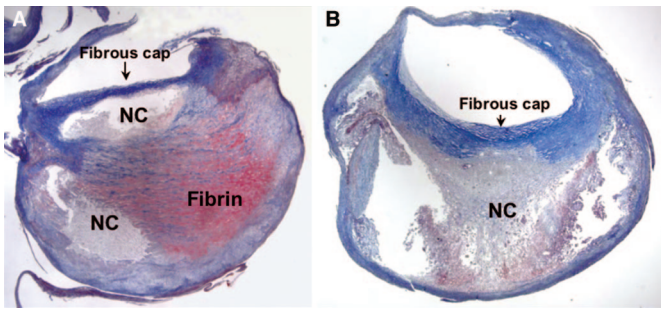

FIGURE 2. *Fibrous cap, carotid atherosclerosis. These photographs of carotid plaques (Masson trichrome stain) demonstrate multiple necrotic cores (NC), with a fibrin rich central area, and a thin fibrous cap* (arrow) *with collagen staining blue* (A). B *shows a single large necrotic core, with a thicker fibrous cap than shown in* A (arrow).

Plaque hemorrhage in the carotid artery is far more frequent than in the coronary arteries and may be related to high flow rates and pressures in the lumen and the vasa vasorum. The maximum frequency of hemorrhage is observed in arteries with 50 to 75% cross sectional area luminal narrowing (7). We have reported in coronary plaques that intraplaque hemorrhage is responsible for necrotic core enlargement and excessive foamy macrophages in the fibrous caps (20). Red blood cell membranes are the richest source of cholesterol as compared with any other cell in the body. The free cholesterol in the necrotic core is thought to arise from apoptotic cell death of foamy macrophages. However, we have shown that free cholesterol in fibroatheromas, thin cap fibroatheromas, and plaque ruptures is also derived from erythrocytes that become trapped in the necrotic core when intraplaque hemorrhages occur. Takaya et al. (31) recently reported that patients with carotid intraplaque hemorrhage at 18 months follow-up had larger necrotic cores as well as accelerated plaque progression as compared with patients without intraplaque hemorrhage.

The frequency of calcification is similar in coronary and carotid arteries, with maximum calcification seen in carotid arteries narrowed greater than 70% cross sectional area. However, the frequency of calcified nodules (*Fig. 5*), a form of calcification that results in irregular nodules of calcium, is higher in carotid disease (approximately 6-7%), as compared with 1 to 2% in coronary artery disease (Virmani R, unpublished observation, 1999). In contrast, plaque erosion, while common in the coronary circulation, is somewhat less frequent in the carotid artery. In carotid arteries, percent stenosis was highest in healed plaque ruptures and was greater than thin-cap atheromas and acute plaque ruptures.

RISK FACTORS CONTRIBUTING TO SYMPTOMATIC CAROTID DISEASE

The correlation of risk factors with stroke is complicated by the multiple etiological categories of stroke, including throm-

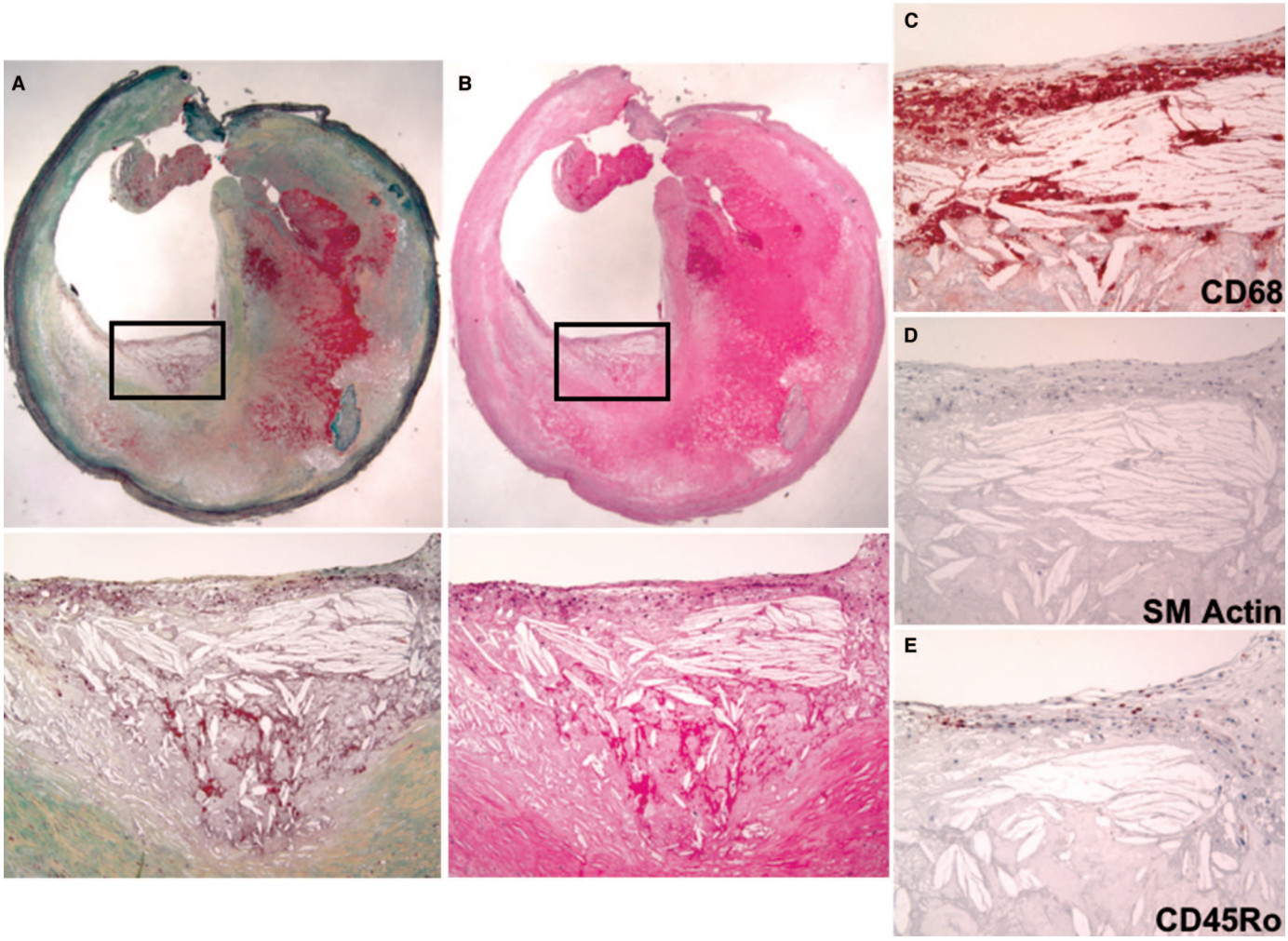

FIGURE 3. *Vulnerable plaque with hemorrhage.* A *(Movat stain) and* B *(hematoxylin and eosin stain) show carotid endarterectomy specimens with a thin fibrous cap* (boxed areas, *and* insets *below).* C *(CD 68 for macrophages),* D *(SM Actin for alpha actin for smooth muscle cells), and* E *(CD45Ro for T cells) demonstrate that, in the area of thinning of the cap, there are numerous macrophages, no smooth muscle cells, and a sprinkling of T lymphocytes.*

boembolism for ischemic strokes, aortic arch plaque embolization, and hypertensive hemorrhagic strokes. Overall, the major independent risk factor is elevated blood pressure. In general, however, carotid risk factors show a spectrum similar to coronary disease, and includes hypertension, and atherogenic and thrombotic factors.

Although hypertension is by far the most important risk factor for the development of all stroke, other risks include impaired cardiac function, diabetes, nonvalvular atrial fibrillation, migraine, family history, and others. Modifiable risk factors are listed as cigarette smoking, low level of physical activity, and obesity (36, 37). The incidence of stroke increases in proportion to both systolic and diastolic blood pressure, and is elevated in African-Americans, who have a high rate of hypertension (17).

Serum lipids have long been associated with coronary artery disease, but not with cerebrovascular disease. It has been shown that lipid-lowering therapy selectively depletes the lipid cores in carotid plaques. Zhao et al. (38) analyzed carotid endarterectomy specimens from patients treated for 10 years with lipid lowering agents in the Familial Atherosclerosis Treatment Study. This study demonstrated that the lipid core was significantly smaller in treated patients, although the extent of calcification was greater than non-treated controls, and the fibrous tissue content was the same.

In addition, clinical trials using β-hydroxy-β-methylglutaryl-CoA reductase inhibitors (statins) have shown a reduction of stroke risk in patients with coronary artery disease and elevated cholesterol levels (35).

Several studies have shown that inflammatory cells, cytokines, adhesion molecules, and other inflammatory mediators may be involved in the pathogenesis of ischemic cerebrovascular injury (15). For example, high C-reactive protein (CRP) levels have been shown to be a predictor of risk of future

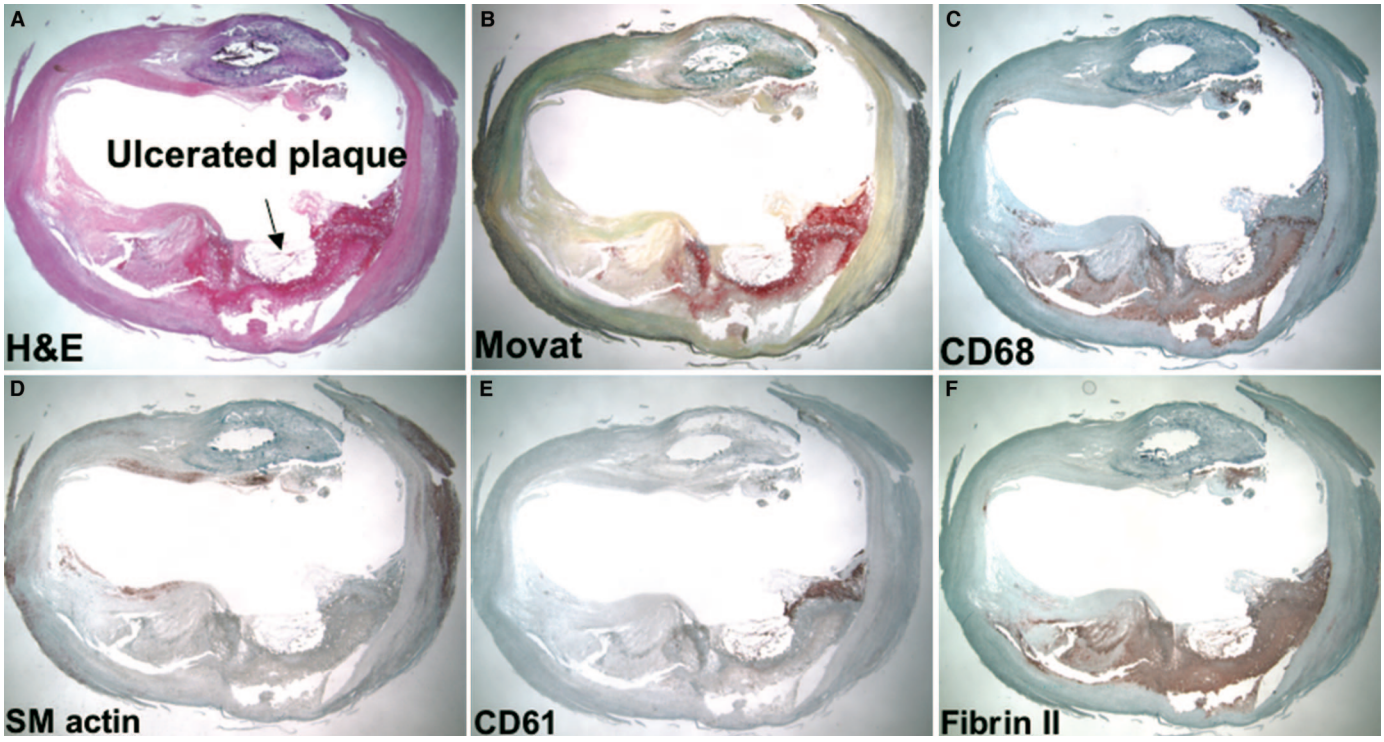

FIGURE 4. *Plaque rupture with thrombosis and ulceration. Unlike coronary arteries, in which ulcers are unusual, plaque disruption in the carotid artery frequently results in embolization and crater formation.* A, *routine hematoxylin and eosin section of a carotid artery with thrombus and ulcer.* B, *corresponding Movat pentachrome stain, which highlights collagen* (yellow) *and elastic tissue* (black). C *to* F, *immunohistochemical stains for macrophages (Kp-1), smooth muscle cells (alpha actin), platelets (CD61), and fibrin (fibrin II). Note that at the ulcer crater, there are abundant macrophages* (C) *with few smooth muscle cells* (D). *The thrombus itself has largely embolized; there are residual platelets* (E) *and fibrin* (E) *at one edge of the crater.* H&E, *hematoxylin and eosin stain.*

cardiovascular events. Similarly, independent of other cardiovascular risk factors, elevated plasma CRP levels significantly predict the risk of future ischemic stroke and transient ischemic attack in the asymptomatic elderly population (26). High CRP at hospital discharge is a predictor of future cardiovascular events and death in patients admitted with ischemic stroke.

Smoking, another independent risk factor for stroke, is associated with an increased arterial wall stiffness, increase in fibrinogen levels, increased platelet aggregation and hematocrit, and decreased high-density lipoprotein cholesterol (17). Hypercoagulable states associated with the development of stroke include antiphospholipid syndrome, Factor V Leiden, prothrombin 20210 mutation, protein C and S deficiency, and high fibrinogen levels. Nonfasting total homocysteine levels are an independent risk factor for incident stroke in elderly persons (6).

CORRELATION OF RISK FACTORS TO PLAQUE MORPHOLOGY

Several studies have correlated plaque morphology to risk factors in the carotid and coronary circulation. Spagnoli et al. (27) have shown that the fibrous carotid plaque correlated with aging and diabetes, the granulomatous plaque with hypertensive females, and the foam cell rich xanthomatous plaque exhibiting extensive alcianophilia with hypercholesterolemia. In smokers, plaques were frequently complicated by mural thrombosis. Mauriello et al. (21) studied carotid endarterectomy specimens and showed that patients with the highest tertile of fibrinogen (>407 mg/dl) had a high incidence of thrombosis (67%) compared with plaques of subjects with the lower and middle tertile (22% and 29%, $P = 0.002$ and $P = 0.009$, respectively). Plaque rupture was significantly associated with high fibrinogen level (54%, $P = 0.003$). Multivariate analysis revealed that hyperfibrinogenemia was an independent predictor of fibrous cap thickness (inverse correlation), macrophage foam cell infiltration of the cap, and thrombosis. When accounting for the other risk factors, hyperfibrinogenemia remained an independent predictor of carotid thrombosis (21). It is becoming increasingly evident that more studies correlating plaque morphology with risk factors are needed to further improve our understanding of carotid disease and target risk factor modification as more detailed assessment of plaque composition is possible with improved imaging techniques.

RECURRENT CAROTID DISEASE

The rate of recurrent carotid stenosis after carotid endarterectomy varies from 4 to 10% and usually occurs more than 3

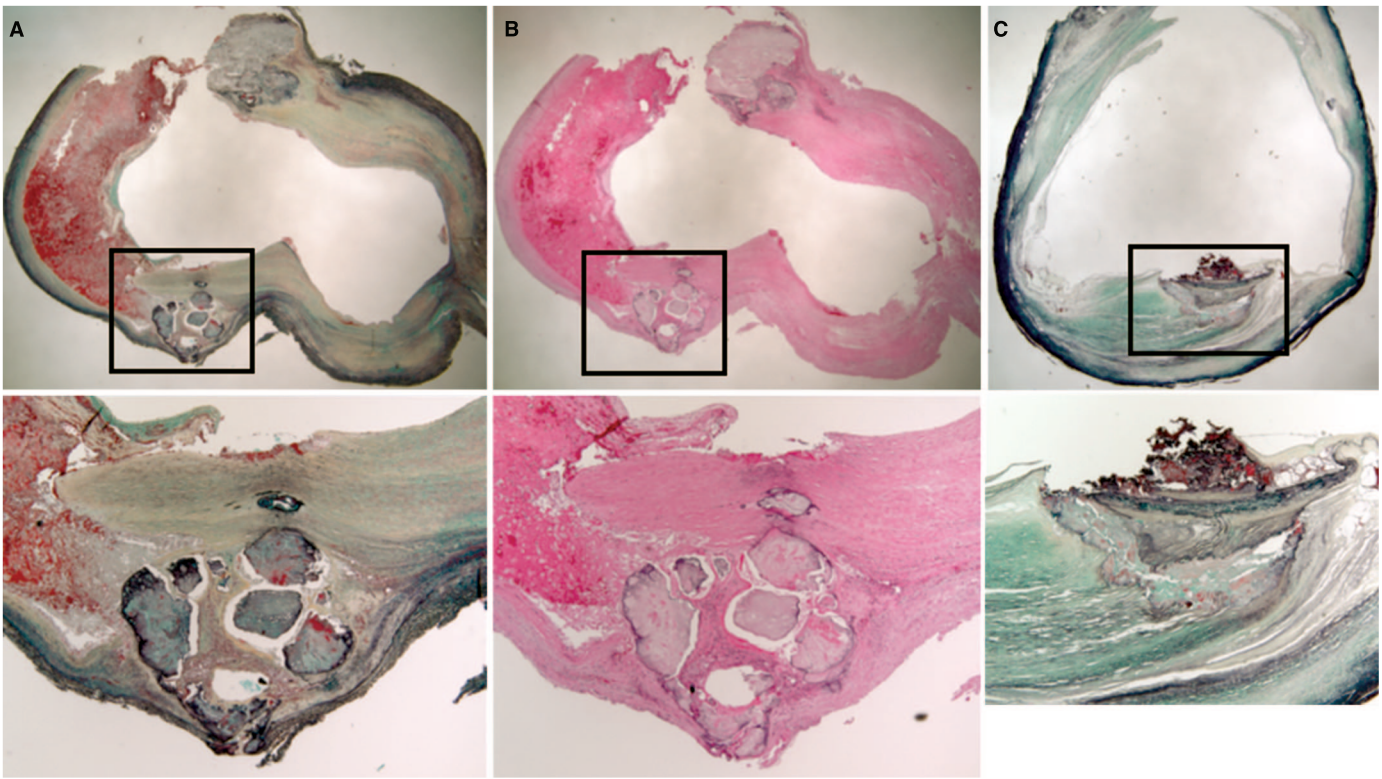

FIGURE 5. *Calcific nodule with luminal thrombus. A form of thrombosis that is more common in the carotid artery than in the coronary is the nodular calcified plaque.* A *shows a Movat pentachrome, and* B *show a hematoxylin and eosin stain of a carotid endarterectomy specimen with a nodular calcified area (*boxes, *and* insets *below).* C *demonstrates an area of surface thrombus (*boxed area, *and* inset *below) overlying the nodular calcification.*

months after surgery (11, 19). In a series of 1726 endarterectomies performed at the Cleveland Clinic from 1983 to 1997, 65 (3.8%) patients were reoperated on for recurrent carotid stenosis occurring 3 to 194 months (mean, 42 mo) after the initial procedure. Of these patients, approximately half were symptomatic with neurological symptoms and half were asymptomatic. The recurrence interval was 57 months in specimens with atherosclerotic disease (n = 37), whereas in specimens with myointimal hyperplasia (n = 28), the recurrence interval was 21 months ($P = 0.0007$). In recurrent disease, the myointimal hyperplasia consisted of smooth muscle cells in a proteoglycan matrix interspersed with fibrin; the collagen and elastin representing organization of the thrombus is sparse. Neovascularity may be present but is usually not extensive and surface thrombi tend to be platelet rich. Evidence of surface thrombosis was found in 77% of cases, but intraplaque thrombi are uncommon; only 15% are found in specimens collected less than 36 months after the initial endarterectomy. A recent review of the literature by Ecker et al. (13), representing a collection of more than 500 carotid endarterectomies that reported restenosis with follow-up periods varying from 18 to 82 months, shows a recurrence rate ranging from 0.7 to 7.9% during an average of 3.5 years. Their own 7.1 year follow-up of 975 patients, however, yielded a restenosis rate (defined as ≥70% stenosis) of only 0.1%.

In our experience, recurrent endarterectomy specimens collected up to 36 months postprocedure typically contain myointimal hyperplasia, and beyond this interval, atherosclerotic lesions are more common (10). Seventy-four percent of specimens with atherosclerotic lesions usually contain fibrin-rich surface thrombi, which are in continuity with an intraplaque thrombus (*Fig. 6*). Extensive neovascularity in lesions with atherosclerosis is common. The plaque components include foam cells, cholesterol clefts, abundant collagen with focal areas of necrosis and calcification. Some cases may show myointimal hyperplasia in the deep intima, but it is usually interspersed with atherosclerotic plaque. Although all the components of atherosclerosis are present in primary and recurrent lesions, the atherosclerotic elements are arranged in a less orderly manner in the latter. Primary plaques demonstrate a central necrotic core with cholesterol clefts beneath a fibrous cap, whereas in recurrent lesions, the necrotic core is superficial and often unsupported by a dense layer of collagen. In recurrent lesions, the thrombus is contained within the plaque, whereas in primary lesions, it is usually associated with intraplaque hemorrhage, which is rarely observed in recurrent lesions (10, 19).

Pauletto et al. (24) report that examination of primary endarterectomy lesions may be predictive of maximum intimal-medial thickness of revascularized vessels. Plaques with an abundance of smooth muscle cells, mostly of the fetal-type

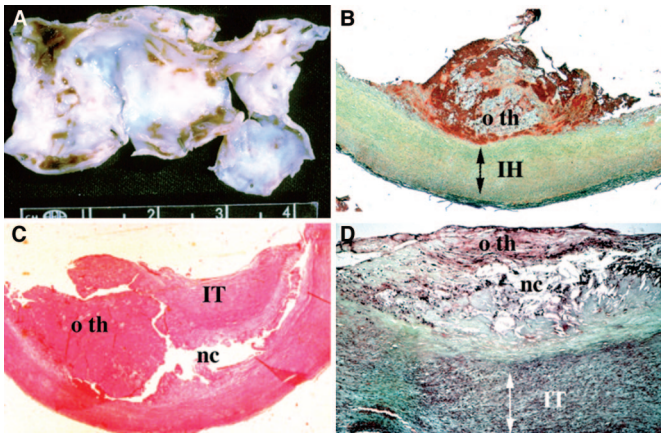

FIGURE 6. *Recurrent carotid disease.* A, *recurrent carotid endarterectomy specimen showing a mostly pearly white appearance from fibrointimal hyperplasia with focal thrombi.* B, *histological section of the same specimen showing organizing thrombus on the luminal surface with underlying fibrointimal hyperplasia (IH,* arrows*).* C, *low-power view of another specimen of a later recurrent lesion showing atherosclerotic change with necrotic core (nc) with fibrointimal thickening (IT) towards the lumen and organizing thrombus (o th) on the left.* D, *high-power view of another atherosclerotic plaque. Note the fibrointimal thickening (IT) underneath the necrotic ore (nc) and surface organizing fibrin thrombus (o th). Note the presence of cholesterol clefts with interspersed macrophage (*arrows*)* (B *and* D, *movat stain,* C, *hematoxylin and eosin stain)* (from, *Virmani R, Kolodgie F, Farb A, Burke A: Pathologic evaluation of carotid endarterectomy.* ***Pathol Case Rev*** 6:236–243, 2001.

(antismooth muscle cell-myosin heavy chain [myosin heavy chain positive]) were more likely to develop greater neointimal growth after surgery compared with lesions rich in macrophages and lymphocytes.

ATHEROSCLEROSIS OF THE AORTIC ARCH AS A RISK FACTOR FOR ISCHEMIC STROKE

Recent evidence shows that atherosclerotic disease of the aortic arch may be a source of cerebral emboli (12). Plaques located proximal to the ostium of the subclavian artery are reported in 60% of patients aged 60 years or more with ischemic stroke and the association was strongest when the plaques were 4 mm or more in thickness (1). In 1996, the French Study of Aortic Plaques in Stroke Group collected data on patients more than 60 years old who had been admitted for brain infarction and followed with transesophageal echocardiography to determine the presence of aortic atherosclerotic disease. The incidence of recurrent brain infarction was 11.9 out of 100 people per year in patients with aortic wall thickness of 4 mm or more, as compared with 2.8 out of 100 people per year in patients with a wall thickness 1 mm or less ($P < 0.001$) (32). It is not unusual to see plaque calcification in the aortic arch of sudden coronary death victims. Plaque ulceration and thrombosis is not an unusual finding at autopsy in patients 60 years of age or older (*Fig. 7*).

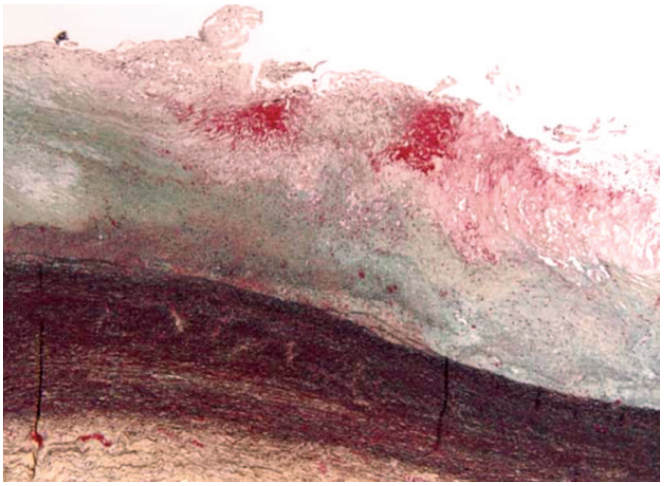

FIGURE 7. *Aortic ulcer. Not all cerebrovascular ischemia is the result of carotid disease. Aortic plaques in the area of the arch and great vessels may undergo rupture and ulceration, with embolization of the plaque and thrombus to the brain.*

CONCLUSION

Although the histopathology of carotid atherosclerotic disease resembles coronary atherosclerosis, there are distinct differences. While small mural thrombi are common, occlusive luminal thrombosis is typically not a major feature of carotid disease (varying from 3% for posterior circulation infarcts to 29% of total anterior circulation infarcts). Plaque ulceration is another common feature of carotid atherosclerosis, but infrequent in the coronary circulation. Similar to coronary disease, symptomatic carotid disease is predominantly associated with plaque rupture, but plaque erosion, an important subset of coronary thrombosis, is uncommon in the carotid circulation (10%). Calcified nodule, another cause of thrombosis, is perhaps more frequent in the carotid artery compared with the coronary circulation. Although there is a higher incidence of plaque rupture in symptomatic carotid disease compared with asymptomatic patients, the extent of lipid area, necrotic core size, and calcification may not be different. Not all cerebrovascular ischemia originates from the carotid atherosclerotic plaque and may frequently arise from atherosclerotic aortic arch disease. Therefore, in patients presenting with ischemic stroke, assessment of both the carotid artery and aortic arch is indicated. Finally, it is important to emphasize that the severity of luminal narrowing does not always correlate with the presence of a vulnerable plaque, and that other lesion morphologies, many of which are still under investigation, are involved in the pathogenesis of ischemic stroke. Further detailed pathological studies of endarterectomy specimens are required to identify specific morphological features that discriminate between asymptomatic and symptomatic carotid plaques, and to correlate the histological findings with existing diagnostic imaging models.

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CERVICAL CAROTID REVASCULARIZATION: THE CASE FOR CAROTID ANGIOPLASTY WITH STENTING

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CAROTID ARTERY ANGIOPLASTY with or without stent placement has evolved as an alternative to carotid endarterectomy, particularly for those patients in whom carotid endarterectomy is associated with a higher risk of complications. This article summarizes the selection criteria for participation in and the results of several carotid intervention trials, reviews the relative indications and limitations for both surgical and endovascular revascularization approaches, and describes the technique for and results associated with carotid stenting. The discussion is presented from the vantage of neurosurgeons who are experienced in both revascularization approaches.

KEY WORDS: Carotid angioplasty with or without stenting, Carotid artery stenosis, Carotid endarterectomy, Treatment

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Carotid endarterectomy (CEA) has been shown in multicenter, prospective, controlled clinical trials to prevent stroke and to improve survival in patients with both asymptomatic and symptomatic carotid artery stenosis (13, 15, 50). Since the publication of the results of these trials, this operation has been considered the "gold standard" for revascularization of extracranial carotid stenosis. With growing recognition that CEA presents a high risk of perioperative complications with increased mortality and morbidity for certain patients (51) and a general trend toward the performance of minimally invasive therapies, carotid artery angioplasty with or without stent placement (CAS) evolved as a less invasive endovascular treatment alternative (51, 60, 74), especially for the many high-risk patients who would not have met the strict criteria for inclusion in the CEA trials.

CEA TRIALS

Major CEA trials involving symptomatic patients with carotid artery stenosis include the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) (3, 13, 14, 50). In the NASCET, which was implemented in 1998, 2885 patients with recently symptomatic carotid stenosis (ischemic stroke or transient ischemic attack [TIA]) were stratified into groups with stenosis of moderate-grade (30–69%) (3) and high-grade (70–99%) (50) severity. All study patients received medical treatment with daily aspirin and, as indicated, antihypertensive, antilipid, and antidiabetic therapy. Patients assigned to surgery underwent CEA. The results of this study demonstrated a highly significant benefit for CEA compared with medical treatment alone in symptomatic patients with high-grade carotid stenosis at a mean follow-up duration of 2 years (50). Moreover, a significant benefit was shown for CEA compared with medical treatment alone in patients with 50 to 69% stenosis at a mean follow-up period of 5 years (3).

The results shown for the ECST were similar to those for the NASCET. In the ECST, 3024 patients were enrolled at 97 centers in Europe and Australia, with a mean follow-up period of 6.1 years (13, 14). In this trial, which was started in 1981, patients with TIA, retinal embolic phenomenon, or nondisabling stroke occurring within 180 days were randomized to receive medical therapy (usually aspirin alone) or medical therapy plus CEA. The final results of this trial showed a reduction in the 3-year risk of major stroke or death in patients with symptomatic carotid stenosis of 80% or more (60% according to the NASCET method for calculating angiographic stenosis) (50) from 26.5% in the medically managed group to 14.9% in the surgical treatment group, an absolute rate reduction of 11.6% in 3 years.

A landmark trial involving asymptomatic patients was the Asymptomatic Carotid Atherosclerosis Study (ACAS) (15). In the ACAS, 1662 asymptomatic patients with 60% or more carotid stenosis (according to NASCET calculations) (50) were randomized to receive CEA or medical therapy. As in the NASCET, the inclusion criteria were strict. Follow-up data for 1659 patients were available (median duration, 2.7 yr); the study was stopped prematurely because a significant benefit for surgery was found. The composite rates of ipsilateral stroke and death projected to 5 years were 5.1% in the CEA group (825 patients) and 11% in the medical group (834 patients). These results were achieved in conjunction with very low rates of death (0.1%) and stroke (2.3%) at 30 days in the CEA group.

The findings of the Asymptomatic Carotid Surgery Trial confirmed those of the ACAS (26). Between 1993 and 2003, 3120 asymptomatic patients with carotid stenosis from 126 centers in 30 countries were randomized to receive CEA or the best medical treatment. The study showed a 3.1% risk of stroke or death within 30 days of CEA. Comparing patients in the surgical group with those in the medical arm, the 5-year stroke risks were 3.8 versus 11%, respectively. When the rates of perioperative and nonperioperative events were combined, the 5-year risks were 6.4% in the surgical treatment group versus 11.8% in the medical treatment group. A summary of the results of these trials is presented in *Table 1*.

HIGH RISK FOR CEA

Although CEA is one of the most common surgical procedures performed in the United States, many patients cannot undergo such an extensive operation safely because of technical or anatomical factors or underlying severe medical illnesses, such as coronary artery disease and cardiac failure (20, 21, 59). In an analysis of the NASCET results, for example, CEA was approximately 1.5 times more likely to be associated with medical complications in patients with a previous history of myocardial infarction (MI), angina, or hypertension (52). Moreover, the benefits of carotid revascularization surgery shown by NASCET (3, 50), ACAS (15), and ECST (14) are lost if the 30-day rate of perioperative stroke or death exceeds 6% for patients with symptomatic carotid stenosis or 3% for those with asymptomatic carotid stenosis.

Evidence in the literature documents that the risk of CEA in clinical practice is much greater than is reflected in major CEA trials in which the lowest risk patients were operated on by experienced surgeons performing a relatively high volume of procedures. Studies reviewing Medicare patients undergoing CEA in 1992 and 1993 found that mortality rates were nearly two to three times greater at hospitals that did not participate in the NASCET and ACAS trials (37, 63, 70). Similarly, a study reviewing community hospital results showed much higher rates of procedure-related morbidity and mortality (5). New York State Statewide Planning and Research Cooperative System data showed that the average number of endarterectomies performed per surgeon was 2.9 (28), a significantly greater volume than the 25 to 50 per year required of NASCET surgeons (50). Nevertheless, although surgical experience may be an important factor contributing to this significant difference in complication rates, careful patient selection has been found to be the key determinant in maintaining a low perioperative complication rate (20, 21, 51, 52).

The conditions or characteristics discussed on the next two pages have been shown to predispose patients to a high perioperative risk of stroke and death in various CEA reports (20, 21, 51, 52). Because patients with one or more of these risk factors generally were excluded from enrollment in prospective CEA trials, the indications for and the results of surgery in these subgroups have not been established. CAS may provide a practicable alternative for revascularization in these patients.

TABLE 1. Landmark carotid endarterectomy trials[a]

Trial	No. of patients	Severity of stenosis	Reduction of ipsilateral stroke risk: Medical treatment	Reduction of ipsilateral stroke risk: Carotid endarterectomy	*P* value
Symptomatic carotid stenosis					
NASCET (50)	659	≥70%	26%	9%	<0.001
NASCET (3)	858	50–69%	22.2%	15.7%	0.045
NASCET (3)	1368	≤50%	18.7%	14.9%	NS
ECST (13, 14)	3008	≥70%	Only proportions analyzed		<0.001
		50–69%			NS
Asymptomatic carotid stenosis					
ACAS (15)	1662	≥60%	11%	5.1%	0.004
ACST (26)	3120	≥60%	11.8%	6.4%	0.001

[a] NASCET, North American Symptomatic Carotid Endarterectomy Trial; NS, not statistically significant; ECST, European Carotid Surgery Trial; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial.

Severe Coronary Artery Disease

Coronary artery disease is one of the most important factors to consider when evaluating the perioperative risk of CEA. The coexistence of severe carotid artery stenosis and symptomatic coronary artery disease presents the physician with a management dilemma (29, 52). The surgical repair of one condition cannot be accomplished without a substantial risk of complication from the other. In an analysis of the NASCET results, a history of treatment of coronary artery disease was associated with a lower CEA complication rate when compared with those with previously undiagnosed coronary artery disease (17). This incongruity may be the result of improved cardiac and general medical care in patients undergoing treatment for coronary artery disease, many of whom previously may not have received regular, long-term medical care. CAS may provide a reasonable alternative for revascularization in these patients (*Fig. 1*).

Adjunct to Coronary Bypass Surgery

Significant carotid artery disease places patients who are undergoing coronary artery bypass grafting (CABG) at an increased risk for stroke, embolization (air or atheromatous), or both. In a series of 539 patients who underwent noninvasive testing for the detection of carotid artery occlusive disease before undergoing CABG, carotid stenosis severity of more than 75% was found to be an independent predictor of stroke risk (odds ratio, 9.9) during CABG (16).

For patients with severe coexistent disease of the carotid and coronary arteries, there is little debate that revascularization is appropriate for both conditions; however, controversy exists regarding the timing of the procedures. Surgical options include the performance of a simultaneous procedure or a staged approach in which one procedure is performed several days after the other. Reports of combined CEA and CABG suggest that the risk of stroke or death ranges from 7.4 to 9.4%, which is roughly 1.5 to 2.0 times the independent risk of each operation (52). In a multicenter review, the composite risk of stroke and death was higher in patients who had CEA performed in conjunction with CABG (18.7%) than in those who had CEA alone (2.1%) (21). Conversely, patients who undergo CEA before CABG also have a higher risk of perioperative complications (11, 29). In this high-risk subgroup, avoiding a major operation or general anesthesia by performing CAS may represent a valid alternative to CEA (44). A meta-analysis of 56 studies regarding staged CEA and CABG published by the American Heart Association reported a composite incidence of stroke, MI, and death of 16.4% for combined carotid and coronary operations, 26.2% for CEA proceeded by CABG, and 16.4% for CABG proceeded by CEA (49). These high complication rates clearly offset the long-term benefit from secondary stroke prevention. Revascularization with CAS was performed at our center before planned CABG in 49 patients with coexistent disease of the coronary and carotid arteries (carotid stenosis $\geq$ 70%) (44). The 30-day mortality rate for the combined procedure was 8%; the stroke rate during the same period was 2%. These complication rates seem to be substantially lower than those associated with combined CABG and CEA or with CABG followed by CEA. In addition, no clinically significant recurrent carotid stenosis was noted during a mean follow-up interval of 27 months. These results support the consideration of CAS as an adjunct to CABG in patients with coexistent severe coronary artery disease.

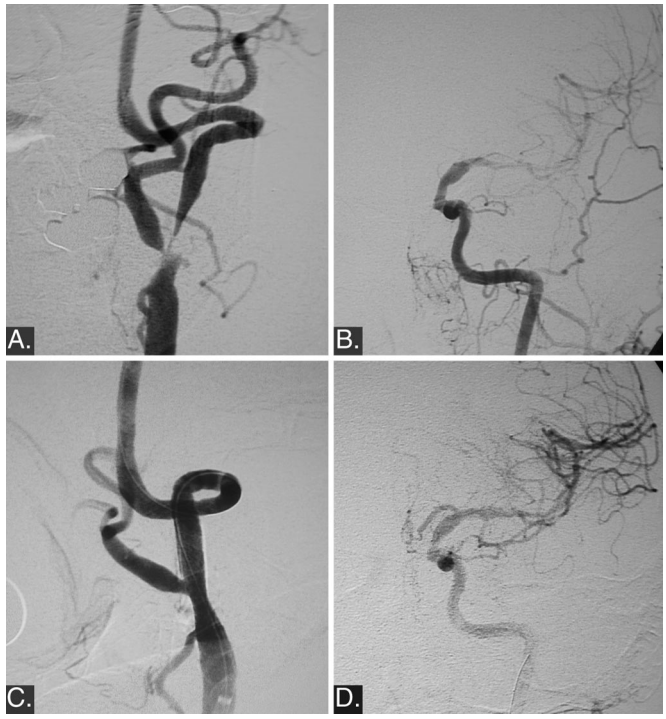

FIGURE 1. *Images obtained from a 74-year-old woman with left hemispheric transient ischemic events. Her past medical history included severe coronary artery disease.* A, *carotid angiogram, lateral view, demonstrating severe stenosis of her external and internal carotid artery on the left side, with difficult aortic arch access (not shown). The extremely complex (>90 degrees) curve in her carotid artery made the use of a distal protection device virtually impossible.* B, *intracranial image, frontal view, revealing good filling of the left middle cerebral artery territory and lack of filling of the anterior cerebral artery, suggestive of a flow-limiting effect of the cervical lesion or the presence of a hypoplastic A1 segment of the anterior cerebral artery. The decision was made to place a 9-French balloon guide catheter (Concentric Medical, Mountain View, CA) in the left common carotid artery for proximal embolic protection.* C, *angiogram showing Acculink stent (Guidant/Advanced Cardiovascular Systems, Menlo Park, CA) placed across the lesion under flow arrest, which was kept throughout the procedure until termination of postdilatation angioplasty.* D, *postprocedural angiogram demonstrating clear improvement of intracranial flow with filling of the left A1 segment.*

Congestive Heart Failure

Patients with congestive heart failure have a higher rate of perioperative stroke or death with CEA. A multicenter review of patients undergoing CEA found a perioperative stroke or

death rate of 8.6% in patients with congestive heart failure as opposed to 2.3% in patients without this condition (20, 21).

Age

Elderly patients seem to have a higher rate of perioperative complications with CEA. An assessment of the perioperative mortality of 113,300 Medicare patients undergoing CEA at trial and nontrial hospitals determined that patients who were 85 years of age or older were three times more likely to die than those younger than 70 years (70). A multicenter review of 1160 CEA procedures reported a postoperative stroke or death rate of 7.5% in asymptomatic patients who were 75 years of age or older versus a rate of 1.8% in patients younger than 75 years (20, 21). Similarly, the risk of postoperative MI associated with CEA was 6.6% in symptomatic patients who were 75 years of age or older versus 2.3% in patients younger than 75 years. However, a NASCET subgroup analysis found that patients aged 75 years or older actually derived a greater benefit from CEA than those in younger age groups (2). The absolute risk reduction was 28.9% for patients aged 75 years or older (n = 71), 15.1% for those between 65 and 74 years (n = 285), and 9.7% for patients younger than 65 years (n = 303). Although CEA definitely seems to benefit older patients, it is reasonable to ask whether CAS could provide similar benefits, as well as lower rates of perioperative complications (20, 58).

Anatomical Features and Tandem Lesions

Anatomic variations may increase the technical difficulty of CEA and may influence the results adversely. A high carotid bifurcation near the cranial base, especially in a patient with a short or thick neck, or a long carotid artery stenosis that extends to the cranial base can be difficult to expose surgically. Surgical dissection of the carotid artery in these patients can be very difficult and often is extremely traumatic. Low lesions can also be technically difficult and should be avoided.

The presence of tandem lesions in which the distal lesion was more severe than the proximal lesion was a NASCET exclusion criterion (50). Among symptomatic patients with ipsilateral carotid siphon stenosis, the risk of postoperative stroke or death associated with CEA in a multicenter review of 1160 procedures was 13.9%, versus 7.9% in patients without distal stenosis (20). In a systemic review of 36 studies, an increased risk for perioperative stroke or death was associated with CEA in patients with stenosis of the ipsilateral siphon (59). At our center, angioplasty was performed with and without stent placement in 11 patients with tandem lesions (38). The proximal lesion was considered to be the flow-limiting lesion and was the only lesion treated in 10 of these patients. In the remaining patient, both lesions were treated. No perioperative stroke or cardiac event or deaths occurred in this series.

Ipsilateral Intraluminal Thrombus

In a multicenter review of 1160 procedures, the risk of postoperative stroke or death with CEA was found to be 17.9% in symptomatic patients with intraluminal thrombus in the ipsilateral carotid artery, versus 8.1% in those without thrombus (20). In a subgroup analysis of 53 patients enrolled in the NASCET who had intraluminal clot superimposed on atherosclerotic plaque identified by angiographic procedures, the 30-day risk of stroke was 10.7% in those randomly assigned to receive medical treatment and 12% in those who underwent CEA (69). The high morbidity rate in this subgroup is related to the presence of fresh clot and the substantial risk of emboli dislodgment during surgical dissection of the carotid artery.

Contralateral Carotid Occlusion

Patients with recent symptoms referable to severe carotid artery stenosis and coexistent contralateral carotid artery occlusion have a high risk of ipsilateral ischemic stroke. The risk of ipsilateral stroke in medically treated patients with severe stenosis of the symptomatic carotid artery and occlusion of the contralateral carotid artery was 69.4% at 2 years in a subgroup analysis of NASCET (18). Although CEA led to a significant reduction in stroke risk in this group, the perioperative risk of stroke or death in the presence of contralateral carotid artery occlusion was a high 14.3%. This increased risk may be related to the use of carotid artery shunting during CEA for patients with contralateral occlusions in up to 83% of cases (18). For these patients, CAS represents a valid alternative to CEA, obviating the need for temporary occlusion in the presence of an already reduced cerebrovascular reserve.

Postendarterectomy Restenosis

Recurrent carotid artery stenosis is a potential problem after CEA (48). Technically, a repeat operation is more challenging than the initial procedure because of scarring around the arteries, friability of the recurrent plaque, and the necessity for complex anastomosis techniques. Among 82 patients undergoing operations for recurrent carotid stenosis at one institution, the composite rate of major morbidity and mortality was 10.8%, a rate that was five times higher than the risk associated with primary CEA at the same institution (48). Investigators at another institution found an increased risk of cerebral ischemic events associated with CEA for recurrent stenosis (1). The 30-day rates of perioperative stroke and TIA were 4.8 and 4%, respectively, in the reoperation group, as compared with 0.8 and 1%, respectively, in the primary endarterectomy group. These investigators also found a high rate (17%) of cranial nerve palsy with reoperation. However, in a review of the results of CAS performed at our center in a similar group of 18 patients with postendarterectomy recurrent carotid stenosis (*Fig.* 2), only a single case of TIA and no periprocedural stroke was identified (40).

Radiation-induced Carotid Stenosis

Accelerated, radiation-induced carotid stenosis presents an increased risk for perioperative complications, primarily because of the technical pitfalls associated with a surgical approach. The presence of a long lesion, lack of well-defined

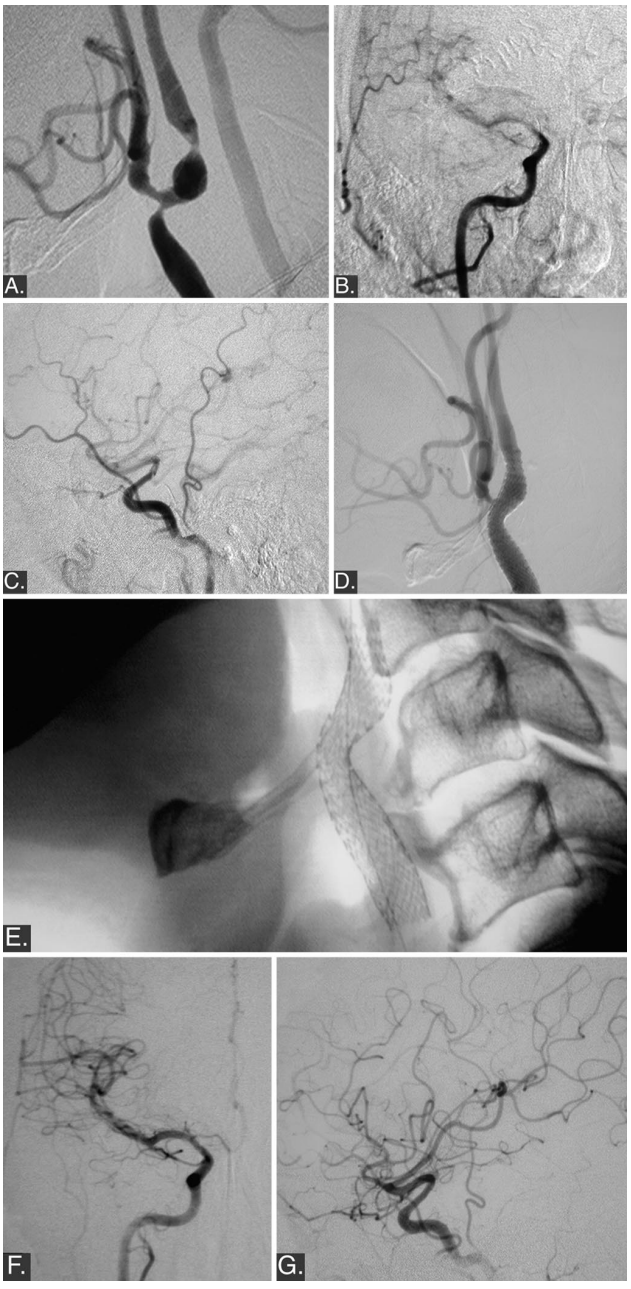

FIGURE 2. *Images obtained from a 54-year-old man with right amaurosis fugax. Four years previously, he underwent a right carotid endarterectomy. Imaging studies revealed postendarterectomy recurrent stenosis of the right carotid artery.* A, *cerebral angiogram, lateral view, demonstrating the presence of a severe stenosis involving the distal right common carotid artery and the internal carotid artery. Note the target vessel tortuosity. Intracranial images, frontal* (B) *and lateral* (C) *views, revealing poor filling of the right middle cerebral artery territory and lack of filling of the anterior cerebral artery suggestive of a flow-limiting effect of the cervical lesion or the presence of a hypoplastic A1 segment of the anterior cerebral artery.* D, *angiogram demonstrating right carotid artery stent placement performed using the combination of an AngioGuard filter and a Precise stent (Cordis/Johnson & Johnson, Warren, NJ). The stent design allowed good conformation to the preexisting carotid curve, as shown by an unsubtracted digital image* (E). F *and* G, *intracranial images obtained after cervical carotid revascularization demonstrating flow augmentation with filling of the anterior cerebral artery territory despite the presence of a hypoplastic A1 segment.*

dissection planes, and scarring around the vessels make the surgery more difficult (43, 47), exposing these patients to a higher risk of wound infections and cranial nerve palsies. Additionally, restenosis occurs more frequently after CEA in patients with radiation-induced atheromatous disease (10, 41). Carotid angioplasty and stent placement could provide a more effective method for the treatment of carotid stenosis associated with radiation therapy (66) (Ecker RD, Donovan MT, Hopkins LN: Endovascular management of carotid artery disease after radiation therapy and radical neck dissection. **Neurosurg Focus** 18:e8, 2005).

CAS: PRELIMINARY RESULTS

The limitations of the CEA trials, the need for a better therapeutic option for high-risk patients, and the wave of minimally invasive surgery spurred the development of CAS. Dissemination of the results obtained with stent-assisted balloon angioplasty in the coronary literature undoubtedly provided an impetus for endovascular treatment of carotid artery occlusive disease (54) and prompted the performance of studies in which carotid angioplasty with or without stenting and CEA were compared. The purported advantages of stent placement compared with simple angioplasty included avoidance of plaque dislodgment, intimal dissection, and late recurrent stenosis, as well as diminution of vessel recoil.

The Carotid and Vertebral Artery Transluminal Angioplasty Study was the first randomized comparison of endovascular versus surgical treatment in patients with carotid artery stenosis (9). Between March 1992 and July 1997, patients from 22 centers in Europe, Australia, and Canada were assigned randomly to received endovascular treatment (n = 251) or surgical CEA (n = 253). Fifty-five patients (26%) in the endovascular treatment group received a stent (stents suitable for use in the carotid artery were developed during the course of this study); the remaining patients received angioplasty alone. Similar rates of stroke and death were reported for endovascular and surgical treatment. The number of recurrent strokes, with a mean follow-up period of approximately 2 years, was also similar in both groups. In a presentation of the 8-year follow-up results, equivalent efficacy in stroke prevention for both therapeutic options was reported (6).

Several other groups reported on the effectiveness, safety, and durability of CAS. One review of a 5-year experience with a series of 528 consecutive patients undergoing CAS described a 30-day major stroke or death rate of 2.6% (60). Among a series of 85 patients who underwent percutaneous angioplasty for symptomatic carotid artery stenosis during a 4-year period, no deaths occurred within 30 days after the procedure, and the major morbidity rate at 30 days was 4.9% (19). Our

group (27) has reported a 30-day major stroke or death rate of 5% in 80 high-risk patients who were considered to be ineligible for NASCET according to the exclusion criteria of that study.

Distal embolic protection (DEP), initially introduced by Theron et al. (65), is considered to be an important advance in the endovascular treatment of carotid occlusive disease. The rationale for using this technique is based on the concept that an embolic shower released from carotid plaque during CAS causes neurological deficits in the periprocedural period (65). Preliminary studies have demonstrated the potential benefits of DEP. The occurrence of cerebral ischemia (detected by diffusion-weighted magnetic resonance imaging) has been reported in 20 (29%) out of 70 patients who underwent CAS without cerebrovascular embolic protection (34). This rate decreased to 7.1% with the use of embolic protection devices (45). At multiple centers in which a balloon device (PercuSurge GuardWire; PercuSurge Inc., Sunnyvale, CA) was used for DEP during CAS in 75 patients, no single case of periprocedural death or major stroke was noted (71).

The Stent and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial also demonstrated the benefits of DEP (25, 67, 75). Patients from 29 centers in the United States were enrolled in this trial. Patients eligible for this study were either asymptomatic with at least 80% stenosis or symptomatic with at least 50% stenosis (stenosis severity was documented by Doppler ultrasonography) and had at least one of the following coexisting conditions that would present a potentially increased risk for CEA: older than 80 years, clinically significant cardiac disease (e.g., congestive heart failure), severe chronic obstructive pulmonary disease, postendarterectomy recurrent carotid stenosis, previous radiation therapy to the neck, previous radical neck surgery, contralateral carotid artery occlusion, or contralateral laryngeal nerve palsy. Eligible patients were screened by a team that included a vascular surgeon, an interventionist, and a neurologist. Consensus that patients were good candidates for either procedure was required before randomization. By the end of the enrollment period in July 2002, 307 patients were randomized, 156 to CAS and 151 to CEA. The devices used for CAS in this trial were the Precise nitinol stent (Cordis/Johnson & Johnson, Warren, NJ) and the AngioGuard (Cordis/Johnson & Johnson) distal protection device. The 30-day composite stroke and death rate was similar for both groups (4.5% for the CAS group versus 6.6% for the CEA group). When the rate of MI was taken into consideration, the CAS group did better, with a major adverse cardiovascular event rate of 5.8%, compared with a 12.6% event rate in the CEA group. The 1-year follow-up data for this study demonstrated overall major adverse cardiovascular event rates of 11.9% for the CAS group and 19.9% for the CEA group. At the 1-year follow-up, the incidence of major ipsilateral stroke was significantly higher in the CEA group (3.3 versus 0% in the CAS group). Regarding ipsilateral minor stroke, there was a trend toward more minor strokes in the CAS group (3.8 versus 2% in the CEA group; $P = 0.5$) (75).

The 30-day and 1-year follow-up results from the Carotid Revascularization using Endarterectomy or Stenting Systems Phase I trial were recently published (7, 8). The Carotid Revascularization using Endarterectomy or Stenting Systems trial is a multicenter, prospective, nonrandomized clinical trial sponsored by the International Society of Endovascular Specialists in collaboration with the industry, the Food and Drug Administration, and the Centers for Medicare and Medicaid Services. This trial was designed as an equivalence cohort study to determine whether or not the rate of stroke or death after CAS with DEP was comparable with that for CEA in patients with at least 50% symptomatic or at least 75% asymptomatic carotid stenosis. The study population represented a broad-risk population typical of patients treated in general vascular practice. The enrollment ratio at each clinical site was designed to be 2:1 CEA to CAS. The devices used in the CAS arm were the Monorail Wallstent carotid stent (Boston Scientific Corporation, Natick, MA) and the GuardWire Plus distal protection device (Medtronic Vascular, Santa Rosa, CA). Primary end points for the Phase I trial included all-cause mortality or stroke within 30 days and 1 year of the procedure. In Phase I, 397 patients were enrolled at 14 clinical sites (254 CEA and 143 CAS; ratio, 1.8:1). The distribution of asymptomatic patients was similar in each treatment group (67% CEA, 69% CAS). Likewise, the medical history before treatment was similar in both groups, with the exception of a more frequent history of previous CEA in the CAS group (30 versus 11% in the CEA group). The 30-day MI, stroke, and death rates were 0.8, 2.4, and 0.4%, respectively, in the CEA group and 0, 2.1, and 0%, respectively, in the CAS group. The 1-year composite analysis for ipsilateral strokes was 4%. Although the overall mortality at 1 year was 4.5%, none of these patients had a neurological cause of death. The results of this study suggested that the risk of death or stroke after more than 1 year after CAS is equivalent to CEA in symptomatic and asymptomatic patients with occlusive carotid artery disease.

The 30-day results of all three phases of the single-arm Acculink for Revascularization of Carotids in High Risk Patients (ARCHeR) Trial have been presented, as well as the 1-year follow-up data for ARCHeR 1 and 2 (72). This trial included a total enrollment of 581 patients enrolled at 48 sites in the United States, Europe, and South America. Eligibility criteria included carotid artery stenosis that was either asymptomatic and more than 80% (by angiography) or symptomatic and more than 50%. High-risk factors established for inclusion in this trial were the presence of two or more of the following criteria: two or more coronary vessels with at least 70% stenosis, MI within 30 days, CABG or valve surgery within 30 days, unstable angina, and contralateral carotid occlusion; plus the presence of one or more of the following criteria: ejection fraction less than 30% or New York Heart Association Functional Class III or greater, forced expiratory volume in the first second less than 30% (predicted), dialysis-dependent renal failure, uncontrolled diabetes, postendarterectomy recurrent stenosis, history of radical neck surgery and/or radiation therapy, surgically inaccessible lesion, spinal immobility, tra-

cheostomy stoma, and contralateral laryngeal nerve paralysis. Eligible patients were assessed by an independent neurologist before enrollment and throughout the CAS follow-up period. Enrollment in the trial included 158, 278, and 145 patients in Phases I, II, and III of the trial, respectively. In ARCHeR 1, patients were treated with use of the Acculink stent (Guidant/Advanced Cardiovascular Systems, Menlo Park, CA) alone. In ARCHeR 2, patients were treated with a combination of the stent and the Accunet Filter (Guidant/Advanced Cardiovascular Systems) for DEP. In ARCHeR 3 (Phase 3), next-generation rapid-exchange versions of both filter and stent were used. The trial results are summarized in *Table 2* (22). The preliminary combined results for Phases I and II of the three-phase ARCHeR trial showed a 30-day composite rate of stroke, MI, and death of 4.5% for 66 patients with contralateral carotid occlusion included in this study (72). The 30-day composite rate of stroke, MI, and death for the 141 patients receiving treatment with CAS for postendarterectomy recurrent stenosis in this study was 0.7%. Overall, carotid stenting with embolic protection using the Acculink/Accunet system compared favorably with CEA performed in a historical control group. Of note, the trial results suggest applicability of CAS for conditions that were exclusion criteria in the major CEA trials. Further data analysis will be possible after the results of the study have been published.

The 30-day and 1-year results of the Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients study and the Carotid Artery Revascularization using the Boston Scientific EPI FilterWire EX/EZ and EndoTex NexStent trial have also been presented (32, 33) and are provided in *Table 2*. The Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients and the Carotid Artery Revascularization using the Boston Scientific EPI FilterWire EX/EZ and EndoTex NexStent studies were single-arm, prospective, nonrandomized, multicenter trials. In the Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients, the devices used were the EPI FilterWire EZ (Boston Scientific Target, Fremont, CA) for DEP and the monorail Wallstent (Boston Scientific Target). In the Carotid Artery Revascularization using the Boston Scientific EPI FilterWire EX/EZ and EndoTex NexStent trial, the devices used were the EPI Filter Wire EX or EZ (Boston Scientific) and the NexStent carotid stent (EndoTex Interventional Systems, Cupertino, CA). The high-risk inclusion criteria for patients enrolled in these studies were similar to those described above for the Stent and Angioplasty with Protection in Patients at High Risk for Endarterectomy and ARCHeR studies.

Several other carotid stent registries are being maintained in the United States (*Table 3*). One randomized, controlled trial currently under way is the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), which is jointly sponsored by the National Institutes of Health and Guidant Corporation (Indianapolis, IN). The results of CREST and other carotid stent studies are expected to provide the Level I evidence necessary for Food and Drug Administration approval for CAS as an optimal technique for carotid revascularization.

Endovascular Management Protocol and Procedural Technique

The technique of CAS varies slightly for each case, depending on the clinical situation. The following is a description of the management protocol and procedural technique used for most patients at our center.

Medical Management

Patient preparation for stenting is dependent on adequate administration of antiplatelet and anticoagulant agents because of the inherent risk of intimal injury and subsequent thrombosis and vessel occlusion associated with endovascular procedures and because all stents are thrombogenic devices (39). Consideration must be given not only to the selection and dosing of antithrombotic medications, but also to minimizing the potential for associated hemorrhagic complications. Most information about treatment with these agents is based on the extensive experience in the coronary vasculature. When pos-

TABLE 2. Summary of major single-arm registry results[a]

	ARCHeR 1 (n = 158)	ARCHeR 2 (n = 278)	ARCHeR 3 (n = 145)	BEACH	CABERNET
Major stroke at 30 d	1.9%	1.4%	1.4%	1%	1.4%
Minor stroke at 30 d	2.5%	4.3%	4.8%	2.5% (1.9% ipsilateral)	2.1%
MI at 30 d	2.5%	2.9%	0.7%	0.8%	0.2%
Stroke-related death at 30 d	0.6%	0.7%	0	1.5% (all deaths)	0
Non-stroke-related death at 30 d	1.9%	1.4%	1.4%		0.5%
Major stroke from Day 31 to 1 yr	0	0.3%	N/A	1.4%	0
Minor ipsilateral stroke from Day 31 to 1 yr	0.6%	1%	N/A	0.5%	0.4%
Stroke-related death from Day 31 to 1 yr	0	0	N/A	1.6%	0

[a] ARCHeR, Acculink for Revascularization of Carotids in High Risk Patients; ARCHeR 1, stent alone; ARCHeR 2, stent plus distal embolic protection; ARCHeR 3, rapid exchange version of stent and filter; BEACH, Boston Scientific EPI: A Carotid Stenting Trial for High Risk Surgical Patients; CABERNET, Carotid Artery Revascularization Using the Boston Scientific EPI FilterWire EX/EZ and EndoTex NexStent; MI, myocardial infarction; N/A, not available.

TABLE 3. Carotid angioplasty and stenting trials[a]

Study (manufacturer or sponsor)	Design	Clinical characteristics and percentage stenosis	Stent	Distal embolic protection device
ACT 1	Randomized trial (3:1, CAS: CEA)	Low risk: asymptomatic ≥80%	Xact	EmboShield
ARCHeR 3 (Guidant)	Prospective single-arm registry (1-year follow-up results to be presented)	High risk: asymptomatic >80%; symptomatic >50%	Acculink RX	Accunet RX
CREATE (ev3)	Prospective single-arm registry	High risk: asymptomatic >70%; symptomatic >50%	Protégé	Spider
CREST (NIH, Guidant)	Randomized trial	Symptomatic > 50%	Acculink RX	Accunet RX
MAVErIC 2 (Medtronic AVE)	Prospective single-arm registry	High risk: asymptomatic >80%; symptomatic >50%	Medtronic AVE self-expanding stent system	PercuSurge
SECURITY (Perclose)	Prospective single-arm registry	High risk: asymptomatic >80%; symptomatic >50%	Xact	NeuroShield

[a] ACT 1, Asymptomatic Carotid Stenosis, Stenting versus Endarterectomy Trial: Carotid Angioplasty and Stenting versus Endarterectomy in Asymptomatic Subjects with Significant Extracranial Carotid Occlusive Disease; CAS, carotid artery angioplasty with or without stent placement; CEA, carotid endarterectomy; ARCHeR 3, Acculink for Revascularization of Carotids in High Risk Patients; CREATE, Carotid Revascularization with ev3 Arterial Technology Evolution; CREST, Carotid Revascularization Endarterectomy vs. Stent Trial; NIH, National Institutes of Health; MAVErIC 2, Evaluation of the Medtronic AVE self-expanding carotid stent system with distal protection in the treatment of Carotid stenosis; SECURITY, Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and Xact Stent in Patients at High Risk for Carotid Endarterectomy.

sible, patients scheduled to undergo CAS are pretreated with aspirin (325 mg daily) and clopidogrel (75 mg daily) for at least 3 days before the procedure or are given a loading dose of clopidogrel (300–600 mg) early on the day of the procedure.

Saline solutions used for irrigation of the catheters are prepared with heparin (1 unit/ml), and catheter systems are flushed continuously with this solution. An intravenous bolus dose of heparin (50 U/kg) is administered after catheterization of the common carotid artery (CCA). The activated coagulation time is maintained in the range of 250 to 300 seconds for the duration of the procedure.

Platelet glycoprotein IIb-IIIa inhibitors, such as abciximab or eptifibatide, are not used routinely during CAS at our center. Our preliminary experience suggests that patients with chronic cerebral ischemia are at an elevated risk for intracranial hemorrhage with the use of these potent antiplatelet agents. We reserve the use of glycoprotein IIb-IIIa inhibitors for patients who experience thromboembolic complications during or soon after the procedure (57). Computed tomographic imaging is obtained first to check for intracerebral hemorrhage, which would contraindicate the administration of these agents.

Bradycardia occasionally occurs during angioplasty, particularly when the plaque involves the carotid sinus. Atropine and a prepared dopamine solution are kept available should significant bradycardia and hypotension occur. We find that medical management of bradycardia during angioplasty is usually sufficient and do not routinely place transvenous pacemakers before performing CAS.

After the stenting procedure, the heparin infusion is generally discontinued. In some situations, such as when angiographically documented dissection or thrombosis is present, the heparin infusion is continued to maintain the activated prothrombin time 1.5 to 2.3 times the baseline value. A 4-week course of aspirin (325 mg daily) and clopidogrel (75 mg daily) is prescribed after the procedure to allow for complete endothelialization of the stent (56). Aspirin is continued indefinitely.

Procedure Preparation

The procedure is performed in an angiography suite with biplane digital subtraction and fluoroscopic imaging capabilities. The patient is kept awake, with local anesthetic agents and intravenous sedative hypnotic agents administered to permit continuous neurological assessment. Dorsalis pedis and posterior tibialis pulses are assessed and marked for later reference, a practice that is particularly important in patients with coexistent peripheral vascular disease. A Foley catheter and two peripheral intravenous lines are placed. Oxygen saturation, cardiac rhythm, and blood pressure are monitored throughout the procedure.

Diagnostic Angiography

A 5-French sheath is placed in the right femoral artery, and a three-vessel diagnostic angiogram is obtained (if not previously performed) using a 5-French Simmons-2 (Medi-tech; Boston Scientific, Natick, MA) or angled glide catheter. An intracranial angiogram with the injection of contrast material into the ipsilateral CCA is necessary for comparison purposes should intracranial thromboembolism be suspected after angioplasty has been performed. After a working projection image of the target vessel has been obtained, measurements are obtained of the vessel diameter proximal and distal to the

lesion, the length of the lesion, and the severity of the stenosis (using the NASCET method) (50).

Vascular Access

The aforementioned loading dose of heparin is administered before the guide catheter is placed within the CCA. When the activated coagulation time reaches at least 250 seconds, the diagnostic catheter is positioned in the CCA and is used to advance a 0.035-inch, 300-cm long stiff glide wire into the distal external carotid artery (ECA). In the setting of ECA stenosis or occlusion, an Amplatz exchange J wire (Cook, Bloomington, IN) is placed in the distal CCA and is used to provide support for the guide sheath. With this stiff wire in position, the diagnostic catheter and femoral artery sheath are removed. A 6-French, 90-cm guide sheath (Cook) is then advanced over the wire and is placed just proximal to the carotid bifurcation. For patients who have undergone complete diagnostic cerebral angiography before the stenting procedure, a combination of a 6-French, 90-cm shuttle select catheter (Cook) and 6.5-French head-hunter 125-cm slip-catheter (Cook) or 5-French, 125-cm Vitek catheter (Cook) can be used. In these cases, the shuttle is introduced primarily in the femoral artery over a 0.35-inch wire and is parked in the descending aorta. The inner obturator and wire are removed. The head-hunter slip-catheter (or the Vitek catheter) is then advanced into the shuttle, and the target vessel is catheterized. At this point, a wire (depending on the patency of the ECA, either a 0.38-inch, 150-cm long glide wire, a 0.35-inch, 300-cm long stiff glide catheter, or an Amplatz exchange J wire) is advanced, followed by the inner catheter and shuttle. The position and integrity of the target vessel and distal ECA territory are assessed by angiography after manipulation with the wire. When the use of proximal embolic protection is anticipated, a 9-French balloon guide catheter (Concentric Medical, Mountain View, CA) is used instead of the 6-French Cook shuttle catheter.

Carotid Angioplasty with Stent Placement Procedure

After the guide catheter is in place, we proceed with the following steps of the CAS procedure. First, the embolic protection device is positioned. If necessary, prestent deployment (predilation) angioplasty is performed to enlarge the stenotic region sufficiently to permit passage of the stent. The stent is then deployed, after which poststent deployment angioplasty is carried out to remodel and fully expand the stent. Finally, the protection device is retrieved. After each step, high-resolution biplanar angiograms are obtained and neurological examinations are performed to allow for prompt recognition of any changes from the patient's baseline status.

Embolic Protection Device Selection and Placement

Filtration, balloon occlusion, and flow reversal embolic protection devices are available. Retrievable filters designed to collect debris during CAS are placed distal to the stenotic region without interrupting flow within the ICA. Examples of filtration devices include the EPI FilterWire (Boston Scientific Embolic Protection, Inc., San Carlos, CA), Accunet, AngioGuard, Mednova EmboShield (Abbott Laboratories, Abbott Park, IL), and Spider (ev3, Plymouth, MN). Balloon occlusion techniques involve inflation of a balloon with interruption of flow in the ICA distal to the stenosis for the duration of the stenting procedure. An example of a balloon occlusion embolic protection device is the PercuSurge balloon (Medtronic, Inc., Minneapolis, MN). The flow reversal technique involves the placement of balloons in the ECA and CCA to interrupt flow in these vessels and cause retrograde flow in the ICA to prevent embolization into the intracranial circulation (53). Unfortunately, flow reversal devices are not available in the United States. The combination of a 9-French Concentric guide catheter (Concentric Medical) at the CCA with a PercuSurge guide wire at the ECA can serve as an alternative method for proximal protection.

Ideally, the selection of embolic protection device should be made on a case-by-case basis. Most often, however, the device to be used is determined beforehand, when the patient is enrolled in one of the many current registries or trials. For patients who are not study participants, we typically use a retrievable filter device, for distal protection. Distal balloon protection with the PercuSurge balloon is used solely for those patients in whom the anatomy is favorable for the placement of a protection device, but the diameter of the distal ICA is less than 3 mm. Proximal protection with the use of a 9-French Concentric balloon guide catheter positioned at the CCA with or without a PercuSurge guide wire located at the ECA is reserved for those patients in whom lesion characteristics and distal ICA tortuosity preclude the use of DEP and the patient cannot safely undergo endarterectomy. At our center, a retrievable filter is used for DEP in more than 95% of the CAS procedures performed.

After the guide catheter is positioned, the retrievable filter (mounted on a 0.014-inch microguidewire) is guided carefully across the stenotic region using a biplanar roadmapping technique. When crossing the lesion, the combination of turning and slightly pushing the device is preferred, rather than simply pushing it. Ideally, the device should be placed in a relatively straight segment of the distal ICA and then deployed. As soon as the filter is deployed, the operator assesses the apposition of this device to the vessel wall to ensure effective containment of embolic debris.

Predilation Angioplasty

Predilation angioplasty is reserved for patients in whom the severity of the lesion is sufficient to justify angioplasty before stenting or for those patients in whom difficulties are found when trying to cross the lesion with the stent. When predilation angioplasty is necessary, the selection of the balloon is based on the dimensions of the lesion. The balloon must be long enough to cover the entire length of the lesion. The inflation diameter should be just enough to allow passage of the stent through the artery. After a cervical carotid artery angiogram is obtained with the embolic protection device in place, the angioplasty balloon is advanced and centered on the

lesion. The balloon is inflated to the manufacturer's recommended nominal pressure for several seconds and then deflated. The blood pressure cuff is set at a continuous mode during angioplasty to allow rapid sequential measurement of blood pressure should bradycardia and hypotension occur.

Stent Placement

Most carotid stents are self-expanding stents composed of stainless steel or nitinol (a nickel–titanium alloy). Selection of the stent is determined by the length of the lesion and the normal diameter of the CCA. The stent should be oversized 1 to 2 mm more than the normal caliber of this artery and should cover the lesion completely. At diameters less than full expansion, nitinol stents exert a chronic outward radial force that maintains apposition of the stent to the vessel wall after deployment. Often the stent extends from the CCA into the ICA, crossing the carotid bifurcation and ECA origin; in these cases, the stent should be sized according to the larger caliber of the CCA. When dealing with patients with preexistent contralateral ECA occlusion, one should be prepared for the potential need—albeit rare—for endoluminal revascularization of the ipsilateral ECA in the event of occlusion after stent deployment and poststent angioplasty.

Before deployment, the position of the stent should be verified. When using distal filter or proximal embolic protection, angiographic images can be obtained to confirm the position of the device before the stent is deployed. However, the use of distal balloon occlusion precludes vessel assessment. In each case, anatomic landmarks should be evaluated carefully before deployment to assure precise positioning of the stent.

Postdilation Angioplasty

After the stent is in place, poststent deployment angioplasty is performed. Balloon selection is based on the diameter of the ICA. The balloon should be kept within the segment of stented artery during the angioplasty to avoid the risk of vessel dissection, especially at the distal ICA. Slow balloon inflation can be used for patients with known overresponsive carotid baroreceptors. The administration of atropine (0.75 mg) can be extremely helpful in these cases.

Embolic Protection Device Retrieval

After poststent deployment angioplasty, cervical and intracranial images are obtained to assess target vessel patency and to exclude evidence of any major intracranial vessel occlusion. After this is done, the filter device is withdrawn, and a final series of cervical carotid and intracranial circulation angiograms are obtained.

The course of the filter device retrieval sheath through the segment of stented vessel should be observed carefully because this sheath can become caught on stent struts that are protruding into the vessel lumen. This is especially important when using a stent with an open-cell design. Several options are available for freeing the retrieval sheath from the stent struts. Bringing the guide sheath closer to the stent may provide enough support to allow the stent to be crossed with the retrieval sheath. An angled 4-French, 100-cm or 125-cm long diagnostic catheter can be used. Substituting the retrieval sheath for this catheter may allow the operator to navigate the tip of the sheath around the protruding stent segment. Another option is to use an angioplasty balloon with a 0.035-inch compatible inner lumen that would allow capture of the filter device. Advancing the balloon into the protruding segment with partial inflation pushes the stent struts against the vessel wall, permitting further advancement of the balloon and subsequent retrieval of the device.

When distal balloon occlusion is used for cerebrovascular embolic protection, 60 ml of blood is aspirated before the balloon is deflated. The aspiration is accomplished by use of an export catheter placed just proximal to the balloon. When proximal protection is used, flow at the CCA and ECA is arrested during stent deployment and postdilation angioplasty; blood is then aspirated from the guide catheter port before flow is restored.

Access Site Closure

After obtaining an angiogram of the femoral access site, the decision to proceed with percutaneous closure is made. If the entry point of the sheath is above the bifurcation of the common femoral artery and the vessel is free of major atherosclerotic disease, the catheter systems and femoral sheath are removed, and a percutaneous closure device, such as the Perclose (Redwood City, CA) or AngioSeal (St. Jude Medical, Minnetonka, MN), is used. Otherwise, the guide sheath is exchanged for a 7-French, 15-cm sheath, which is left in place and removed when the activated coagulation time has normalized.

Postprocedural Management

After the intervention, the patient is admitted to the intensive care unit for monitoring overnight. Close observation with assessments of neurological condition and monitoring of hemodynamic parameters is crucial. Ideally, a systolic blood pressure of 110 to 160 mmHg is maintained. A baseline carotid Doppler ultrasound study is obtained within 24 hours of the procedure to assess vessel patency and to provide a reference for further Doppler evaluations. This test allows the operator to compare and establish baseline velocity levels in comparison with the final angiographic result. Most patients are discharged within 24 hours of the procedure. As mentioned, aspirin and clopidogrel are prescribed.

Boundaries of CAS

The interventionist performing CAS should be cognizant not only of the indications and technique for the procedure, but also of the limitations of the procedure. By being able to identify markers of high-risk CAS, procedural complications can often be prevented.

High-risk CAS

Several unfavorable anatomic and lesion characteristics can present risk for the performance of CAS. Those characteristics

making CAS technically challenging, especially to less-experienced operators, are presented in *Table 4*. Endovascular access to the carotid arterial system can be problematic in patients with severe peripheral vascular disease that affects the iliac or femoral arteries and in those with a bovine configuration to the aortic arch, a tortuous aortic arch, or an ectatic CCA. The impossibility of manipulating the external carotid artery because of occlusion or severe origin disease of the vessel can complicate guide sheath or catheter placement. Near-complete occlusion of the carotid artery (string sign) can impair safe passage of a DEP device, and a tortuous distal cervical ICA can hinder device deployment. Also, because antiplatelet therapy is strongly recommended, an inability to tolerate these agents may be considered a relative contraindication to carotid stent placement.

CAS in the Elderly

The issue of safety of CAS for elderly patients was raised after the CREST investigators determined that the incidence of stroke and death during CAS was directly related to patient age during the lead-in phase of the study and stopped enrolling patients aged 80 years and older (31). The lead-in phase included symptomatic (>50% stenosis) and asymptomatic (>70% stenosis) patients. The incidence of stroke and death for patients younger than 60 years, 60 to 69 years, 70 to 79 years, and 80 years or older was 1.7, 1.3, 5.3, and 12.1%, respectively. The CREST investigators reviewed narrative summaries available for 10 out of 12 elderly patients experiencing complications. The complications consisted of six major strokes and four minor strokes, resulting in death in one patient. Hemodynamic instability was noted in seven of these 10 patients, and severe vessel tortuosity made embolic protective device placement impossible in two patients (in one patient, this resulted in distal emboli, stroke, and the one death).

The results of our experience with CAS in patients who are 80 years and older (non-CREST patients) was somewhat different (68). During an 8-year period, 75 patients were identified retrospectively. Stenosis severity ranged from 60 to 95% (mean, 78.3%). Forty-two patients (56%) were symptomatic. Thirty-five patients were treated in the pre-embolic protective device era; use of DEP was intended in the remaining 40 patients. Four CAS procedures were aborted; DEP was used in 38 patients. The major stroke or death rate was 14.3% (five patients) in the unprotected group versus 0% in the protected group ($P < 0.05$).

Several factors may account for the differences in our experience and that reported for the CREST lead-in phase, but cautious analysis of the patient's underlying anatomic and medical features on a case-by-case basis performed by a group of experienced operators is probably the key to complication avoidance. When severe tortuosity, lesion length, or another high-risk feature for CAS is identified, the procedure is contraindicated. Our results suggest that CAS can be carried out safely in those 80 years and older, but meticulous preprocedure analysis is warranted to minimize the risk of complications.

CAS and Plaque Echolucency

The relationship between the characteristics of carotid plaque and presence or absence of neurological symptoms was evaluated in early studies with conflicting results (4). However, the advent of high-resolution B-mode ultrasonographic scanners and the use of a quantitative computer-assisted index of echogenicity, such as the gray-scale median (GSM) introduced by El-Atrozy et al. (12), have greatly improved the correlation of plaque characterization with clinical features. On the gray scale, plaques with higher fat contents (showing dark on Doppler ultrasound imaging) have lower GSM scores and, theoretically, greater potential to cause embolic complication. After the introduction of image normalization, GSM became a highly reproducible index of the echolucency of carotid plaques with low interobserver and interscanner variability (61). Several studies indicated that echogenicity was related to the histological components of carotid plaques (24, 64) and that carotid plaque echolucency (i.e., low echogenicity) was associated with the development of neurological events (23, 46, 55). On the basis of these assumptions, the Imaging in Carotid Angioplasty and Risk of Stroke study was designed (4) to evaluate the relationship of plaque echolucency measured by the GSM and the risk of stroke during CAS. The Imaging in Carotid Angioplasty and Risk of Stroke registry included 418 cases of CAS collected from 11 international centers. An echographic evaluation of carotid plaque with GSM measurement was obtained routinely before the procedure. The overall rate of neurological complications was 3.6% (minor stroke, 2.2%; major stroke, 1.4%). Patients having carotid plaques with GSM echolucency measurements of 25 or less had a significant incidence of

TABLE 4. Access and lesion characteristics associated with high-risk carotid artery angioplasty with or without stent placement

Anatomy	Unfavorable characteristics
Iliac vessels and abdominal aorta	Stenotic or occluded iliac arteries, tortuous iliac or abdominal aorta, occluded abdominal aorta
Aortic arch	Arch Type 2 or 3 anatomy, bovine configuration, arch disease (calcifications and plaque)
Supra-aortic vessels	Origin disease, tortuous proximal target vessel or trunk
Target vessel	Occluded external carotid artery, stenosis at the bifurcation involving both the internal and external carotid arteries, lesion located at a curve, distal internal carotid artery tortuosity (especially just distal to the lesion)
Stenotic lesion	Severe and circumferential calcification, length, plaque echolucency, intraluminal thrombus

complications, with an overall incidence of strokes of 7.1% in these patients, versus 1.5% in those with measurements of more than 25. The study investigators concluded that carotid plaque echolucency, as measured by GSM of 25 or less, increases the risk of stroke in CAS. The value of carotid plaque echolucency remains to be confirmed in larger clinical studies, but the inclusion of GSM measurements of echolucency in procedural planning may allow stratification of patients at different levels of risk for complications during CAS.

Durability of CAS

Major concerns regarding the durability of carotid revascularization with CAS are the efficacy of CAS in preventing long-term recurrence of ischemic events and the occurrence of in-stent stenosis after CAS. In the 8-year follow-up results of the Carotid and Vertebral Artery Transluminal Angioplasty Study, no clinical ipsilateral ischemic events occurred in 90.8% of patients (6). Few accounts exist of restenosis rates after stenting. In the Carotid and Vertebral Artery Transluminal Angioplasty Study, severe (70–90%) restenosis was found in 14% of patients treated with angioplasty with or without stenting (only 26% of patients enrolled in the endovascular group in that study received stents), versus 4% of those receiving surgery (9). In a retrospective report of 183 patients undergoing 119 procedures for de novo stenosis and 76 for postendarterectomy stenosis, Doppler results of more than 80% recurrent stenosis (confirmed by angiographic evidence) after stent placement were found in 5.2% of the lesions stented, with restenosis after CEA representing the main risk factor for in-stent stenosis (the cause in all but one artery) (62).

Similarly, we found a 5% rate of significant (either symptomatic or ≥80%) in-stent stenosis (by digital subtraction angiography) in our series of 141 patients (42). To determine the rate of hemodynamically significant recurrent carotid stenosis after stent-assisted angioplasty (in-stent stenosis) for carotid occlusive disease, we analyzed Doppler ultrasonography data that had been collected prospectively from October 1998 through September 2002 for patients enrolled in carotid stent trials at our center. Patients included in this analysis had undergone at least 6 months of follow-up evaluation with serial Doppler studies or had been found to have elevated in-stent velocities (>300 cm/s) demonstrated on postprocedural Doppler imaging. Hemodynamically significant recurrent stenosis (≥80%) was determined using the following Doppler criteria: peak in-stent systolic velocity of at least 330 cm/s, peak in-stent diastolic velocity of at least 130 cm/s, and peak ICA-to-CCA velocity ratio of at least 3.8. Follow-up studies were obtained at approximate fixed intervals of 1 day, 1 month, 6 months, and yearly. Angiography was performed for patients with recurrent symptoms, Doppler evidence of hemodynamically significant stenosis, or both. Retreatment was performed in patients who were symptomatic, had angiographic evidence of severe (≥80%) recurrent stenosis, or both. In our study, stents were implanted in 142 vessels in 138 patients (all but five were considered to be high-risk surgical candidates); 25 patients were subsequently lost to follow-up. For the remaining 112 patients (117 vessels), the mean Doppler follow-up duration was 16.42 ± 10.58 months (range, 4–54 mo). Using one or more of the Doppler criteria, severe (≥80%) in-stent stenosis was detected in six (5%) patients. Eight patients underwent repeat angiography. Six patients (three symptomatic) required repeat intervention (four, angioplasty alone; one, conventional angioplasty plus angioplasty with a Cutting-Balloon [Boston Scientific Interventional Technologies, San Diego, CA]); one, stent-assisted angioplasty). Thus, in a subset of primarily high-risk surgical candidates treated with stent-assisted angioplasty, hemodynamically significant restenosis rates were comparable with published rates of restenosis after surgery; moreover, treatment of recurrent stenosis in this limited number of patients incurred no periprocedural neurological morbidity.

In reports evaluating recurrent carotid stenosis after angioplasty alone, no restenosis was found in one series of 57 patients (35, 36), whereas a 5.5% incidence of restenosis was found in another series consisting of 100 carotid angioplasties (follow-up period, 3 mo–7 yr) (30). In a report describing patients treated with stent-assisted angioplasty for postoperative restenosis, no stenosis recurred in eight out of 22 patients who returned for follow-up angiography at 6 months (74). Perhaps the largest collection of patients for whom restenosis rates are available includes the global carotid stent registry of 12,392 procedures (73). In this registry, the restenosis rates after carotid stenting were 2.7, 2.6, and 2.4% at 1, 2, and 3 years, respectively.

CONCLUSION

One should keep in mind that CAS and CEA are complementary procedures, with CAS being borne out of a need to provide a less invasive treatment alternative for patients at high-risk for CEA. Alternatively, CEA may be a better therapeutic option for high-risk CAS candidates. Studies are underway to assess the efficacy and long-term durability of CAS (with embolic protection) in both NASCET- and ACAS-eligible populations.

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ENDOVASCULAR MANAGEMENT OF ACUTE SYMPTOMATIC INTRACRANIAL ARTERIAL OCCLUSION

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OBJECTIVE: Acute ischemic stroke has reached epidemic proportions in the United States, affecting approximately 700,000 people annually. With the recent technological advancements in endovascular devices, clinicians now have tools capable of recanalizing acute intracranial occlusions. The combination of pharmacological thrombolysis and mechanical clot perturbation may result in increased rates of angiographic recanalization, which may lead to improvement in patient outcomes after acute stroke.

METHODS: In this article, the various intra-arterial pharmacological and mechanical therapies used by interventionists to treat acute stroke are described. Strategies for using combinations of these therapies are discussed, as are preliminary radiographic and clinical outcomes. Techniques for complex mechanical stroke interventions are discussed in detail.

RESULTS: Several advances in endovascular stroke technologies are becoming increasingly available.

CONCLUSION: With proper patient selection, these therapies may lead to increased recanalization rates and better patient outcomes.

KEY WORDS: Fibrinolytics, Mechanical, Stroke, Thrombolysis

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Evidence-based rationale for the treatment of acute ischemic stroke has accumulated since the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (30) first reported improved outcomes at 3 months associated with treatment instituted within 3 hours. The results of the trial led to United States Food and Drug Administration (FDA) approval of intravenous (IV) administration of tissue plasminogen activator (t-PA) for acute stroke, revolutionizing the treatment and diagnosis of patients with acute ischemic stroke. Despite this advance in treatment, results with IV thrombolysis remain suboptimal, and several randomized studies have failed to demonstrate significant benefit (1, 5, 8, 15, 16, 28, 29). More recently, intra-arterial (IA) thrombolysis has been found to be safe and effective in the treatment of acute, anterior-circulation occlusion if instituted within 6 hours of symptom onset (7, 10). Nevertheless, reocclusion has been found to occur relatively frequently during IA thrombolysis for ischemic stroke and seems to be associated with poor clinical outcomes (33, 35). Currently, accepted therapies for patients with contraindications for IV thrombolysis or occlusive lesions refractory to thrombolytic therapy include a combination of IA pharmacological thrombolysis and/or mechanical thrombolysis. New techniques are constantly being developed. The recently FDA-approved Merci retriever thrombectomy device (Concentric Medical Inc., Mountain View, CA) and stent-assisted recanalization are steps toward the future (9, 11, 14, 22, 23, 34, 36, 40). Clearly, in all treatment options, prompt diagnosis and treatment are paramount to good outcomes. Advancements in neuroimaging techniques have also improved the selection of candidates for acute stroke revascularization.

IA APPROACH

IA treatment of acute ischemic stroke offers many advantages compared with IV treatment alone. Most importantly, direct visualization of the occlusive lesion afforded by angiographic evaluation offers the advantage of site-specific treatment. Once the exact vessel occlusion is identified, treatment can be tailored to the type of occlusion, that is, soft or hard (fibrinous, plaque-laden) clot. The amount of systemic anticoagulation can also be titrated to the amount of recanalization achieved. After attempted thrombolysis in the event of a persistent occlusion, mechanical thrombolysis can also be instituted. Presently, IA pharmacological thrombolysis has not been approved by the FDA of the treatment of acute stroke.

Grading

The grading system used most commonly to assess angiographic recanalization of cerebral vessels after intervention as a marker of procedural–technical success is the Thrombolysis in Myocardial Infarction (TIMI) or modified TIMI classification (*Tables 1* and *2*) (38, 42). This classification system was developed for coronary arteries; although useful, it does not account for the variability of the cerebral vasculature. Qureshi (31) proposed a new grading scheme that is more indicative of outcomes and takes into account cerebral perfusion and collateral circulation unique to the cerebral vasculature (*Table 3*). Application of the new grading scheme revealed 7-day outcomes that were inversely associated with good recovery, whereas the TIMI classification did not correlate with either good recovery or death (31). More recently, Higashida et al. (17, 18) proposed a modification of the TIMI classification for thrombolysis trials specific to the intracranial circulation: the Thrombolysis in Cerebral Infarction (TICI) grading system (*Tables 1* and *2*). To adequately determine and compare the results of the many ongoing trials, angiographic recanalization and associated clinical outcomes must be objectively measured. Some investigators are accumulating pretreatment Alberta Stroke Programme Early Computed Tomography scores (3) in an attempt to determine the risk of intracerebral hemorrhage (ICH) associated with a particular stroke therapy.

Thrombolytic Agents

Currently, several agents are commonly used for IA thrombolysis. A summary of these is provided in *Table 4*. In general, the second-generation thrombolytics, such as alteplase and prourokinase (r-proUK), are the most widely used. Third-generation thrombolytics, such as tenecteplase and reteplase, are being evaluated and have been found to have longer half-lives and more effective thrombolytic potency (6). At present, there are no evidence-based data determining the most effective agent.

Treatment

Two multicenter, randomized, placebo-controlled trials evaluating the safety and efficacy of IA thrombolysis have been completed. In the Prolyse in Acute Cerebral Thromboembolism (PROACT I) trial, patients with acute ischemic stroke resulting from middle cerebral artery occlusion and stroke onset within 6 hours were eligible for IA thrombolysis with r-proUK (7). The modified TIMI classification was used for determination of recanalization (*Tables 1* and *2*) (38). In PROACT I, TIMI 2 or 3 recanalization was achieved in 58% of patients in the treated group and in 14% in the placebo group (7). Although this study proved safe, the number of patients was too low to provide statistically significant proof of efficacy. PROACT II was designed to evaluate the efficacy of IA thrombolysis as measured by the modified Rankin scale score at 3 months (10). In this study, 9 mg of r-proUK was administered for 2 hours in contrast to the 6 mg given in PROACT I. Recanalization rates of TIMI 2 or 3 were achieved in 66% of the treated group and in 18% of the placebo group. For the outcome measure of efficacy, 40% of patients receiving r-proUK had a modified Rankin scale score of 2 or better at 90 days ($P = 0.04$) in contrast to 25% of those treated with placebo. An overall 15% absolute increase in favorable outcome was shown in the r-proUK treatment group. Although the treatment group had an increased rate of ICH, there was a significant improvement in clinical outcome at 3 months.

TABLE 1. Modified thrombolysis in myocardial infarction grading system

Grade	Definition
0	No flow
1	Some penetration past the site of occlusion but no flow distal to occlusion
2	Distal perfusion but delayed filling in all vessels
3	Distal perfusion with adequate perfusion in less than half of the distal vessels
4	Distal perfusion with adequate perfusion in more than half of the distal vessels

Indications

The indications for IA thrombolysis in acute ischemic stroke described below are based on previous inclusion criteria from studies such as PROACT I and II and the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial and treatment protocols at the authors' respective institutions. As in IV therapy, the crucial factor is timely intervention, which necessitates an understanding of urgency on the part of the neurologists, emergency room physicians, and technical and nursing staff. Once a diagnosis of ischemic stroke is made, the staff and resources are coordinated. Through a team effort, laboratory and imaging studies are obtained, and the endovascular suite is prepared. The routine laboratory evaluation includes coagulation profile and hemoglobin, hematocrit, and serum electrolyte levels. Blood glucose levels have been shown to directly correlate with the rate of ICH and outcome (19). Computed tomographic and/or magnetic resonance imaging scans are obtained immediately to allow for cerebral angiography and treatment to be initiated within 6 hours (pharmacological) to 8 hours (mechanical) of symptom onset. If computed tomography or magnetic resonance perfusion and diffusion-weighted imaging show completed areas of infarction (usually 2 cm in diameter or greater), recanalization is not attempted because of the risk of hemorrhagic transformation of the completed infarction.

In the case of posterior-circulation ischemia, there is general agreement that the time window for recanalization is longer. However, only anecdotal reports are available, and no trial to date has shown safety or efficacy past 6 hours, although some data highly suggest benefit with interven-

TABLE 2. Thrombolysis in Myocardial Infarction and Thrombolysis in Cerebral Infarction perfusion grading scales[a]

Grade	Modified TIMI (38)	Original TIMI (42)	TICI (17, 18)
0	No perfusion: no antegrade flow beyond the point of occlusion	No perfusion: no antegrade flow beyond the point of occlusion	No perfusion: no antegrade flow beyond the point of occlusion
1	Penetration with minimal perfusion: contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence	Penetration without perfusion: contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence	Penetration with minimal perfusion: contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run
2	Partial perfusion: contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite coronary artery or the coronary bed proximal to the obstruction)	Partial perfusion: contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite coronary artery or the coronary bed proximal to the obstruction)	Partial perfusion: contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction)
2a	No distinction	No distinction	Only partial filling (less than two-thirds) of the entire vascular territory is visualized
2b	No distinction	No distinction	Complete filling of all the expected vascular territory is visualized, but the filling is slower than normal
3	Complete perfusion: antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed in the same vessel or the opposite artery	Complete perfusion: antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery	Complete perfusion: antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction, and clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery

[a] TIMI, Thrombolysis in Myocardial Infarction; TICI, Thrombolysis in Cerebral Infarction.

tion delayed as long as 20 hours when IA thrombolysis is augmented with angioplasty (21, 24). In a recent review of the literature, basilar artery recanalization was noted more frequently after IA thrombolysis than IV thrombolysis and more commonly for distal than proximal arterial segments (26). Recanalization occurrence did not influence clinical outcomes between treatment groups. It must be noted, however, that this review was limited to case series involving pharmacological therapy administered via IA or IV routes. Currently, the authors treat basilar artery occlusion in the absence of evidence of brainstem ischemic changes up to 12 hours after symptom onset, predominantly with mechanical thrombolysis.

TABLE 3. Grades of increasing severity of arterial occlusion[a]

Grade	Type of Occlusion		
0	No occlusion		
1	MCA occlusion (M3 segment)	ACA occlusion (A2 or distal segments)	1 BA and/or VA branch occlusion
2	MCA occlusion (M2 segment)	ACA occlusion (A1 and A2 segments)	≥2 BA and/or VA branch occlusions
3	MCA occlusion (M1 segment)		
3A	Lenticulostriate arteries spared and/or leptomeningeal collaterals visualized		
3B	No sparing of lenticulostriate arteries and no meningeal collaterals visualized		
4	ICA occlusion (collaterals present)	BA occlusion (partial filling direct or via collaterals)	
4A	Collaterals fill MCA	Anterograde filling[b]	
4B	Collaterals fill ACA	Retrograde filling[b]	
5	ICA occlusion (no collaterals)	BA occlusion (complete)	

[a] MCA, middle cerebral artery; ACA, anterior cerebral artery; BA, basilar artery; VA vertebral artery; ICA, internal carotid artery.
[b] Predominant pattern of filling. Data are from Qureshi AI: New grading system for angiographic evaluation of arterial occlusions and recanalization response to intra-arterial thrombolysis in acute ischemic stroke. **Neurosurgery** 50:1405–1415, 2006.

TABLE 4. Thrombolytic agents[a]

	Half-life (min)	Description
First generation		
Urokinase	14–20	Serine protease
Streptokinase	18–23	Protein from group C β-hematolytic streptococci
Second generation		
Pro-urokinase	20	Proenzyme precursor of urokinase
Alteplase	3–5	Serine protease
Third generation		
Tenecteplase	17	t-PA mutant
Reteplase	15–18	Deletion mutant of t-PA

[a] t-PA, tissue plasminogen activator.

Inclusion and Exclusion Criteria

In general, a patient may be a candidate for IA therapy if recanalization of the occluded vessel can be achieved within 6 to 8 hours and there is no evidence of completed stroke or ICH (*Table 5*). The authors follow the exclusion criteria used in the National Institute of Neurological Disorders and Stroke study (*Table 6*) (30). As mentioned, these criteria pertain to anterior-circulation ischemic stroke.

The efficacy of basilar artery thrombolysis has not been assessed in randomized clinical trials. As such, there are no uniformly applied selection criteria.

TABLE 5. Recommended indications for intra-arterial thrombolysis in acute ischemic stroke

Presentation after 3 hours from onset of symptoms with the ability to initiate treatment within 6 hours of onset of symptoms
Baseline National Institutes of Health Stroke Scale score of 10 or higher
Major surgery within 2 weeks (mechanical and/or pharmacological thrombolysis may be considered)

TABLE 6. Recommended contraindications for intra-arterial thrombolysis in acute anterior-circulation ischemic stroke

- Failure to initiate treatment within 6 hours from onset of symptoms
- Baseline National Institutes of Health Scale score of less than 10
- Rapidly improving neurological status
- Intracranial hemorrhage, parenchymalhypodensity in more than one-third of the affected vascular territory, mass effect with midline shift, or intracranial tumor (except small meningioma) on computed tomographic scanning
- Seizures at onset
- Stroke within previous 6 weeks
- Head trauma within 90 days
- Active or recent hemorrhage within 30 days, or known hemorrhagic diathesis
- Baseline international normalized ratios >1.7, activated partial thromboplastin time >1.5 times normal, baseline platelet counts <100,000/μl
- Known sensitivity to contrast agents
- Uncontrolled hypertension (defined as blood pressure >180 mmHg systolic or >100 mmHg diastolic) on three separate occasions at least 10 minutes apart or requiring continuous intravenous therapy

[a] Data are from National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. **N Engl J Med** 333:1581–1587, 1995.

Pharmacological Thrombolysis

The following treatment protocol is used at the first author's institution and was devised over the course of several years. Although there are many variations of this protocol, institution of therapy within 6 hours, adequate preprocedure imaging, and close monitoring of blood pressure and anticoagulation are paramount. Knowing when to stop the procedure after prolonged catheterization and administration of anticoagulation is often determined by the operator's experience.

On arrival, any patient receiving IV t-PA has a computed tomographic scan if one has not already been performed. All patients are placed under general anesthesia to allow for closer blood pressure control. Somatosensory-evoked potentials and electroencephalographic activity are monitored. Any decreased latency from baseline status warrants an immediate postprocedure computed tomographic scan to assess for hemorrhage. Before microcatheterization of small vessels and after groin sheath placement, incremental bolus doses of heparin (50 units per kg) are given to obtain an activated coagulation time twice that of the baseline value. Simultaneously, a 2.3-French microcatheter is positioned proximal to the occlusion, and an initial bolus of 100,000 units of urokinase is injected for 10 minutes. Angiograms are intermittently performed through the 6-French guide catheter to assess recanalization (32). At the first author's institution, if there is no appreciable lysis of clot after the administration of 800,000 units of urokinase, mechanical thrombolysis is performed. If recanalization is achieved, heparin is discontinued. If no hemorrhage is detected after the procedure, an antiplatelet agent is administered the next day and is continued for 6 weeks.

Mechanical Thrombolysis

Pharmacological IA thrombolysis fails to recanalize vessels in approximately 50% of patients (19, 35, 41). This is largely attributable to underlying atherosclerotic disease and "hard clot" (7, 10). The safety and efficacy of the Merci retriever embolectomy device was evaluated in the MERCI Phase I clinical trial (11, 40). Part I of the MERCI trial was completed in 2004 and demonstrated TIMI/TICI Grade 2 or 3 flow in 12 out of 28 (43%) patients treated with the retriever alone and in 18 out of 28 patients (64%) treated with the retriever plus additional IA t-PA (11). The results of both parts of this trial (40) documented recanalization rates of 33% without thrombolytics versus 51% with additional thrombolytics. The FDA approved the retriever for mechanical thrombolysis in 2004.

The latest-generation Merci device (L5) was evaluated in the Multi-MERCI prospective single-arm study consisting of patients ineligible for IV t-PA or those in whom recanalization had failed after IV t-PA thrombolysis (39). In this study, subsequent passes could be made with the L5 device or the first-generation devices (x5 and x6). Adjuvant therapy with IA t-PA was allowed after attempts had been made with the retriever. One hundred eleven patients were enrolled, with a median age of 68 years (range, 24–93 yr) and baseline National Institutes of Health Stroke Scale score of 19 (range, 4–42). Thirty patients (27%) received IV t-PA before the intervention. Successful recanalization after Merci retriever use was obtained in 60 out of 111 (54%) treatable vessels, and successful recanalization was achieved after adjunctive therapy (IA t-PA, mechanical) in 77 out of 111 (69%) treatable vessels. Clinically significant procedural complications occurred in 11 out of 111 (9.9%) cases. The rate of symptomatic ICH was 9.0% (10 out of 111) overall (symptomatic ICH occurred in two out of 30 patients with IV t-PA pretreatment versus in eight out of 81 patients without). Good neurological outcome (modified Rankin scale score of 2 or less) was achieved in 32% of the population treated.

Another mechanical thrombolysis trial was the Phase II Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA trial, in which complete recanalization or substantially improved clinical condition was observed in 31 out of 63 (49%) patients in the ultrasound plus IV t-PA group versus 19 out of 63 (30%) patients in the control group (t-PA only) (2). There was a trend toward improved clinical outcome for recanalization augmented by ultrasonography, but no statistical significance was reached.

The authors have used the Merci retriever, balloons, snares, microwires, microcatheters, and stent implantation (22, 23) for mechanical thrombolysis. For mechanical thrombolysis, a 6-French guide catheter is placed in the parent vessel proximal to the occlusion. In general, a 0.14-inch microwire with a microcatheter is used to cross the occlusion with multiple passes to disrupt the clot (*Fig. 1*) (4, 23). If the clot persists after several passes, an angioplasty balloon system (Sentry; Boston Scientific, Natick, MA or CrossSail; Guidant, Temecula, CA) is used to disrupt the clot. This has proven to be the most effective means in larger caliber vessels (*Fig. 2*). In the event that balloon disruption proves ineffective, a snare (In-time Retrieval Device; Boston Scientific, Natick, MA) (*Fig. 3*) or a stent may be used. Snares must be used with caution because they are not compliant, and vessel disruption in distal vasculature may occur.

Stenting is an appealing alternative that has been useful in achieving recanalization in the context of acute intracranial vessel occlusion. Self-expanding and balloon-mounted stent-assisted recanalization of embolic occlusion has been tested in vivo in a canine model at the second author's institution (25). Recanalization of 90% of vessels acutely occluded with either soft or hard clot was achieved. Buttressing of the clot by the stent is likely the main mechanism involved.

Stents seem to be of value in the clinical setting as well. At the second author's institution, intracranial stent implantation with coronary and balloon-expandable stents after failed pharmacological and/or mechanical thrombolysis was found to reestablish flow (TICI 2 or 3) in medium or large intracranial vessels in 15 out of 19 (79%, excluding T-lesions) patients in whom no other therapeutic options were available (23). On the basis of this preliminary experience, the struts of the stent prevent recoil of thrombi or emboli into the vessel lumen, as is observed after coronary artery balloon angioplasty (13).

Self-expandable stent implantation also seems to have potential utility as shown in two recent reports (9, 36). The

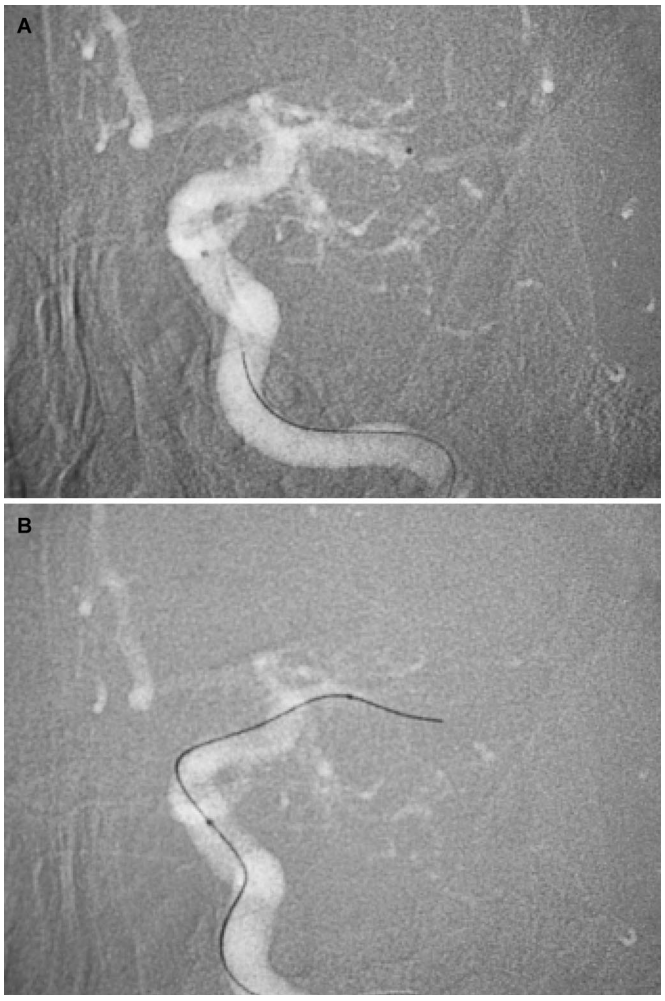

FIGURE 1. A, *microcatheter placement at the proximal occlusion of the proximal middle cerebral artery.* B, *microwire (0.14 inches) placed distal to the occlusion in an attempt to disrupt the clot after the failure of pharmacological thrombolysis.*

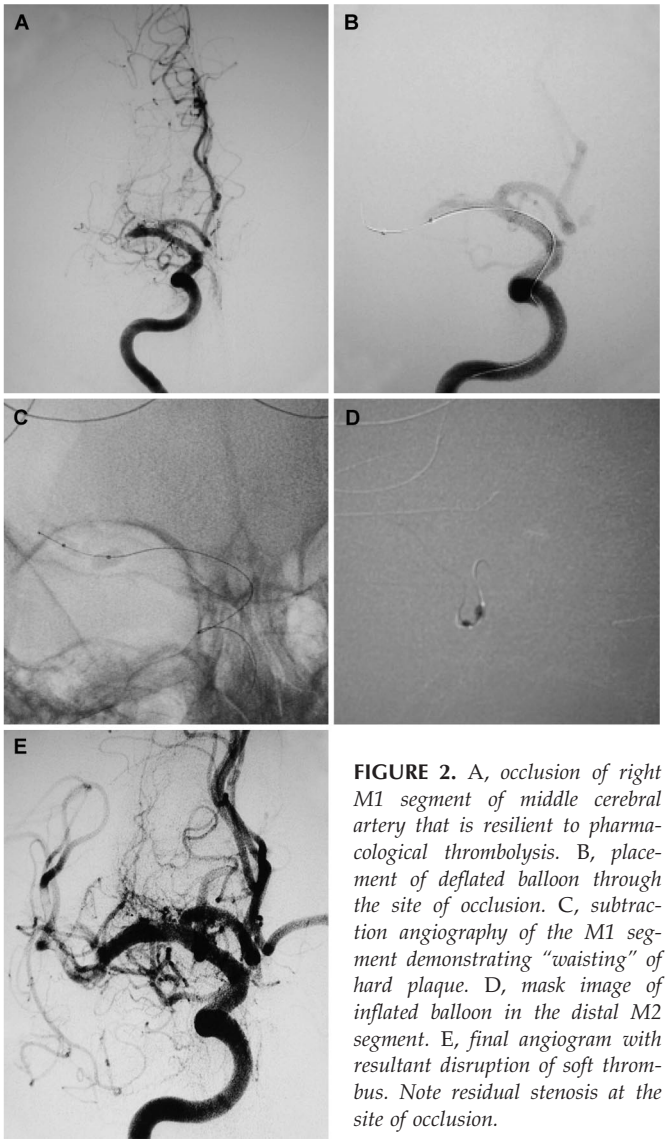

FIGURE 2. A, *occlusion of right M1 segment of middle cerebral artery that is resilient to pharmacological thrombolysis.* B, *placement of deflated balloon through the site of occlusion.* C, *subtraction angiography of the M1 segment demonstrating "waisting" of hard plaque.* D, *mask image of inflated balloon in the distal M2 segment.* E, *final angiogram with resultant disruption of soft thrombus. Note residual stenosis at the site of occlusion.*

Wingspan stent (Boston Scientific, Natick, MA), the first FDA-approved self-expanding stent for intracranial stenosis, provides a promising option for acute stroke treatment. Although not approved for acute ischemic disease, the first prospective multicenter experience shows it to be safe and efficacious for intracranial stenosis, with a 2% major morbidity in 50 vessels treated (Fiorclla D, Levy EI, Turk AS, Albuquerquc FX, Niemann DB, Aagaard-Kienitz B, Hanel RA, Woo H, Rasmussen PA, Hopkins LN, Masaryk TJ, McDougall CG, unpublished data, June 2006). When a stent is used, care must be taken to provide an appropriate antiplatelet regimen to prevent acute stent thrombosis. If a loading dose of aspirin (325–650 mg) and clopidogrel (300–600 mg) cannot be given, an infusion of a glycoprotein IIb/IIIa inhibitor should be administered intraprocedurally (or immediately after a postprocedure computed tomographic (CT) scan showing no ICH). Patients are discharged on a maintenance dose of aspirin (325 mg daily) and either clopidogrel (75 mg daily for 1 mo) or ticlopidine (250 mg twice daily for 1 mo).

In a recent report of IA therapy in 168 patients with acute stroke, the combination of IV GP IIb/IIIa inhibitors (eptifibatide) and IA thrombolytics (t-PA or urokinase) in the setting of multimodality therapy was an independent predictor of recanalization of occluded vessels ($P < 0.048$) (14).

Complication Recognition and Management

Periprocedural hemorrhage represents the most frequent complication. Systemic bleeding that is potentially associated with the use of heparin and thrombolytic agents includes ICH, gastrointestinal hemorrhage, urinary tract hemorrhage, retroperitoneal hemorrhage, and access site hematoma. Because these complications may not be clinically obvious, the results

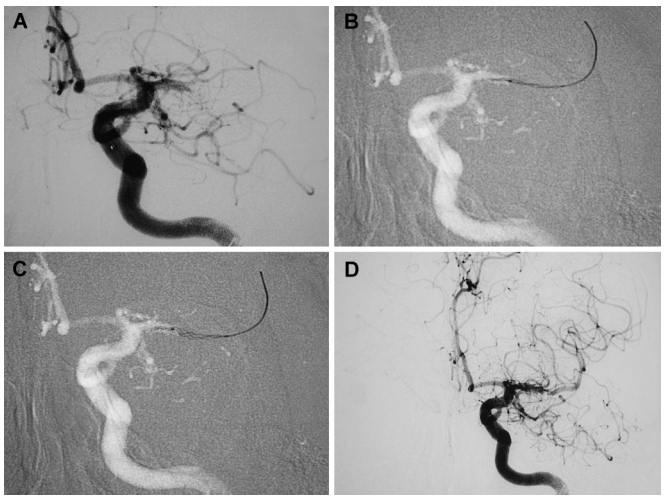

FIGURE 3. A, *angiogram demonstrating complete occlusion of the left middle cerebral artery after administering 800,000 units of urokinase and performing balloon angioplasty in a 38-year-old man.* B, *in-time snare (Boston Scientific, Natick, MA) positioned over hard plaque.* C, *opened snare in the occluded segment of the middle cerebral artery.* D, *angiogram demonstrating filling of the distal vasculature.*

of daily laboratory tests such as hematocrit and hemoglobin levels must be monitored. Retroperitoneal hemorrhage with or without any abdominal symptoms, which can develop from a complication of a femoral artery puncture or inadequate closure of the puncture site, should be suspected if the patient displays signs or symptoms of hemodynamic compromise or if the patient's hemoglobin level decreases. Routine CT imaging of the abdomen and pelvis should be performed if there is clinical suspicion or a retroperitoneal hemorrhage or a declining hematocrit level (in the absence of an obvious bleeding source).

ICH represents the most feared and potentially life-threatening procedural complication of IA thrombolysis. If ICH is suspected during the procedure because of contrast extravasation outside the vessel, the thrombolytic agent should be discontinued and protamine should be administered to reverse the heparin effect (1 mg of protamine per 100 U of heparin given, but not to exceed 50 mg). A cranial CT scan should be obtained immediately. It may be difficult to distinguish ICH from contrast enhancement in the affected area because of disruption of the blood-brain barrier (27). Although Hounsfield units can be used to differentiate the two similar-looking signal densities, a follow-up CT scan obtained 24 to 48 hours later may show clearance of the contrast material in the absence of ICH. ICH without significant mass effect, midline shift, uncal herniation, or neurological deterioration can be managed medically. Ventriculostomy may be indicated in cases of hydrocephalus or in situations for which increased intracranial pressure needs to be controlled and monitored, but care should be taken when inserting drains in anticoagulated patients because of the increased risk of hemorrhage. The authors recommend that surgical evacuation be reserved for intracranial hematomas in easily accessible locations in select patients with progressive neurological deterioration and substantial mass effect observed on cranial computed tomography scan.

Rigorous medical management of these patients is paramount to improved outcome. Airway protection and oxygen saturation should be optimized. The authors recommend maintaining the systolic blood pressure within the range of 120 to 160 mmHg and diastolic blood pressure less than 90 mmHg after the procedure. Fluid and electrolytic status should be closely observed to avoid dehydration, hypotension, fluid overload, and cerebral edema. Daily evaluation of clotting times, platelets, and hematocrit are important for prevention of secondary bleeding complications or worsening ischemia. Patient care in stroke units may lead to a reduction in secondary complications of stroke and ICH.

In PROACT II, symptomatic ICH occurred in 12 patients who had baseline National Institutes of Health Stroke Scale scores of 11 or higher (10). Death occurred after symptomatic ICH in 10 of these patients (83%). A serum glucose level exceeding 200 mg/dl at stroke onset was associated with risk of symptomatic ICH (19). Severity of stroke, longer time to recanalization, and high glucose levels have been reported as independent predictors of ICH in other IA thrombolysis series (20, 41, 43).

The use of a mechanical device as a first-line therapeutic alternative may positively affect the rate of ICH. In the MERCI trial, symptomatic intracranial bleeding occurred in 11 patients (40). Five out of the 11 hemorrhages were subarachnoid and were attributed to vascular perforation. Of the six patients with parenchymal blood, only two had hemorrhages large enough to contribute to neurological decline. For the purpose of comparison with other trials, the MERCI trial investigators have estimated the rate of symptomatic ICH rate to be seven out of 141 patients, or 5%. As indicated in the aforementioned intracranial stenting experience at the second author's institution, only one postoperative asymptomatic ICH occurred, and this complication did not result in an adverse affect on outcome (23).

CONCLUSION

Evidence-based data are accumulating in support of acute ischemic stroke therapy. Although the treatments now available offer a major advance compared with earlier treatments, public and physician awareness of "time is brain" (12, 37) is still a major obstacle. Without timely intervention, no treatment will provide acceptable safety or efficacy. Educational programs to instruct physicians and the public about "brain attack" in acute ischemic stroke are crucial.

Combined IV and IA therapies at centers staffed with experienced personnel will likely be the new treatment paradigm. Advances in neuroimaging will help to better define eligible candidates to ensure better outcomes and may obviate the need for chronological criteria for treatment decision making. Newer fibrinolytic agents and advances in device technology

will allow more patients to be treated. As data accumulate, the indications and limitations of this new technology will allow neurointerventionists a greater opportunity to treat patients with acute thrombolysis.

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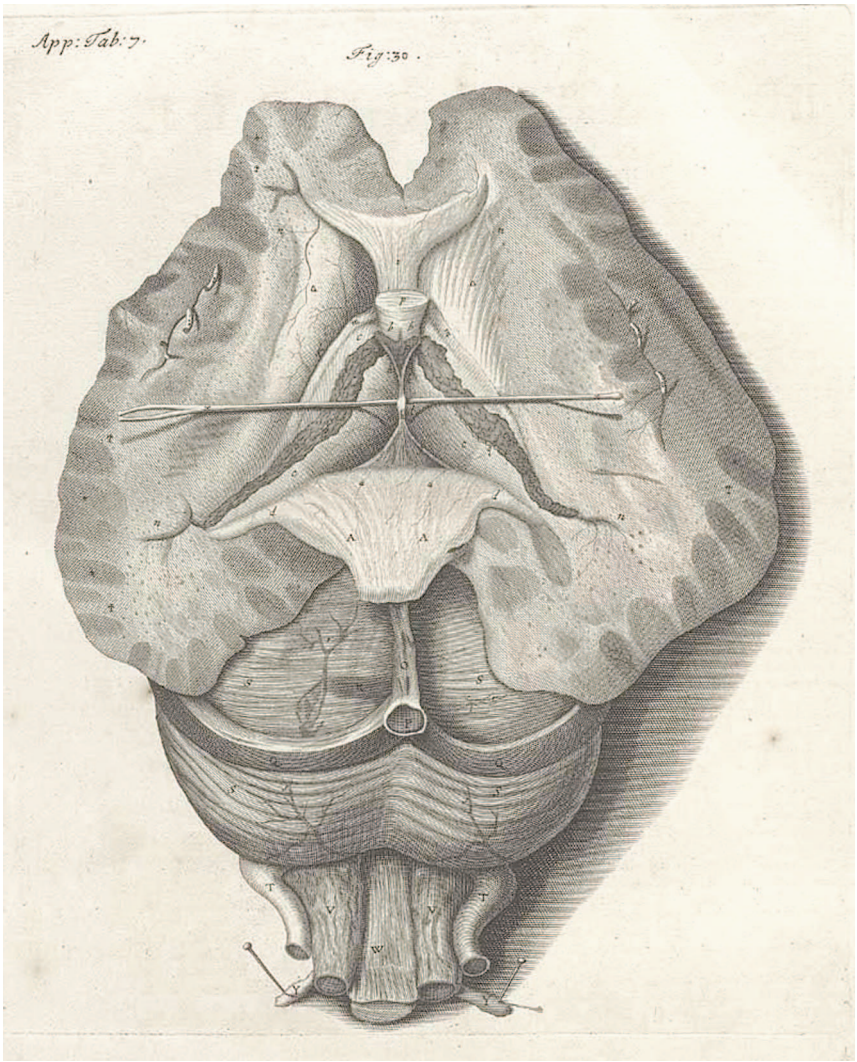

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INTRACRANIAL HEAD AND NECK TUMORS: ENDOVASCULAR CONSIDERATIONS, PRESENT AND FUTURE

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TO REVIEW THE literature on endovascular therapies available to clinicians to aid in the management of head, neck, and intracranial tumors. Hypervascular tumors of the head and neck region, as well as the intracranial region, are associated with large amounts of blood loss intraoperatively. Preoperative embolization of selected hypervascular tumors has been proposed in the literature as a method of reducing blood loss intraoperatively. This technique involves superselective catheterization of the feeding arteries to the tumor bed and then by infusion of embolic particles to saturate the tumor bed in the hopes of inducing necrosis. For less vascular tumors, selective infusion of chemotherapeutic agents has been reported as a method of reducing the systemic toxic effects of these medications. Endovascular therapies for hypervascular and less vascular tumors hold promise, although multicenter randomized controlled trials are required to help identify the patients that will benefit the most.

KEY WORDS: Angiography, Embolization, Endovascular therapy, Intra-arterial chemotherapy, Neoplasm

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There are roughly 39,000 new cases of central nervous system (CNS) tumors (46) and 37,000 new cases of head and neck cancer (64) diagnosed in the United States each year. Embolization of these tumors has become an important adjunct to the surgical treatment of these tumors. In addition to facilitating surgery, they can be used in isolation as palliative treatment for nonresectable tumors and for delivering chemotherapeutic agents. One of the earliest reported cases of a successful embolization was in 1974 by Hekster et al. (29). Since then, many reports or series have been published examining the potential benefits of this therapy, but no consensus has been reached.

Endovascular therapies are not limited to embolization procedures for head and neck tumors. Nonvascular CNS tumors, such as lymphomas, can be treated with blood–brain barrier (BBB) disruption, and squamous cell carcinomas (SCC) can be treated with intra-arterial chemotherapy infusions. In this review, we will discuss the endovascular management of CNS and head and neck tumors.

INDICATIONS AND GENERAL PRINCIPLES

Embolization is generally used only in the management of vascular tumors. *Table 1* summarizes the indications for embolization of tumors. *Table 2* summarizes the common hypervascular tumors that are treated with embolization preoperatively.

Embolizations can be performed by either an endovascular approach or direct injection of embolic agents into the tumor. The aim of embolization is to devascularize the tumor bed by saturating these capillaries, with the hope of promoting tumor necrosis. Sacrificing proximal arterial feeders will do little to help with this endeavor. The smallest particles that are feasible should be used with embolization to penetrate the small capillary beds. The size of these capillary beds varies based on tumor pathology. The limiting factor in using smaller particles is recognition of dangerous anastamoses that can occur between the external carotid artery (ECA) and internal carotid artery (ICA) branches and arteriovenous shunting within the tumor bed. *Table 3* lists some of these anastomoses (71). In addition, there is

TABLE 1. Indications for tumor embolization

1. Control surgically inaccessible arterial feeders
2. Decrease surgical morbidity by reducing blood loss
3. Shorten the operative procedure time
4. Increase the chances of complete surgical resection
5. Decrease the risk of damage to adjacent normal tissue
6. Relieve intractable pain
7. Decrease expected tumor recurrence
8. Allow better visualization of the surgical field with decreased overall surgical complication

blood supply to vital structures such as cranial nerves and nerve roots via ECA and vertebral artery branches as listed in *Table 4*. In general, particles smaller than 150 μm in diameter and liquid embolization should be avoided if these anastamoses are seen or if embolization is being performed in branches supplying cranial nerves or nerve roots (7).

Embolic material can be divided into three major categories: liquid, particulate, and coils. *Table 5* summarizes these various embolic agents and the advantages and disadvantages of each of them. Liquid and particulate agents are used primarily to aid in necrosing of the tumor capillary bed when the microcatheter can be placed in a safe position. Selection of each agent is based on location of the feeding artery (i.e., risk of injuring normal structures) and the desired effect in relation to the planned surgery. If surgery is planned within a few days of embolization, selection of temporary occlusive materials such as particles is reasonable. Fibered and nonfibered detachable coils are used to sacrifice the feeding pedicle to reduce the rate of recanalization, especially when using particulate embolization.

TABLE 2. Common head and neck tumors that are treated with endovascular embolization

1. Hemangioblastomas
2. Meningiomas
3. Intracranial and extracranial metastases
4. Hemangiopericytomas
5. Neurogenic tumors (e.g., schwannomas)
6. Paragangliomas
7. Juvenile nasopharynegeal angiofibromas
8. Hemangiomas

TECHNIQUES

A diagnostic angiogram is performed using the transfemoral technique with cannulation of the common carotid arteries and selective injection of the ICA and ECA. Selective catheterizations of the feeding vessels are performed to provide complete vascular mapping of these lesions. Embolization procedures are initiated with superselective catheterization of the distal most vessel. By entering the distal most vessel, the operator avoids the problem of proximal vasospasm precluding embolization of more distal vessels. On entering the distal arterial feeding vessel to the tumor bed, the feeding pedicles are tested for supply to cranial nerves. An injection of 3 ml of lidocaine is administered, and the patient is tested for cranial nerve and vision deficits before embolization proceeds. If the patient does not incur a deficit with testing, the tumor's capillaries are slowly saturated with embolic particles under constant fluoroscopic guidance. It is important to maintain a slow but steady injection rate while watching for reflux of particles, which would signal the operator to stop injecting. Once the tumor is saturated, the proximal feeding vessel is occluded with either Gelfoam (Upjohn Co., Kalamazoo, MI) or platinum coils before the process is repeated on the next most distal vessel and on through all of the feeding vessels.

For tumors with small arterial feeders coming off larger vessels supplying normal neural structures, we use a technique of liquid embolization using alcohol. By temporarily occluding the larger vessel with a balloon distal to the feeding artery site, we have found that alcohol can be safely injected into these small feeders to aid in devascularizing a tumor (32). Others have described similar techniques (80). However, this technique is still controversial because it can lead to complications. After the balloon is deflated, particles may still be floating in the ICA, and they might distally embolize and cause stroke.

Periprocedurally, it is important to ensure that the patient is well hydrated with intravenous fluids to help protect the kidneys from the iodinated contrast load. Postembolization, patients undergo surgical resection

TABLE 3. Dangerous anastamoses from external carotid artery branches to consider before embolization procedures[a] (71)

Vessel	Anastamoses
Anterior deep temporal artery	Ophthalmic artery
Accessory meningeal	ICA
Middle meningeal	Ophthalmic, inferolateral trunk (cavernous ICA)
Ascending pharyngeal	VA (via hypoglossal art), ICA (via carotid branch)
Occipital artery	VA
Facial artery	Ophthalmic
Vidian artery	Remnant communication between ECA and petrous ICA
Artery of foramen rotundum	Internal maxillary artery to cavernous ICA connection

[a] ICA, internal carotid artery; ECA, external carotid artery; VA, vertebral artery.

within 7 days. This is to avoid neovascularization and new collaterals that can form rapidly. Swelling after embolization is often a concern, and patients can be treated with steroids pre- and postprocedure to help reduce edema.

MENINGIOMAS

Meningiomas account for roughly 15% of all intracranial tumors and typically occur in adults between the ages of 40 and 60 years (71). These tumors can be cured through surgical excision (1), although considerable debate exists in the literature as to the advantages of presurgical embolization.

Meningiomas are usually supplied by dural arteries. These arteries include the middle meningeal artery, accessory meningeal, ascending pharyngeal, or occipital transmastoid-perforating branches of the ECA. Dural arteries also include the tentorial and inferolateral trunk branches of the ICA, as well as the posterior meningeal branch of the vertebral artery. There is often additional supply derived from pial vessels (56). The vascular supply to meningiomas typically varies based on the location of the tumor (*Table 6*).

The aim of embolization is to help reduce blood loss intraoperatively and induce necrosis of the tumor (81). Studying the effectiveness of embolization has been challenging because of the varied sizes, location, and vascular supply to meningiomas. In addition, most studies have relied on subjective reports of blood loss during surgeries, although recent studies have considered gadolinium enhancement on magnetic resonance imaging as a marker of efficacy (25). *Figure 1* shows an example of pre- and postembolization treatment of a sphenoid wing meningioma with marked reduction in gadolinium enhancement. A reduced perioperative blood loss was highly correlated with a reduction in the degree of gadolinium enhancement (25). One of the larger randomized controlled trials has shown that preoperative embolization can reduce blood transfusions perioperatively and may also be more cost-effective in treating patients with meningiomas (14). Wakhloo et al. (81) showed that the blood loss was moreover related to the size of particles used during embolization. A 500- to 2600-ml perioperative blood loss was noted in 70% of cases in which polyvinyl alcohol (PVA) particles that were 150 to 300 μm in diameter were used. When PVA particles that were 50 to 150 μm in diameter were used, the blood loss was less than 500 ml in all but two patients of a total of 20 patients. In those two patients, the blood loss was limited to 800 ml. On histological examination, it was noted that 15 out of the 20 patients treated with particles 50 to 150 μm in diameter had evidence of particles in the tumor capillary bed (81).

Superselective angiography of the feeding vessels with mi-

TABLE 4. Vascular supply to cranial nerves and nerve roots of commonly embolized vessels

Artery	Nerves
Middle meningeal artery	VII, Vm, V3, gasserian ganglion
Accessory meningeal artery	V3, Vm, V2, VII
Inferolateral trunk	III, IV, V1, V2, V3, Vm, gasserion ganglion, VI
Marginal tentorial artery	III, IV
Ascending pharyngeal artery	Gasserion ganglion, VI, IX, X, XI, XII, C3 and C4 roots, Jacobson nerve
Occipital artery	C1 and C2 roots

TABLE 5. Summary of the various embolic agents used during endovascular treatment of central nervous system and head and neck tumors[a]

Agent	Specific material	Advantages	Disadvantages
Liquid	Ethanol NBCA Onyx Hydrogels	Can penetrate into the capillary bed of the tumor	Can cause angionecrosis Injure normal structures (i.e., cranial nerves) Cytotoxic edema Requires changing of microcatheter for each pedicle
Particulate	PVA Gelfoam Microfibrillar collagen	Less likely to injure normal structures with increased particle size	Less likely to penetrate capillary bed Not felt to be permanent Necrosis/edema possible
Microspheres	Gelatin Dextran Poly (D, L lactide/ glycolide) copolymer	Precise control Less likely to injure normal structures	Often resorbable Temporary effects
Coils	Fibered Detachable (i.e., GDC)	Used in conjunction with particles to reduce rate of recanalization	Temporarily reduces blood supply to tumor No effect at capillary level

[a] NBCA, *n*-butylcyanoacrylate; PVA, polyvinyl alcohol; GDC, Guglielmi detachable coils.

TABLE 6. Typical blood supply to meningiomas based on location[a] (9)

Location meningioma	Typical blood supply
Parasagittal/falx	MMA, contralateral MMA, anterior ethmoidal
Olfactory groove	Anterior/posterior ehtmoidal
Sphenoid wing	Sphenoidal branches MMA
Parasellar	ICA branches, MMA, artery of the foramen rotundum
Tentorial	Marginal tentorial artery, basal tentorial artery
Posterior fossa	MMA, occipital artery, ascending pharyngeal artery

[a] MMA, middle meningeal artery; ICA, internal carotid artery.

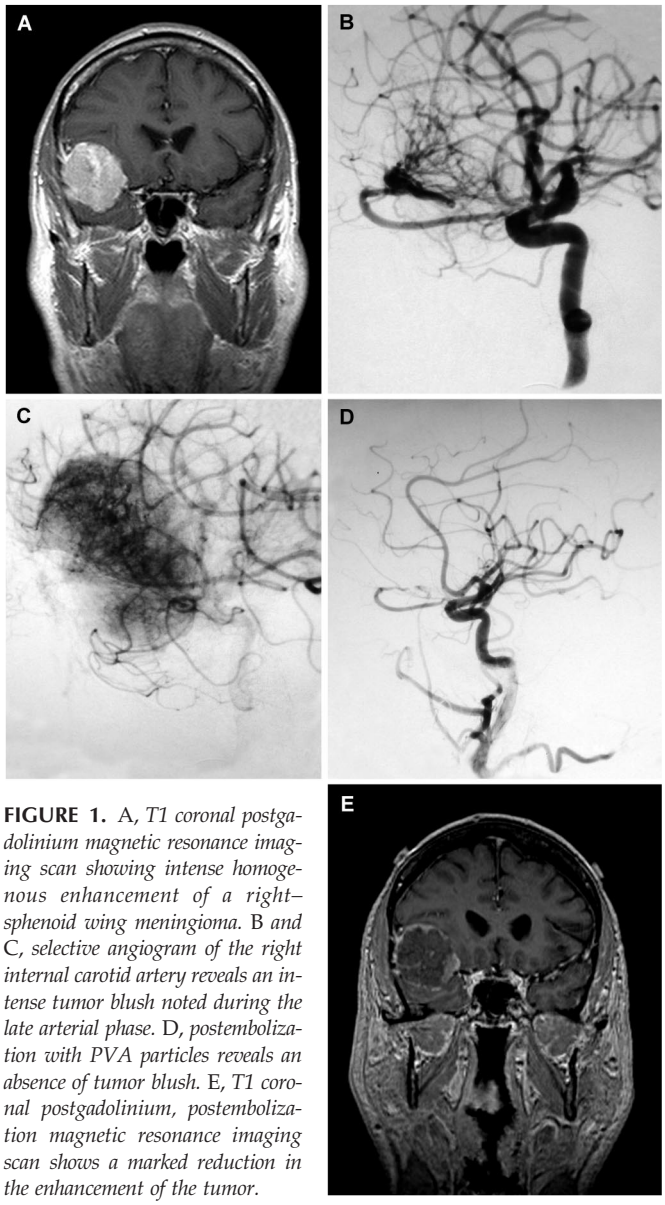

FIGURE 1. A, *T1 coronal postgadolinium magnetic resonance imaging scan showing intense homogenous enhancement of a right–sphenoid wing meningioma.* B *and* C, *selective angiogram of the right internal carotid artery reveals an intense tumor blush noted during the late arterial phase.* D, *postembolization with PVA particles reveals an absence of tumor blush.* E, *T1 coronal postgadolinium, postembolization magnetic resonance imaging scan shows a marked reduction in the enhancement of the tumor.*

crocatheters aids with planning the size and type of materials that will be used during the procedure. The purpose of this technique is to lay out the dangerous anastomoses that can occur, especially from the ECA circulation. Some of the complications reported in the literature occur from the opening of these anastomoses during embolization. If a dangerous anastomosis is identified, the catheter is repositioned or the anastomosis is occluded using a microcoil. Provocative testing is performed as described before with lidocaine to identify blood supply to cranial nerves. If neurological changes occur with lidocaine testing, the catheter is repositioned and the test is repeated. The other option would be to use particles larger in diameter than the vasa nervorum, which would be at least 300 μm.

Particulate material such as PVA and Trisacryl gelatin microspheres are commonly used for embolization (81). The permanence of liquid agents, such as alcohol and cyanoacrylate, is not needed because most of these lesions are resected after embolization. Moreover, liquid agents are riskier because they can cross the anastomotic channels and can cause damage of important neural structures. Other agents that have been used include fibrin glue, lyophilized dura Gelfoam particles, and *n*-butylcyanoacrylate (47, 62). Embolization is done slowly, and vigorous embolization is avoided to prevent reflux of embolic material into normal proximal branches. The pial supply is generally not embolized because of the higher risk of stroke.

This emphasizes the importance of using smaller particles, but care must be taken because this also increases the risk of the procedure. A risk of using particles less than 150 μm in diameter is injuring cranial nerves via the vasa nervorum (43). Embolization procedures should be performed distally to these branches if smaller particles are to be used. Larger particles can be used if the catheter is proximal to branches supplying normal structures.

Large centers report low complication rates with embolization of meningiomas. Berenstein et al. (7) reported that three patients out of 185 (1.6%) developed permanent neurological deficits as a result of embolization, whereas five (2.7%) had transient neurological events. Our experience at the University of Pittsburgh combined with the University of Texas Southwestern Medical Center has shown that four patients out of 111 (3.6%) developed cranial nerve injury or monocular blindness as a result of embolization. The two patients who developed blindness were embolized with 50- to 150-μm PVA particles despite passing provocative testing with lidocaine.

A technique using temporary balloon occlusion has been used for branches of the ICA that may feed the tumor. The authors inflated a balloon distal to the tumor's arterial feeders

and then injected PVA particles, thereby occluding the arterial feeders to the tumor (80). As noted earlier, this technique is controversial and requires further study.

Embolization of meningiomas is feasible and can be done safely at an experienced center, although the risk of this procedure may elevate with the use of smaller particles (81). Preliminary data from case series and single-center randomized trials seem to favor the use of this method for larger tumors, although larger clinical trials are required to delineate the precise role of embolization.

PARAGANGLIOMAS

Paragangliomas are derived from neuroendocrine cells and are a rare entity in the head and neck region. The most common location in the head and neck region for these tumors is along the temporal bone involving the tympanic nerve or jugular fossa, followed by the carotid bifurcation and vagus nerve (4, 74). Angiographically, the typical appearance involves the "splaying" of the carotid bifurcation, with an intense blush denoting its hypervascularity (39). Clinical presentation for these tumors varies based on location. *Table 7* outlines the names given to paragangliomas based on location along with typical clinical presentations. These tumors can be multicentric, although this is more common in patients with a positive family history (21, 26, 61). Paragangliomas rarely secrete catecholamines, especially when they are located at the carotid bifurcation, although patients with labile hypertension should arouse clinical suspicion (63, 66).

It has generally been accepted that definitive treatment for these tumors involves surgical excision. A recent review of the case series presented between 1992 and 1995 of 178 patients undergoing surgical excision of carotid body tumors showed a 0% mortality, 2.2% rate of stroke, and 22% rate of cranial nerve palsies (54). This was in contrast to earlier reports from the 1940s, which had shown a 40% morbidity from excision (52). Preoperative arterial embolization has been used for select cases of head and neck paragangliomas. Because these tumors are rare, it is difficult to study the potential benefits of embolization. Currently, reports from experienced centers have helped in the identification of patients who may potentially benefit from embolization (60).

Preoperative angiography is considered vital by many surgeons because it can aid in determining the arterial supply to the tumor based on vessels that have been displaced (36). In addition, the circle of Willis can help determine how safe it is to temporarily occlude the carotid artery during surgery (60). Once arteriography has been performed, a decision must be made as to the benefits and risks of arterial embolization. These surgeries can often result in significant blood loss of up to 2 L (28). Tikkakoski et al. (78) compared blood loss between patients embolized before surgical excision with that of nonembolized patients and showed a significantly lower amount of blood loss in the embolization group (588 versus 1374 ml, $P < 0.04$) (78). Much of this decision rests on the experience of the interventionalist, along with location and size of the tumor.

It is generally felt that larger tumors will likely benefit from embolization (33, 40), although a cutoff value for size has never been established. Arterial supply to these tumors often involves branches from the ECA and ICA, but almost all patients have some supply from the ascending pharyngeal arteries (60). *Figure 2* shows an example of a typical carotid body tumor with supply from the ascending pharyngeal artery. Different techniques for embolization have been described in the literature. Many advocate catheter placement in the distal part of the feeding vessel with fluoroscopy-guided administration of embolic particles such as PVA, Gelfoam, or cyanoacrylate. Administration should occur with continuous fluoroscopy, and care should be taken to avoid reflux of particles into the normal circulation (33). Proximal embolization of feeding vessels often does not help with reduction of blood loss because ICA collaterals can develop around the tumor. In addition, access to further embolization procedures is lost (60). The capillary bed to these tumors is roughly 200 μm, and thus 150- to 250-μm particles are usually appropriate (7). Catheter-directed embolization can be performed safely, as shown in a series of 47 patients from New York University. Only one patient had a permanent sequela (facial nerve palsy after the procedure); three patients had cranial nerve palsies but also had tumor encapsulating those nerves, one patient had an asymptomatic dissection, and one patient had a transient hemiparesis (60). Surgical excision should occur within 1 week after embolization to ensure that the new collaterals do not form in the interim.

When a large number of branches come off of the ICA and feed the tumor, consideration can be given to a balloon test occlusion. At our institution, we use xenon computed tomography as a physiological test (77) to determine patient tolerance to a balloon test occlusion. If a patient tolerates the

TABLE 7. Clinical symptoms associated with paragangliomas (17, 18)

Location	Tumor name	Clinical symptoms
Middle ear	Tympanic paraganglioma	Hearing loss, tinnitus, discharge, VIIth nerve palsy
Vagus nerve	Vagal paraganglioma	Neck mass, painful, involvement of Xth and XIIth cranial nerves
Carotid bifurcation	Carotid body tumor	Neck mass, painless, rare hoarseness or hemiatrophy of tongue (XIIth)
Jugular bulb	Glomus jugularae	Involvement of the XIth and XIIth cranial nerves
Adrenal gland	Pheochromocytoma	Labile hypertension

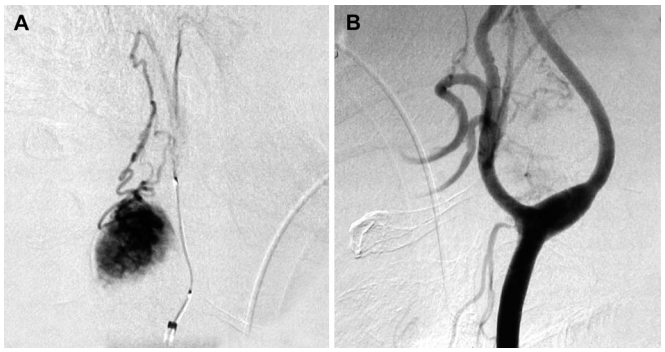

FIGURE 2. A, *selective microcatheter injection of the right ascending pharyngeal artery revealing a hypervacular blush to a carotid body tumor.* B, *postembolization angiography of the right common carotid artery showing splaying of the bifurcation, with an absence of hypervascularity. The patient underwent successful resection of the tumor.*

occlusion, consideration can be given to sacrificing the ICA, although some have recently reported the use of grafted stents to maintain ICA patency while excluding arterial feeders to the tumor (12). Others have reported success with direct percutaneous injection of cyanoacrylate or alcohol into these hypervascular tumors, with successful devascularization of the tumor, but without significant complications (9).

Paragangliomas prove to be challenging tumors to treat and require a team approach towards the goal of successful removal. Endovascular approaches can be used to help reduce blood loss through devascularization of the tumor bed.

HEMANGIOPERICYTOMA

Hemangiopericytoma is a rare tumor of the CNS that accounts for roughly 1% of all intracranial tumors and 2 to 4% of meningiomas (24, 27). These tumors often present clinically and have radiographic features that are similar to those of meningiomas. On magnetic resonance imaging scans, hemangiopericytomas are less likely to have associated calcifications and may have a tendency to uptake contrast in a heterogenous pattern (13, 58). Based on a small number of case series in the literature, it is felt that these tumors have a higher frequency of recurrence in comparison with meningiomas (27). Currently, most authors recommend a radical surgical excision of these tumors (3).

Angiographically, these tumors are typically supplied by branches coming off the ICA and vertebrobasilar circulation and, occasionally, branches from the ECA. The classic feature to the tumor is an intense tumor blush followed by a long-lasting venous phase, along with corkscrew-type vessels within the tumor itself (2, 49).

These tumors are highly vascular and associated with large amounts of blood loss intraoperatively. Earlier reports note intraoperative mortality attributable to blood loss from surgical resection (34). Presurgical embolization has been performed in a limited number of cases in the literature. In addition, direct tumor embolization through percutaneous entry has also been described (23).

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Juvenile nasopharyngeal angiofibroma (JNA) is a rare tumor of adolescence that most commonly affects males (55), although there are rare reports involving females (30). The typical clinical presentation for patients presenting with a JNA is unilateral nasal obstruction with epistaxis. These masses are highly vascular and are associated with arteriovenous fistulae that generate increased feeding artery pressures (73) and may extend intracranially in 10 to 20% of cases (35). JNAs can be staged according to the Fisch classification system (18) (*Table 8*), and surgical excision has been advocated by many authors (59). Despite removal of these tumors, recurrence rates have been reported between 20 and 40% (17, 65). Recurrence rates are most likely related to initial staging of the tumor (45).

The role of preoperative embolization for these vascular tumors has been debated in the literature (51, 53). As with other vascular tumor surgeries, presurgical embolization seems to reduce blood loss during surgery (45, 48, 72). In addition, it may be useful in larger tumors and those extending intracranially because devascularization can help shrink the tumor and make surgical excision easier. The majority of the blood supply comes from the internal maxillary artery, sphenopalatine artery, ascending pharyngeal artery, and smaller branches off the carotid artery (41). Angiography of both carotid systems is necessary because supply can be bilateral in 30% of patients and from branches of the ICA in 30% of patients (59). *Figure 3* shows the typical radiographic features of a JNA tumor pre- and postembolization.

Complication rates from these procedures reported in the literature seem to be low at experienced centers (42, 48). Many of the complications reported in the literature are attributable to poor recognition of dangerous anastomoses, inappropriate embolic material, and size or reflux of particles (59). There has been concern that embolization may be a risk factor for recur-

TABLE 8. Fisch classification for staging of juvenile nasopharyngeal angiofibromas (18)

Class	Location
I	Mass in nasopharynx and nasal cavity without bony disruption
II	Invasion of the maxillary, ethmoid, and sphenoid sinus
III	Invasion of the pterygo–palatine fossa, intratemporal fossa, orbit, and parasellar region
IV	Invasion of the cavernous sinus or optic chiasm or pituitary fossa

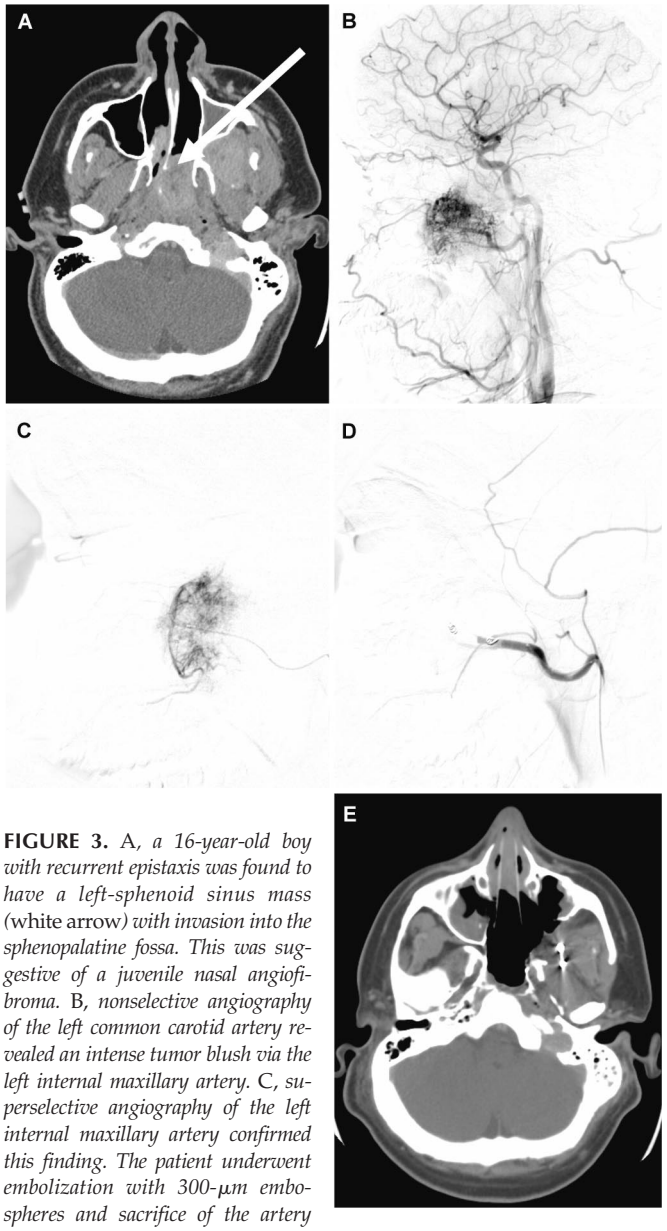

FIGURE 3. A, *a 16-year-old boy with recurrent epistaxis was found to have a left-sphenoid sinus mass* (white arrow) *with invasion into the sphenopalatine fossa. This was suggestive of a juvenile nasal angiofibroma.* B, *nonselective angiography of the left common carotid artery revealed an intense tumor blush via the left internal maxillary artery.* C, *superselective angiography of the left internal maxillary artery confirmed this finding. The patient underwent embolization with 300-μm embospheres and sacrifice of the artery with fibered coils.* D, *postembolization reveals an absence of tumor blush.* E, *computed tomographic scan after surgical removal of the tumor reveals resection of the mass and the nasal septum.*

rence of tumor, although this was from a small series of 33 patients (51).

As with other embolization procedures, if significant blood supply occurs from the ICA, some have used balloon inflation distally to the branches, but proximally to the ophthalmic artery. Particles are then released into the ICA under continuous fluoroscopy to watch for reduction of tumor blush via these ICA branches. Saline can be infused after ceasing embolization to dilute the particles before deflation of the balloon (20). In addition, direct puncture of the tumor can be performed with an 18-gauge needle followed by injection of cyanoacrylate. This can be used in patients with prior proximal ligations within the ECA, thereby restricting endovascular access to feeding arteries; it can also be used in patients with a large supply from ICA branches (79). There are few reports of this technique, and further study is required to assess safety and efficacy.

As with the other tumors discussed thus far, no multicenter large clinical trial data are available to help define the role of embolization of JNAs. These tumors can be safely embolized, although the single-center report of embolization procedures leading to an increased rate of recurrence (51) is concerning.

SQUAMOUS CELL CARCINOMA

SCC is the most common tumor of the head and neck region and is most commonly treated with a combination of surgical resection and radiation therapy. Unfortunately, long-term survival is poor for patients with advanced disease (15). Surgery can often be disfiguring, with associated difficulties in swallowing and chewing secondary to resection of the oral mucosa (68). Cisplatin with or without 5-fluorouracil is used as the chemotherapy regimen for SCC, but it has toxic side effects with escalating doses (37). Intra-arterial administration of cisplatin has been used in limited centers as an alternative to systemic chemotherapy.

Intra-arterial administration of cisplatin into the feeding vessels of the tumor offers the advantage of reduced systemic toxicity along with the ability to give higher doses of the medication. A second problem with systemic doses of cisplatin is that resistance may develop after a few doses, thereby rendering this therapy ineffective (5). Giving higher doses may potentially offset resistance and help induce the tumorcidal effects of cisplatin (67).

These tumors are generally avascular; thus, embotherapy is difficult to perform. Infusion of chemotherapy via intra-arterial means has not gained widespread acceptance, although many reports have been published in the literature showing the potential benefits of this approach (7, 69). These tumors are fed by ECA branches and can be accessed via catheterization of the femoral artery. The catheter can be placed in the proximal ECA before determining which vessels supply the tumor. The catheter is then advanced into the feeding vessel, where infusions of chemotherapeutic agents can be given.

Table 9 summarizes the long-term results from some of the recent studies performed with intra-arterial infusions. Historical comparison shows that patients with advanced head and neck cancer have poor long-term survival, ranging from 15 to 40% (50). Unfortunately, large-scale randomized controlled studies are lacking. The largest, a series of 385 patients, looked at complications associated with intra-arterial chemotherapy infusions and found 10.6% of patients had chemotoxic events, with the majority involving the mucosa, 5.7% groin hematomas, and 1.5% neurological events (22). The chemotoxic events

TABLE 9. Summary of recent studies looking at long-term survival rates in patients with advanced head and neck cancer being treated with intra-arterial cisplatin

Series (ref. no.)	No. of patients	Adjuvant therapy	3-yr survival	No. (%) of patients with stage T3/T4
Kovacs, 2004 (38)	52	Surgery	82%	19 (37%)
Robbins et al. (68)	25	Surgery and radiation therapy	54% (5 yr)	20 (80%)
Balm et al., 2004 (6)	79	Radiation	43%	79 (100%)
Homma et al., 2005 (31)	53	Radiation	54%	53 (100%)

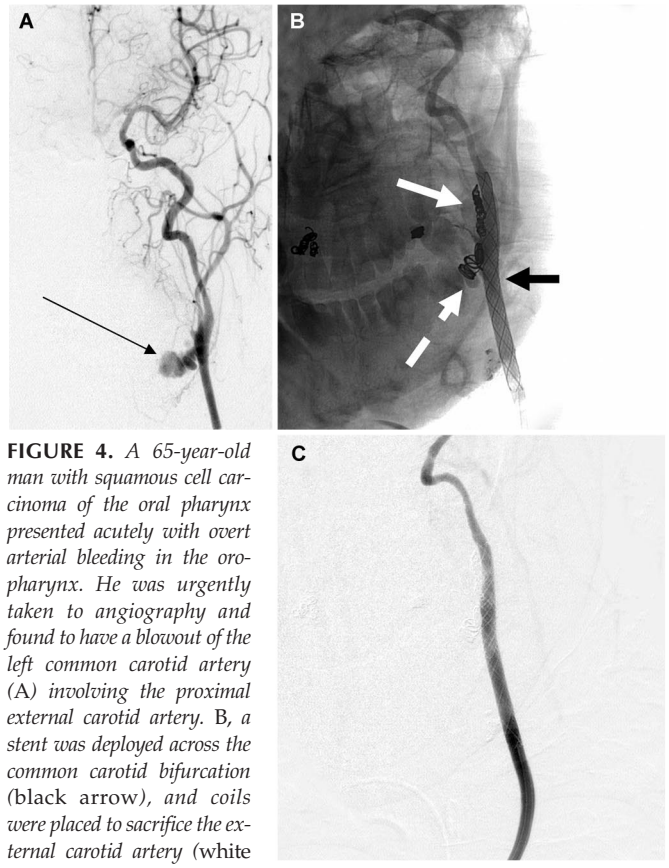

FIGURE 4. *A 65-year-old man with squamous cell carcinoma of the oral pharynx presented acutely with overt arterial bleeding in the oropharynx. He was urgently taken to angiography and found to have a blowout of the left common carotid artery (*A*) involving the proximal external carotid artery.* B, *a stent was deployed across the common carotid bifurcation (*black arrow*), and coils were placed to sacrifice the external carotid artery (*white arrow*) and into a pseudoaneurysmal pouch (*white dashed arrow*). A Wallgraft (Gortex-covered stent) was then placed across the common bifurcation to exclude the tumor-encased arterial segment from the arterial circulation.* C, *poststent and coil placement, the extravasation ceased.*

reported were lower then those noted with intravenous administration of cisplatin (8).

Intra-arterial infusions of chemotherapy seem to be safe and effective relative to historical controls. Results of these studies may help guide future study of intra-arterial therapy for intracranial tumors. Future randomized control studies will hopefully help to clarify the indications and dosages for this therapy.

CAROTID BLOWOUT SYNDROME

Carotid blowouts typically occur in the extracranial segment of the carotid artery as a result of invasion of malignant head and neck carcinomas into the carotid artery. The mortality rate for blowouts is 40% because of extravasation (10). The typical presentation is copious, pulsating bleeding from the oropharynx.

This condition can be managed through endovascular methods. In patients with an intact circle of Willis who are able to tolerate a balloon test occlusion of the ipsilateral artery, complete sacrifice of the carotid artery is an option. This can be performed with detachable coils or detachable balloons with low morbidity (11). Patients deemed to be at a high risk of stroke based on a failed balloon test occlusion can potentially be treated with stents covering the injured segment of artery (*Fig. 4*). The placement of such stents is feasible and can stop extravasation (44), but this is not a long-term solution. In the longer term, the artery continues to deteriorate, and the stents can extrude or become occluded over time, thus causing neurological morbidity (76, 82). Additionally, patients are placed on antiplatelet therapy to maintain the patency of the stent, which may not be optimal in this group of patients.

CNS LYMPHOMA/GLIOMAS

Current therapies for malignant gliomas and lymphomas involve combination therapy using radiation, chemotherapy, and palliative surgery. Survival rates have been dismal despite such aggressive therapies, and newer therapeutic interventions have been studied using BBB disruption in combination with intra-arterial chemotherapy infusions.

This technique involves placing patients under general anesthesia. Selective catheterization of the target vessel ipsilateral to the tumor (i.e., ICA or vertebral artery) is performed. After injections of contrast material are performed, a determination is made as to the rate of infusion of mannitol based on the lowest infusion rate to achieve slight retrograde arterial filling from the catheter. At this point, 25% mannitol is infused for 30 seconds into the catheter at the rate determined necessary to disrupt the BBB. After 15 to 20 minutes, infusion of the chemotherapeutic agent is initiated (57). Methotrexate is used for lymphomas, and carboplatin regimens are used for gliomas. Such protocols have been shown to be safe in Phase II studies enrolling more than 6000 patients and can be replicated across specialized centers (16).

A Phase III randomized trial comparing the infusion of intra-arterial carmustine versus intravenous delivery postresection of malignant gliomas showed no difference between

the two groups. Moreover, the intra-arterial group had significant side effects including white matter changes and encephalopathy (75). Currently, a Phase III study is underway to determine the effectiveness of combing BBB disruption to intra-arterial delivery of chemotherapeutic agents in the hopes of extending life expectancies for these malignant tumors (19).

CONCLUSION

We have summarized some of the therapies used by neurointerventionalists in the treatment of intracranial and head and neck cancers. Small case series have shown that there may be a role for these therapies in the future. Large multicenter randomized clinical trials are required to answer vital questions as to the risks and benefits of these therapeutic interventions.

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CURRENT STATUS OF MANPOWER NEEDS FOR MANAGEMENT OF CEREBROVASCULAR DISEASE

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THE CEREBROVASCULAR DISCIPLINE has undergone dramatic changes in recent years. The advent, development, and now widespread application of endovascular therapy for various cerebrovascular diseases has been the predominant influence behind many of these changes, but other factors (some scientific, others less so) have also contributed significantly. As our discipline evolves, it is critical to periodically examine how such changes have altered our manner of practice and to determine what impact such changes might have on manpower allocation and training for the future. This article is our attempt at providing such an assessment. First, we will critically review recent trends within the fields of intracranial aneurysms, arteriovenous malformations, carotid atherosclerotic occlusive disease, and ischemic stroke and how these trends have impacted our profession. Thereafter, we will provide a perspective on what the cerebrovascular manpower needs of the future might be and by whom these needs will be met. Finally, we will examine how the new generation of cerebrovascular specialists, including neurosurgeons, neuroradiologists, and some neurologists, will attain their requisite surgical or endovascular training and attempt to determine which careers, pathways, and opportunities will be available to these individuals in the future.

KEY WORDS: Cerebrovascular surgery, Endovascular, Manpower, Training

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The management of patients harboring vascular diseases, such as cerebral aneurysms, arteriovenous malformations (AVMs), and carotid artery stenosis, has experienced a rapid evolution in recent years, as many factors, mostly scientific, but some economic and political, have impacted the manner in which we, the healthcare professionals entrusted to care for such patients, practice our discipline. As changes in practice patterns occur, it is prudent to periodically examine those factors that have been most influential in the evolution and to attempt an assessment on how such changes may impact the future manpower and training needs of our profession. Workforce assessments for physicians, however, are notoriously imprecise because they invariably rely upon predictions based on issues such as future scientific advances, epidemiological and demographic trends, economic factors, and even political agendas. Similar difficulties can be predicted when assessing the future training needs for cerebrovascular practitioners, particularly when multiple specialties with overlapping expertise are involved. Notwithstanding these limitations, this article will strive to provide an analysis of those factors that have most impacted our field in recent years and will put forth a perspective on the future manpower and training needs of those neurosurgeons, neuroradiologists, and neurologists who have devoted themselves to the surgical or endovascular treatment of cerebrovascular disease.

EVOLUTION OF PRACTICE

Although significant advances in the treatment of many cerebrovascular diseases have occurred in recent years, we will focus our analysis on those that are most common and, therefore, most likely to impact the manpower and training needs of our specialty in the future: intracranial aneurysms, AVMs, atherosclerotic carotid occlusive disease, and ischemic stroke. We will examine these issues both in the context of our experience at Wash-

ington University in St. Louis and in the context of our discipline as a whole.

INTRACRANIAL ANEURYSMS

Perhaps the most important disease to analyze in regard to recent technological advances and the impact these new techniques have had on practice patterns is that of intracranial aneurysms. The successful treatment of cerebral aneurysms with the Guglielmi detachable coil, including approval of this technique by the Food and Drug Administration (FDA) in 1995, has led to substantial growth in the use of this technique and has forever impacted the distribution of manpower and the nature of training in specialties such as neurosurgery and neuroradiology. We will first examine our institution's experience during the platinum coil era and then assess how our experience relates to that of the general neurological community.

The treatment of cerebral aneurysms with endovascular techniques began in earnest at our institution in 1997 and has grown consistently in volume since that time. Our endovascular team consists of three interventional neuroradiologists, all of whom have joint appointments in the department of neurosurgery, and our neurosurgical team consists of four cerebrovascular surgery specialists. All aneurysms are evaluated by both a neurosurgeon and an interventional neuroradiologist to determine the most appropriate treatment choice for an individual patient. The effect of our endovascular treatment program can be assessed, at least in part, by evaluating the volume and manner in which aneurysms at our institution have been treated during the platinum coil era.

At our institution, endovascular therapy has become increasingly popular as a primary treatment modality for selected cerebral aneurysms, particularly for lesions of the basilar apex and basilar trunk, and for older patients with unruptured lesions. Approximately half of the aneurysms being treated at Washington University today are done so through endovascular means. Yet the number of aneurysms treated surgically during this time has remained stable as the overall aneurysm volume has grown substantially. Undoubtedly, having expert endovascular capabilities at our institution has contributed significantly to this increased aneurysm volume. Several publications (5, 15) have supported the notion that centers providing both exovascular and endovascular therapy may provide superior results compared with those that lack endovascular capabilities. The reasons for this are likely multifactorial, but having the ability to selectively recommend either coiling or clipping for aneurysm treatment and having the capability to aggressively treat vasospasm with angioplasty are likely at the heart of these observations. As platinum coil therapy has become increasingly validated by the medical community and better appreciated by the public, its availability at our institution has made our center increasingly attractive for aneurysm referrals. However, other factors and trends have also likely contributed.

The use of ever improving noninvasive imaging modalities has led to a heightened sensitivity for the detection of unruptured, and often asymptomatic, intracranial aneurysms. Magnetic resonance angiography and computed tomographic angiography have both proven at least complementary to the "gold standard," cerebral angiography, and each have become increasingly used in the workup of patients with complaints such as headaches and other neurological symptoms. Therefore, increasing numbers of patients harboring incidental aneurysms are being seen in our clinics, many of whom ultimately require either open surgical or endovascular intervention.

Another significant factor for our aneurysm volume growth likely reflects a general national trend toward increased referral of patients requiring craniotomies (other than for trauma) to high-volume centers (3). This may be especially true for patients harboring cerebral aneurysms. The etiology for this trend is surely multifaceted, but several underlying reasons likely contribute.

One reason for this trend, particularly at academic centers, has been the profound effect of rising professional liability insurance costs. This has been a particularly acute problem in our region because both Missouri and Illinois are considered states in "crisis." In a recent analysis, Jimenez (14) chronicled the precipitous rise of professional liability insurance premiums in the state of Missouri, its effect on the state's neurosurgeons, and the consequences to the people of Missouri. The mean percentage increase in annual premiums was 116% from 2001 to 2003, with some premiums increasing as much as 295%, leading 40% of respondents to indicate they were considering retirement and 27% to indicate they were considering relocating to another state. Fully two-thirds of respondents noted that they had or were planning to reduce the types of service they provide in their communities, the most common being cerebrovascular surgery (43%). Increasing malpractice premiums have also affected academic neurosurgeons. For example, our premiums have doubled during this time period. Overall, this crisis has contributed to a relative decline in intracranial surgery in the local community and the subsequent referral of such patients to the region's academic centers.

The second reason for the recent trend toward increased referrals to higher-volume/academic centers involves the availability of endovascular therapy. Although its effect has already been discussed, its influence cannot be underestimated, especially after the recent publication of the International Subarachnoid Aneurysm Trial (16). In this study, 2143 patients harboring ruptured cerebral aneurysms deemed equally amenable to either surgical or endovascular intervention were randomized to either surgical clipping or endovascular therapy with platinum coils. Outcome was assessed at 1 year. Despite endovascular therapy carrying a higher risk of postprocedure hemorrhage and an increased need for additional procedures, the rate of dependency and death at 1 year was significantly lower in the endovascular group. Although the trial is ongoing with planned outcome reassessment at 5

years (a time when additional aneurysm ruptures in incompletely treated lesions might impact overall outcome), these interim results have led many physicians to refer increasing numbers of aneurysm patients for endovascular therapy. Because fully 90% of platinum-coil procedures are currently being performed within university settings (9), it is likely that the majority of these additional aneurysm patients being referred for endovascular therapy will ultimately be treated at academic centers.

Although the number of aneurysms being diagnosed and referred to higher-volume centers has increased in recent years (as noted above), the indications for aneurysm treatment have concomitantly become somewhat more conservative, at least for some neurological practitioners. This trend is the direct result of two studies published by the International Study of Unruptured Intracranial Aneurysm Investigators. The findings of the first study (20), which included a retrospective analysis of patients harboring unruptured aneurysms that had been conservatively managed, was met with much skepticism, whereas the follow-up study (16), which analyzed patients harboring untreated, unruptured aneurysms in a prospective manner, has experienced less criticism and has provided intriguing results. In general, the prospective study revealed rupture rates that, although considerably higher than that reported in the retrospective study, were lower than many previous reports estimating the risk of aneurysm rupture (21). This was particularly so in patients harboring small aneurysms (<7 mm in diameter) of the anterior circulation apart from the posterior communicating artery region, whereas aneurysms located in the posterior circulation or in the posterior communicating artery region carried significant risk even if small in size (<7 mm in diameter). On the basis of these results, we, as well as many in the neurological community, have, in general, become somewhat more conservative with our recommendations for aneurysm treatment, especially for lesions less than 7 mm in diameter and located in the anterior circulation apart from the posterior communicating artery.

Two other factors deserve mention in the context of practice patterns for aneurysm treatment. The first is the increasing number of reports suggesting that hospitals or individuals that treat higher volumes of cerebral aneurysms may have superior outcomes in comparison with those treating lower volumes (4, 5, 7, 13, 19). Although not conclusive (11, 12), it is plausible that data such as these might influence practice patterns, especially as insurance companies and the public become increasingly cognizant of such findings.

The second factor that may also carry influence over time has been the inception and establishment of primary stroke centers. There has been growing support by the stroke community as a whole for the concept of establishing and operating primary stroke centers throughout the country in an effort to improve the care of patients with ischemic and hemorrhagic stroke. Members of the Brain Attack Coalition, a multidisciplinary group of representatives from major professional organizations involved with the delivery of stroke care, have reviewed the literature extensively to determine what components are necessary for the establishment of a primary stroke center, recommendations that were published in 2000 (2). These guidelines led to the establishment of multiple primary stroke centers throughout the country in an effort to promote the transfer of stroke patients to hospitals with particular cerebrovascular expertise. In addition, the Brain Attack Coalition also recommended the establishment of comprehensive stroke centers where patients experiencing the most complex strokes requiring specialized testing and highly technical interventions would be provided. Although the establishment of such comprehensive centers is in its infancy, it is possible that, as this comprehensive stroke infrastructure matures, cerebrovascular disease, including the treatment of cerebral aneurysms, may become more regionalized, akin to the shift of trauma patient care to designated trauma centers in the 1990s.

ARTERIOVENOUS MALFORMATIONS

In contradistinction with the recent rapid changes in intracranial aneurysm treatment, the major evolution in AVM therapy occurred significantly earlier, beginning in the late 1980s and early 1990s, as radiosurgical treatment for AVMs gained prominence. During the ensuing years, it has become clear that radiosurgery for smaller AVMs (<3 cm in diameter) has become a viable option for many patients. Radiosurgery, in fact, has become the treatment of choice for smaller AVMs that reside within critical structures such as the basal ganglia, thalamus, and brainstem. Whether or not this holds for smaller AVMs within or near other eloquent regions such as the motor cortex, visual cortex, and primary language centers continues to be a subject of debate. On the other hand, surgical extirpation continues to be the treatment of choice for smaller lesions residing within surgically accessible areas of the brain, and it is often the best treatment for Spetzler-Martin Grade III lesions that are too large (>3 cm in diameter) for radiosurgery. Overall, a relative balance between these two primary treatment modalities has occurred over time, and it is unlikely that a major change in practice pattern will occur in the foreseeable future.

The same cannot be said for larger and more complex AVMs because a general trend toward more conservative management of such lesions seems to have taken hold. A recent report by Han et al. (10) eloquently illustrates this general inclination toward a more cautious management strategy for high-grade AVMs. This intention-to-treat analysis from Han et al. reveals that, even in the hands of an acknowledged cerebrovascular surgery expert, only the minority (5%) of Spetzler-Martin Grade IV and V AVMs were recommended for surgical intervention, reflecting the exquisite selection process that an experienced surgeon must undergo when considering patients for surgical intervention. Much more commonly, these authors recommended no intervention at all, the justification of which was based on two specific observations. First, their analysis of those lesions that underwent palliative or incomplete treatment through endovascular embolization

suggests that not only does this intervention not reduce the chance of hemorrhage over time, but it, in fact, likely significantly increases this risk as compared with natural history. Second, their study provides some evidence that higher-grade AVMs may have a better overall natural history than lower-grade lesions because their hemorrhage risk may be less. With its conclusions that only a highly selected group of Grade IV and V AVMs should undergo intervention of any kind, the impact of this article, combined with the recent opinions of other senior cerebrovascular surgeons with extensive experience with such lesions (12), is likely to dampen any remaining enthusiasm for an aggressive approach to these formidable lesions.

CAROTID ARTERY STENOSIS

The cerebrovascular intervention that has undergone, by far, the most rigorous scientific validation of its efficacy is that of carotid endarterectomy (CEA). This procedure has become the gold standard for most patients harboring significant extracranial carotid artery stenosis. When evaluating practice pattern changes for this disease, two factors have had particular significance for the neurological practitioner. The first involves the decline in the number of CEAs performed by neurosurgeons in favor of peripheral vascular surgeons, a change that occurred insidiously over the past two decades; whereas the second involves the introduction of endovascular techniques for the treatment of extracranial carotid artery stenosis, a change that has rapidly developed in recent years.

In many centers across the country, CEA had become an integral component of the procedures performed by neurosurgeons during the 1970s and early 1980s; however, for many reasons, including the advent and expansion of noninvasive vascular laboratories principally run by peripheral vascular surgeons, the flow of patients diagnosed with carotid artery stenosis was progressively diverted away from neurosurgeons. In addition, the high prevalence of asymptomatic carotid stenosis in patients with peripheral vascular disease gives vascular surgeons ready access to a large population of asymptomatic patients. Currently, fewer than 10% of CEAs are performed by neurosurgeons across the United States, and whether or not this decades-long trend can be reversed is not clear. Through initiatives such as the Carotid Endarterectomy Task Force, established by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, and through individual practitioner effort at the local level (particularly neurosurgeon involvement in regional primary and comprehensive stroke centers), it is hoped that the current disparity in the distribution of CEAs might be impacted.

A more recent, and somewhat disturbing, practice pattern change for carotid artery stenosis treatment has developed after the advent of carotid angioplasty and stenting as an alternative to CEA. Results from two initial studies designed to directly compare CEA with carotid angioplasty and stenting have proven inconclusive (1, 8), leaving validation of endovascular treatment for the carotid stenosis patient population elusive. Yet, the use of angioplasty and stenting as a primary treatment modality continues to grow. The results of new clinical trials (e.g., Carotid Revascularization Endarterectomy versus Stent Trial) that seem more rigorously designed will hopefully help determine the proper role for carotid angioplasty and stenting in the future.

One trial that has been completed and recently published by Yadav et al. (22) has been met with considerable intrigue. The Stenting and Angioplasty with Protection in Patients with High Risk for Endarterectomy trial was designed to compare the safety and efficacy of carotid artery angioplasty and stenting (with the use of a distal protection device) to CEA in treating "high-risk" carotid artery stenosis patients. High risk was defined as age greater than 80 years, presence of congestive heart failure, severe chronic obstructive pulmonary disease, previous CEA with restenosis, previous radiation therapy or radical neck surgery, or lesions distal or proximal to the usual cervical location. The primary result of this study was that carotid stenting with the use of an emboli-protection device was not inferior to CEA among patients with "high-risk" severe carotid artery stenosis. A trend toward superiority of carotid stenting with distal protection over CEA in this patient was also noted, but did not reach statistical significance ($P = 0.053$). Whether or not the outcome of these high-risk patients, many of whom were asymptomatic, would have been better with medical treatment alone, however, remains unknown.

Despite these recent influences and their impact on the number of CEAs being performed, CEA still remains the gold standard for the general (i.e., "low-risk") patient population. It is likely that this operation will remain prominent in the treatment armamentarium for carotid atherosclerotic occlusive disease in the short term, although even this may be threatened by events such as the recent approval of carotid stents by the FDA (despite lack of evidence for its efficacy in this patient population) and the possibility of reimbursement for this procedure outside of clinical trials.

CAROTID OCCLUSION

Extracranial to intracranial bypass for carotid occlusive disease was widely used in North America until the publication of the extracranial to intracranial bypass trial results in 1984. The use of this procedure in the late 1970s was similar to that of CEA. The trial showed no benefit for the procedure when applied to a general population of patients with symptomatic stenosis or occlusion of the internal carotid artery or middle cerebral artery, and this operation is now only rarely performed. However, many of these patients may have had normal cerebral hemodynamics because of adequate sources of collateral flow and therefore nothing to gain with revascularization. Conversely, it is possible that the subgroup of patients with severe hemodynamic impairment benefited from the procedure, but this benefit was missed in the broader group. A randomized clinical trial of superficial temporal artery to mid-

dle cerebral artery anastomosis for carotid occlusion patients with severe hemodynamic impairment is currently underway, the Carotid Occlusion Surgery Study. If positive, this would resurrect this operation and could significantly impact the future manpower needs of cerebrovascular surgery.

ISCHEMIC STROKE

Ischemic stroke therapy underwent a dramatic change in 1995 when the FDA approved the use of intravenous tissue plasminogen activator for the treatment of ischemic stroke for patients presenting within 3 hours of symptom onset. Since that time, an increasing number of patients has been treated with intravenous thrombolysis, although the percentage of ischemic stroke patients being treated with intravenous tissue plasminogen activator has been estimated to be as low as 2% nationally (17, 18). The short therapeutic window afforded by intravenous thrombolysis has been, at least in part, responsible for this low treatment rate, and considerable investigation into strategies for lengthening the therapeutic window has been initiated. One such strategy, intra-arterial thrombolysis, is of particular interest to the endovascular practitioner and could greatly impact the manpower needs within this specialty.

The Prolyse in Acute Cerebral Thromboembolism II trial by Furlan et al. (9a) provided the first evidence that an intra-arterial thrombolytic paradigm may very well benefit certain ischemic stroke patients and seems to have a longer therapeutic window of opportunity. In this trial, patients with angiographically proven middle cerebral artery occlusion who, within 6 hours of symptom onset, were treated with either intra-arterial recombinant prourokinase plus intravenous low-dose heparin versus intra-arterial low-dose heparin alone. A significant improvement in primary outcome measures (modified Rankin score, 0–2) was seen in those patients treated with prourokinase plus heparin as compared with patients treated with heparin alone. To date, however, intra-arterial thrombolysis has not been approved by the FDA and currently remains a procedure under investigation.

Another endovascular technology with potential use in ischemic stroke, the Merci microsnare device (Concentric Medical, Mountain View, CA), was recently approved by the FDA. The device is designed to remove clots from arteries in the brain. Its efficacy for the treatment of patients with ischemic stroke is also unproven and is currently under study in an National Institutes of Health funded clinical trial (Merci Retriever Rescue trial).

MANPOWER

Unquestionably, the tremendous progress made within the endovascular arena has been the single most influential technological advancement to have impacted and enhanced our discipline in recent years. Certainly, many patients who, in a previous era, would have either been left untreated or would have required higher-risk surgical intervention (e.g., medically infirm patients with high-grade symptomatic carotid artery stenosis or those patients with high Hunt and Hess grade ruptured aneurysms) are now frequently being effectively treated through endovascular means. In this light, endovascular therapy has added significantly to the number of patients who may benefit from a cerebrovascular procedure. On the majority of fronts, however, endovascular therapy has either essentially supplanted surgery as the primary mode of treatment for certain diseases (e.g., vein of Galen aneurysms) or has become a viable treatment alternative for diseases traditionally cared for through surgical means (e.g., cerebral aneurysms, carotid artery stenosis, and some AVMs). It is likely that, as endovascular techniques continue to improve and further evidence for their efficacy is documented, the number of cerebrovascular surgical procedures performed each year will steadily decline, to a point. Although attempting to specifically predict the manpower needs for the future of both open vascular and endovascular specialties is fraught with difficulties, we will put forth some general statements regarding each treatment modality in reference to the primary diseases that we have already discussed.

In regard to the treatment of intracranial aneurysms, it has been estimated that as many as 27,000 aneurysms may require treatment in the United States each year (6). What percentage of these aneurysms will be treated through endovascular versus open surgical means remains unclear, but, on the basis of our experience during the platinum coil era, it is likely that at least a portion of aneurysms (e.g., lesions that are broad based, incorporate critical vessels, are larger in size, or are difficult to access with a microcatheter) will still likely require microsurgical repair. It is important to note that, for the majority of patients screened and not randomized in the International Subarachnoid Aneurysm Trial, microsurgical repair was thought to be the best mode of therapy (16). It is, therefore, our opinion that, over time, a balance between surgical intervention and endovascular therapy for most cerebral aneurysms will be achieved, similar to the balance currently established between radiosurgery and surgery for the treatment of smaller AVMs. Where exactly this equilibrium becomes established it difficult to ascertain, but this balance will largely determine the overall manpower needs for both open vascular and endovascular specialists.

In regard to the treatment of cerebral AVMs, although significant advances in the endovascular armamentarium for such lesions have certainly occurred (e.g., newer embolic agents and improved microcatheter technology), effective primary treatment through endovascular means remains the exception. Currently, microsurgical extirpation and radiosurgery remain the two primary definitive treatment modalities for most AVMs. That said, as superior techniques for AVM embolization have developed over time, it is likely that the safety profile for such therapy has also improved, allowing for a more liberal use of this technology as a pretreatment adjunct to definitive surgical resection. Certainly, at our own institution, we have found ourselves increasingly using endovascular embolization as a preoperative adjunct. On the whole,

despite this modest increase in the use of endovascular embolization as a presurgical adjunct for AVM treatment, we do not envision a major change in the allocated manpower required for the optimal treatment of cerebral AVMs in the near future.

In regard to the treatment of carotid artery stenosis, endovascular therapy with angioplasty and stenting may be the treatment of choice for certain high-risk patients, whereas CEA currently remains the gold standard for the general carotid artery stenosis population. Results of ongoing trials (*Table 1*) that directly compare these two modalities in the low-risk patient population will hopefully help determine which treatment modality provides the best stroke prevention with the lowest risk profile for the general patient. Unfortunately, these results will not be available for several years. In addition, the recent approval of carotid stents from two vendors (Guidant and Johnson and Johnson Cordis) and the possibility of reimbursement for the procedure outside of clinical trials may be setting the stage for a rapid shift from CEA in good surgical candidates despite the lack of evidence for efficacy. These uncertainties make predictions on the impact of angioplasty and stenting techniques on future cerebrovascular manpower quite speculative at this time.

Finally, in regard to ischemic stroke, endovascular therapy (i.e., intra-arterial thrombolysis) currently remains an investigational treatment modality at this juncture, and only time will tell whether or not this or other endovascular techniques (e.g., mechanical thrombolysis) will become an integral component of the treatment of ischemic stroke. Because more scientific study is needed, and because this treatment requires a significant coordination and mobilization of personnel in a relatively short period of time (<6 hr), it is unlikely that substantial growth for this particular application of endovascular therapy will be realized in the near future. The projected impact on manpower allocation in the short-term has, therefore, been minimal, although the long-term impact may be profound.

Overall, the use of endovascular therapy for the treatment of a variety of cerebrovascular diseases is unquestionably on the rise. Industry estimates regarding the number of endovascular practitioners that might be needed for the future care of cerebrovascular disease have ranged as high as 1000 individuals, whereas opinions from experts in the endovascular field suggest that only 500 to 600 endovascular neurointerventionalists may be needed. Currently, there are approximately 250 endovascular neuroradiologists practicing in the United States, and there are an additional 50 neurosurgeons with endovascular skills practicing at this time. In addition, neurologists are beginning to obtain training in endovascular techniques and other specialties, such as cardiology, and are expanding their role into the treatment of certain cerebrovascular disorders (i.e., carotid artery stenosis). Which of these practitioners will eventually provide for the increased endovascular demand is unclear, although two groups, the neuroradiologists and neurosurgeons, seem strategically situated at this time.

Neuroradiologists have been the clear leaders in this field for many years and currently represent the overwhelming majority of individuals with endovascular expertise. They also run the majority of training programs across the country and, therefore, have tremendous influence on who the future endovascular practitioners will be. Neurosurgeons, although present at the field's inception, have only recently gained a sizable market share in the endovascular arena. But, with the number of neurosurgeons with endovascular expertise growing and the number of neurosurgeon-led endovascular training programs expanding, it is likely that neurosurgeons will be increasingly filling the need for additional endovascular expertise. Ultimately, those disciplines that most aggressively and cohesively address the issues of attracting appropriate candidates, providing such candidates with excellent training opportunities, and promoting these individuals within their specialty and beyond will be the disciplines that are best positioned to address the additional demand for endovascular expertise.

Regarding open cerebrovascular surgery, clearly, changes in the distribution of manpower have already begun, and further changes may be on the way. The number of dedicated cerebrovascular surgery positions throughout the country has

TABLE 1. Ongoing clinical trials investigating carotid angioplasty and stenting versus carotid endarterectomy[a,b]

Study abbreviation	Study	Sponsor	Study size (actual/planned)	Status
CREST	Carotid Revascularization Endarterectomy versus Stent Trial	NINDS	840/2500	Recruiting patients
EVA-3S	Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis	Sainte-Anne Hospital, France	135/1000	Recruiting patients
ICSS	International Carotid Stenting Study	Stroke Association (UK)	201/2000	Recruiting patients
SPACE	Stent-protected Percutaneous Angioplasty of the Carotid versus Endarterectomy	BMBF, DFG, Guidant	581/1900	Recruiting patients

[a] NINDS, National Institute for Neurological Disorders and Stroke, National Institutes of Health; BMBF, German Ministry of Science; DFG, German Research Council; Guidant, Boston Scientific Guidant.
[b] Adapted with permission from the Internet Stroke Center, www.strokecenter.org.

dwindled markedly in recent years because most institutions are seeking individuals who combine open cerebrovascular surgery capabilities with other expertise, such as endovascular, cranial base, or research proficiency. It is the rare individual at present to have a predominantly open cerebrovascular practice, even among the most well-known vascular surgeons of our era. This new emphasis on combined expertise puts the dedicated cerebrovascular surgeons of the future in a somewhat difficult position because they must maneuver through their training with particular efficiency to obtain the appropriate combined expertise in a reasonable amount of time. Some of these individuals will truly dedicate their careers to open cerebrovascular surgery, whereas many others will gravitate toward their other clinical or research interests. The overall effect, in our opinion, will be a relative diminution in truly expert cerebrovascular surgeons in the not so distant future.

This naturally leads to the following complex and contentious issue: how should patients who need surgical intervention for a complex vascular lesion be best treated in the future? Should they, as a group, be treated by many neurosurgeons throughout the country, even though their cerebrovascular surgical volume has declined, or should they be treated through a more regionalized approach in which fewer neurosurgeons who maintain higher cerebrovascular volumes perform the requisite surgery? This controversial issue is sure to be hotly debated as time passes and as the reality of fewer truly expert vascular surgeons becomes increasingly appreciated.

TRAINING AND CAREER DEVELOPMENT

Now that we have reviewed the rapid evolution in cerebrovascular practice patterns and have outlined the major manpower issues that face our discipline today and in the future, it is critical to also examine how we will train those physicians seeking expertise in the treatment of cerebrovascular disease. Our analysis will first focus on how individuals from potentially disparate clinical backgrounds will obtain the requisite training in the two fields that currently dominate the treatment of cerebrovascular disease: microsurgery and endovascular therapy. We will also provide a perspective on how both techniques, either in combination or as a single discipline, might be integrated into various career paths. As guidelines for training programs in "endovascular surgical neuroradiology" have been specifically established by the Accreditation Council for Graduate Medical Education (ACGME), let us first examine the training pathway for those interested in establishing endovascular neurointerventional expertise.

The ACGME-accredited training program was established in 1998 and unanimously endorsed by the Joint Section of Cerebrovascular Neurosurgery, the Executive Council of the American Association of Neurological Surgeons and Congress of Neurological Surgeons, the Executive Committee of the American Society of Interventional and Therapeutic Neuroradiology, and the American Society of Neuroradiology in 1999. This training involves a 1-year interventional program that must be preceded by 1 year of neuroradiology. The initial year of neuroradiology training is designed to provide the nonradiologist time to become proficient with catheter-based techniques used in cerebral angiography (with a requirement of at least 100 angiograms) in addition to providing a fundamental foundation in radiation sciences (including knowledge in radiation physics and in interpretation of neuroradiological studies). For the radiologist, this year of training is designed to provide a similar experience in basic angiographic techniques and neuroimaging methods. Radiologists must also spend 3 months on a clinical neurosurgery service before the fellowship. The final 1-year period of endovascular training is designed as a dedicated experience using catheter-based techniques for neurointervention, including coiling, angioplasty, stenting, and embolization procedures, among others. Although the ACGME guidelines for endovascular surgical neuroradiology fellowships were established 6 years ago, to date, there are only three accredited programs, including one at our institution. The slow adoption of accreditation is primarily because of financial factors. It is not legal to bill Medicare/Medicaid for the services of fellows in ACGME-approved residencies or fellowships because some portion of their salaries is theoretically paid by the federal government. Fellows in programs that do not have ACGME-approval may serve as attending physicians, and these services may be reimbursed. Consequently, most fellowship positions in endovascular neuroradiology are not ACGME-approved. Accurate numbers are not available, but it is likely that the proportion of these positions filled by neurosurgeons may be approaching that of neuroradiologists.

For radiologists interested in endovascular neurointerventional training, the path is clear. Such individuals generally complete a 5-year radiology residency followed by a 2-year interventional neuroradiology fellowship, making the total length of training 7 years. For neurologists, the path is less clear, but will likely include completion of a 4-year residency, as well as a vascular neurology fellowship, and then 2 years of endovascular fellowship training, making the total length of training 7 or 8 years. For neurosurgeons, the path is somewhat more complex because the majority of neurosurgery residents wishing to pursue endovascular training also wish to establish particular expertise in open vascular microsurgical techniques. This makes the length of training for such individuals as many as 10 or 11 years (6–8 years of neurosurgery residency, 2 years of endovascular training, and 1 year of open cerebrovascular fellowship). Many individuals within the neurosurgical community have voiced concern regarding this extended period of training currently required for those inclined to pursue both endovascular and open vascular training. As such, a number of residents throughout the country, in conjunction with their program directors, have pursued endovascular training as a component of their neurosurgery residency. Although this pathway is not ACGME-accredited, these "in-residency" fellowships allow a shortening of the overall number of training years required for such individuals.

The requirements for open cerebrovascular surgical training have traditionally been less precise. Certainly, the foundation lies with excellent microsurgical training and ample cerebrovascular exposure during an individual's neurosurgical residency. For those individuals wishing to dedicate themselves to cerebrovascular surgery, however, it is the opinion of many that additional postresidency training is required. Now more than ever, it is very unlikely that an individual neurosurgery resident could acquire the kind of open microsurgical experience required for a dedicated career in cerebrovascular surgery. Because of the inroads of endovascular therapy, as well as radiosurgery, the availability of more routine cerebrovascular lesions has steadily declined, making the number of cerebrovascular cases available to a particular resident less and less abundant. In this environment, only the exceptional resident in an exceptional residency will have the surgical experience necessary for a dedicated cerebrovascular surgery career. It is also possible that some individuals who, after the completion of a neurosurgical residency, but without pursuing further fellowship training, may find a practice opportunity that allows a gradual and mentored experience with cerebrovascular surgical techniques, eventually allowing that individual to develop the surgical capabilities needed to become an accomplished cerebrovascular surgeon. But, for the majority of neurosurgeons wishing to dedicate themselves to open cerebrovascular surgery, now more than ever, these individuals will be largely required to complete a dedicated cerebrovascular fellowship.

Let us now consider the career opportunities that lay ahead for these various practitioners. We will first examine the scenario of the interventional neuroradiologists. These individuals, once their endovascular fellowship is complete, may likely find plentiful opportunities in the academic and private sectors because the potential for growth in the need for endovascular expertise seems great, particularly for the field of aneurysm treatment, but also for carotid artery stenosis therapy and possibly ischemic stroke intervention. Yet, the interventional neuroradiologist will also likely find an increasingly competitive environment as more neurosurgeons and some neurologists become equally accomplished in endovascular techniques. They may even find that they are at a relative disadvantage to neurosurgeons and neurologists because these specialists have undergone a more clinically oriented training program and often have immediate access to patients with certain cerebrovascular diseases. That said, the interventional neuroradiology community has clearly been at the forefront of advancing endovascular techniques and has been the leader in the training of future endovascular practitioners for many years. It is, therefore, likely that interventional neuroradiologists will maintain a strong and leading presence in the field of endovascular therapy for the foreseeable future.

For the neurologist who has completed an endovascular fellowship, potential career paths are currently poorly defined, mainly because of the fact that neurologists have only recently begun to enter the field. That said, it is conceivable that both academic and private practice opportunities will become available for these individuals over time, particularly if endovascular techniques, such as intra-arterial thrombolysis for acute ischemic stroke, become validated and broadly accepted.

For the neurosurgeon wishing to dedicate him or herself to the treatment of cerebrovascular disease, several career pathways and opportunities may be available, based predominantly on the particular expertise (endovascular, microsurgical, or both) he or she has attained. Before examining each career possibility in detail, however, one fact of present day cerebrovascular practice must be stated: the days of a neurosurgeon dedicating him or herself exclusively to the field of open surgical treatment for cerebrovascular disease are numbered. Even the majority of senior cerebrovascular surgeons have found it necessary to supplement their cerebrovascular practice with other neurosurgical pursuits, including general neurosurgery, cranial base surgery, or endovascular therapy, with a distinct minority pursuing the latter. This has become necessary as decreasing numbers of cerebrovascular cases have become available for the reasons detailed above.

For those young neurosurgeons wishing a career dedicated to cerebrovascular surgery, it is highly likely that additional pursuits will be required to adequately fill out a neurosurgical practice. Typically, three main complementary disciplines are considered. The first involves augmenting a dedicated cerebrovascular surgery practice with considerable protected time for pursuing laboratory research. Those who will flourish most in this type of academic opportunity will be those individuals who developed an interest and established a true track record in basic research during their residency. Although relatively plentiful in the past, when academic departments had sufficient clinical funds to help new faculty establish a dedicated laboratory effort, today's environment of decreasing renumeration has provided fewer and fewer academic departments the luxury of providing new neurosurgeons this form of laboratory support. Yet, those who have the requisite background and have been fortunate enough to find such an opportunity are likely to find a rewarding faculty position with considerable opportunities for scientific accomplishment and rapid academic advancement, although likely at the expense of a somewhat reduced compensation in the early years of their career (because of initial constraints on their clinical practice).

The second possibility for individuals wishing to pursue a dedicated cerebrovascular surgery practice includes complementing this open surgical interest with endovascular expertise. This has been a very popular route in recent years because many departments have aggressively sought to add endovascular expertise to their neurosurgical armamentarium. In the past, program chairs might have sought a neurosurgeon with open vascular surgery expertise in an effort to address a clinical need, whereas, today, a neurosurgery department would most likely seek an individual who could carry some of the cerebrovascular surgery load, but also add an endovascular component to the practice. Although certain exceptional individuals may be able to establish themselves as true experts

in both complex cerebrovascular surgery and state-of-the-art endovascular therapy, it is likely that the majority of individuals will naturally gravitate toward one treatment modality or the other. Some might eventually dedicate themselves to an exclusively endovascular practice (likely a minority), whereas others would develop a predominantly endovascular practice coupled with general neurosurgery or perhaps more routine cerebrovascular surgery. Still others would gravitate toward a more dedicated cerebrovascular surgery practice, where they become proficient in the treatment of even the most complex vascular lesions, and supplement this primary interest with more routine endovascular procedures, perhaps leaving more complex endovascular interventions to others. Whatever the ultimate desirable balance between open vascular and endovascular procedures might be for a given individual, care must be taken when considering positions in which both exovascular and endovascular expertise are sought: the mix of cases for a given position must be commensurate with the young neurosurgeon's desired career path. This is most important for those with a greater interest in open cerebrovascular surgery because many positions available today seem to have the greatest emphasis on endovascular therapy. For those with the aptitude, desire, and stamina necessary for completion of combined open vascular and endovascular training, this career path is, by far, the most marketable in terms of a cerebrovascular practice, both in the academic and private sector. This career also likely offers considerable room for rapid academic advancement (because endovascular surgery is still a relatively immature field replete with research opportunities) and comfortable compensation packages (consistent with a predominantly clinical practice).

The third consideration for neurosurgeons wishing to specialize in cerebrovascular surgery is obtaining complementary expertise in cranial base surgery. The two fields have great natural overlap because many vascular lesions require extensive cranial base surgery approaches for optimal treatment, and the microsurgical technique garnered from cerebrovascular surgery has direct application to the removal of many cranial base tumors, especially those with extensive vascular and cranial nerve involvement. Although this has been a popular complement to many senior vascular neurosurgeons' practices, opportunities for truly combined training in cerebrovascular and cranial base surgery are somewhat limited, as, it seems, are the employment opportunities. Also, pursuing a career that combines a dedicated cerebrovascular practice with that of cranial base surgery, both of which are relatively mature fields, may not provide the same opportunities for academic advancement as one might find with basic research or endovascular therapy.

CONCLUSION

This is an exciting time to be entering the cerebrovascular discipline, although the landscape has changed dramatically in recent years. Interventional neuroradiologists no longer have the endovascular field to themselves; neurosurgeons wanting to pursue cerebrovascular surgery must also become proficient in complementary disciplines, such as cranial base surgery, endovascular therapy, or research, to be competitive in today's job market, and neurologists interested in endovascular therapy must work diligently to find appropriate training positions and employment opportunities. Results from ongoing clinical trials, such as Carotid Revascularization Endarterectomy versus Stent Trial and long-term follow-up data from the International Subarachnoid Aneurysm Trial, will likely have a significant impact on the manner in which we practice our discipline in the relatively near future, as may, unfortunately, other nonscientific influences such as the malpractice crisis. Periodic examination of the current status of our discipline and critical assessment of its future are essential endeavors, which, if performed thoughtfully and acted upon appropriately, will ultimately lead to a suitable allocation of manpower for the field of cerebrovascular disease, allowing for both rewarding employment opportunities for our practitioners and optimal care for our cerebrovascular patients.

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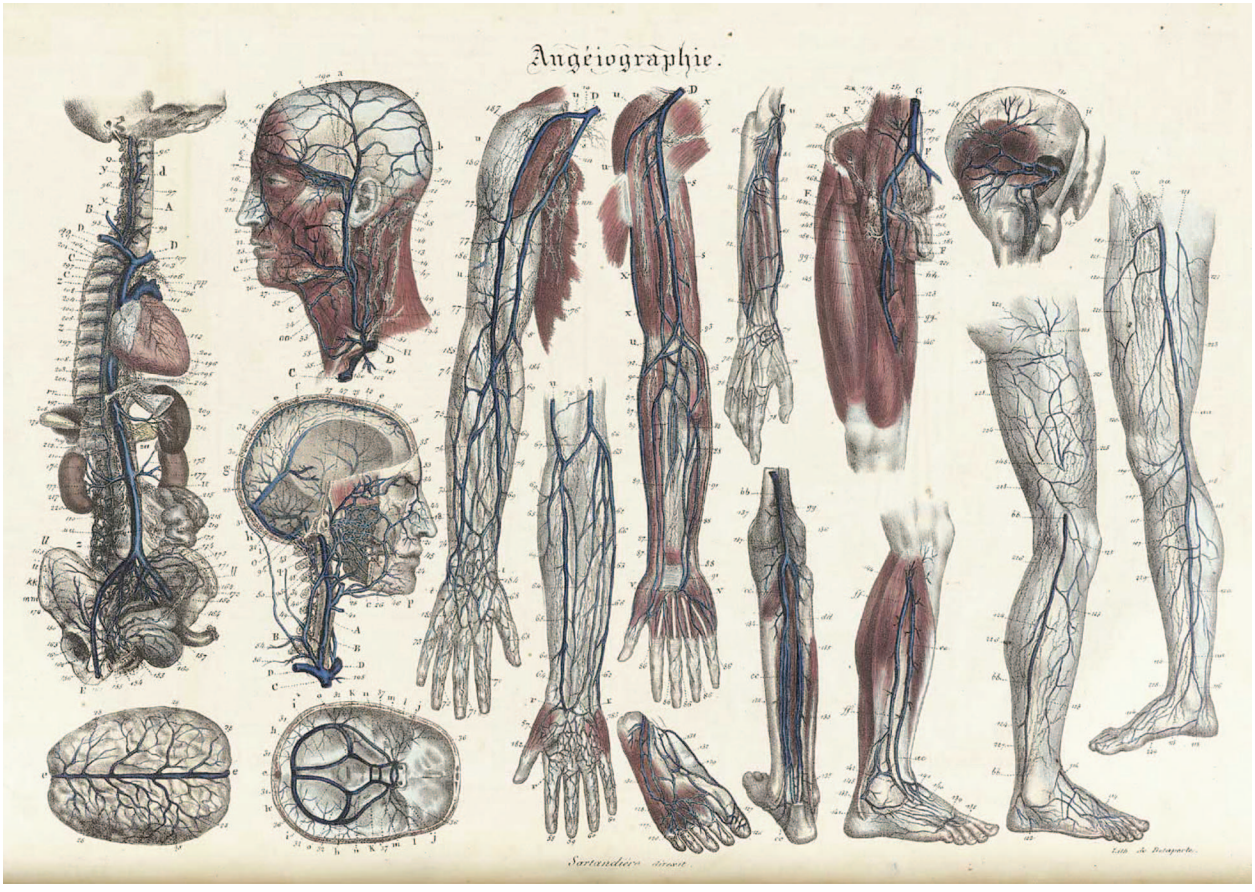

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WORKFORCE NEEDS FOR ENDOVASCULAR NEUROSURGERY

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DURING THE PAST decade, endovascular techniques and clinical experience have matured to the point that all or a significant part of the treatment of acute ischemic stroke, cerebral aneurysms, brachiocephalic occlusive disease, and arteriovenous fistulae or malformations is performed in angiography suites by neuroradiologists, vascular surgeons, peripheral interventionists, cardiologists, neurologists, and neurosurgeons worldwide. With improvements in technology and lower morbidity rates, the scope of endovascular techniques will only increase. Currently, in the United States alone, this amounts to a volume of more than 500,000 patients annually. Neurosurgeons currently provide only a small portion of the care of these patients. The workforce needs for endovascular surgeons in neurosurgery will be determined by the patients, the willingness of neurosurgeons to embrace endovascular techniques, and the broad scope of cerebrovascular disorders that can be treated.

KEY WORDS: Cerebrovascular disorders, Endovascular therapeutics, Workforce

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It must be remembered that there is nothing more difficult to plan, more doubtful success, nor more dangerous to manage, than the creation of a new system. For the initiator has enmity of all who would profit by preservation of the old institution and merely lukewarm defenders in those who would gain by the new one.

—Machiavelli, 1513

In the past 15 years, endovascular techniques have revolutionized the practice of vascular neurosurgery. Aneurysm coiling, carotid or great vessel angioplasty and stenting, intra-arterial treatment of acute stroke, angioplasty and stenting of intracranial atherosclerotic disease, and intra-arterial and transvenous embolization of arteriovenous malformations and fistulae have safely provided thousands of patients with minimally invasive approaches to lesions that previously would have been treated with open surgery. Also within the bailiwick of endovascular neurosurgery are percutaneous procedures such as vertebroplasty and kyphoplasty, tumor embolization, treatment of traumatic vascular injuries, embolization of venous malformations of the head, neck, and extremities, Wada examination, and placement of inferior vena cavae filters for venous thrombotic disease. Although every practitioner may not perform each of these techniques, they are available at most large endovascular centers.

Sound clinical data supporting the use of endovascular techniques have now been published. The results of the International Subarachnoid Aneurysm Trial (ISAT) (24) support endovascular coiling of aneurysms in cases of clinical equipoise (*Table 1*). At the 1-year follow-up examination, 23.5% of patients in the endovascular arm were dead or dependent versus 30.9% in the surgical group, for an absolute risk reduction of 7.4% (25). This benefit was maintained out to 7 years ($P = 0.03$). This benefit exists even with the slightly higher late rebleeding rate in the endovascular arm at 4.2 versus 3.6%. Epilepsy was higher in the surgical group. The prospective arm of the International Study of Unruptured Intracranial Aneurysms (ISUIA) (30) supports the use of endovascular techniques, particularly in older patients, and its retrospective arm demonstrated that the morbidity and mortality of open surgery is much higher than previously thought (21) (*Table 1*). In recent carotid angioplasty and stenting trials, the major adverse event rates (representing the composite incidence of stroke, death, and myocardial infarction) have been lowered to between 2 and 8.3% (*Table 2*). The National Institutes of

TABLE 1. International Study of Unruptured Intracranial Aneurysm and International Subarachnoid Aneurysm Trial results[a]

Trial	Surgical Treatment		Endovascular Treatment	
	No Previous SAH	Previous SAH	No Previous SAH	Previous SAH
ISUIA				
(Hemorrhage rate [%] at 1 year after treatment for patients with asymptomatic unruptured aneurysms)				
Retrospective (1998)	15.7	13.1	N/A	N/A
Prospective (2003)	12.6	10.1	9.8	7.1
ISAT				
(Patients [no.] dead or disabled by treatment strategy)				
2002	N/A	30.6	N/A	23.7
2005	N/A	30.9	N/A	23.5

[a] ISUIA, International Study of Unruptured Intracranial Aneurysm; SAH, aneurysmal subarachnoid hemorrhage; ISAT, International Subarachnoid Aneurysm Trial; N/A, not applicable.

TABLE 2. Recent carotid angioplasty and stenting trials[a]

Trial	Sample size	Results	Status
ARCHeR	581 (Phases I–III)	Composite 30-day MAE I–III: 8.3%	Closed
BEACH	747 (pivotal and registry groups)	Composite 30-day MAE: 5.8%	Closed
CABERNET	443	Composite 30-day MAE: 3.9%	Closed
CaRESS	2000	Composite 30-day MAE: CEA: 3% CAS: 2% ($P = 0.5494$)	Closed
CREATE	400	N/A	Closed
CREST	2500	Lead-in phase, 30-day stroke and death rates: 191 Symptomatic patients: 5.7% 395 Asymptomatic patients: 3.5%	Enrolling
ICSS (CAVATAS-2)	2000	N/A	Enrolling
MAVErIC	99 (Phase I)	Composite 30-day/1-year MAE: MAV I: 5.1%;	Currently in 1-year follow-up
	399 (Phase II)	Composite 30-day MAE: MAV II: 5.3%	
	Phase III	N/A	
PASCAL	115	Composite 30-day MAE: 8%	N/A
SAPPHIRE	724	Composite 30-day MAE: CEA: 12.6% CAS: 5.8%	Closed
SECURITY	320	Composite 30-day MAE: 7.2%	N/A
SHELTER	400	N/A	N/A
SPACE	1900	N/A	N/A

[a] ARCHeR, ACCULINK for Revascularization of Carotids in High-Risk Patients; BEACH, Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients; CABERNET, Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent; CaRESS, Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; CREATE, Carotid Revascularization with ev3 Arterial Technology Evolution; CREST, Carotid Revascularization Endarterectomy Versus Stenting Trial; ICSS (CAVATAS-2), International Carotid Stenting Study (Carotid and Vertebral Artery Transluminal Angioplasty Study-2); MAE, major adverse event rate; MAVErIC, Evaluation of the Medtronic AVE Self-Expanding Carotid Stent System with Distal Protection In the Treatment of Carotid Stenosis; N/A, not applicable; PASCAL, Performance And Safety of the Medtronic AVE Self-Expandable Stent in Treatment of Carotid Artery Lesions; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SECURITY, Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy; SHELTER, Stenting of High risk patients Extracranial Lesions Trial with Emboli Removal; SPACE, Stent-Protected Percutaneous Angioplasty of the Carotid Versus Endarterectomy.

Health (NIH)–sponsored Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) has reported 30-day lead-in-phase stroke and death rates of 5.7% for 191 symptomatic patients (stenosis ≥ 50%) and 3.5% for 395 asymptomatic patients (stenosis ≥ 70%) (18). Vein of Galen malformations are now almost exclusively treated with endovascular embolization (23). Diseases such as symptomatic extracranial vertebral artery stenosis are treated easily with stent placement, whereas extensive surgery was required previously (2). The results of the recently completed Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial (10), which demonstrated a higher major morbidity and death rate for warfarin versus high-dose aspirin for symptomatic intracranial atherosclerotic disease, are a call for a new treatment paradigm. Approximately 700,000 strokes occur annually in the United States (27). Based on the results of the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial (15) and the Standard Treatment with Alteplase to Reverse Stroke (STARS) study (1), which showed a 79% decreased likelihood of good outcomes in patients with admission NIH Stroke Scale scores greater than 10, stroke centers such as ours treat patients with acute ischemic stroke with various intra-arterial pharmacological and mechanical therapies and are developing new techniques. The Merci retriever device (Concentric Medical, Inc., Mountain View, CA), recently approved by the Food and Drug Administration, (16) is one step toward this future.

TRAINING MODEL

The modern cerebrovascular neurosurgeon needs to be trained in the complementary techniques of endovascular therapy and open surgery. Most residents graduating from neurosurgery training programs today are comfortable with pedicle screw instrumentation, lateral mass screw insertion, anterior cervical discectomy, and fusion with anterior plating. The modern acoustic neuroma practitioner can perform both radiosurgery and microsurgery. Trigeminal neuralgia should be treated by surgeons who are familiar with radiosurgery, microsurgery, and percutaneous procedures. Similarly, the modern cerebrovascular surgeon should be able to gain most of the skills necessary for practice in both endovascular and open cerebrovascular surgery during residency training. Fellowship should serve to refine techniques learned in training. Inefficiencies in residency training exist, and these should be addressed to avoid the onerous solution of a decade of training.

A revised 7-year residency would start with the internship year encompassing the neurosurgery-relevant core curriculum of trauma evaluation and care, intensive care, general neurology, and wound closure and care, all of which could be incorporated in rotations with other training programs, such as general surgery, plastic surgery, vascular surgery, and orthopedics. The second and third years would be the core years of training, with the resident rotating through all the neurosurgical fields to include trauma, spine, cerebrovascular, tumor, functional, pediatrics, and peripheral nerve. The specifics of neurosurgical critical care should also be learned during these foundation-building years. The fourth, fifth, and sixth years should be critical years for personal development of the neurosurgeon in his or her field of choice. In the fourth year, the written board examination should be passed and some time should be devoted to neuroradiology and neuropathology. However, in the case of the surgeon interested in cerebrovascular disease, time can be spent learning angiography. With the mastery of cerebral angiography, the fifth and sixth years could be tailored to cover the attainment of necessary endovascular and open cerebrovascular skills, in addition to focused training in clinical and basic research. Time can also be spent in the cadaver and microsurgery laboratories. Certainly, many of today's leading open cerebrovascular fellowships are 1 year in duration, consisting of 6 months of research and 6 months of operative time. According to the model conceptualized here, after the technique of cerebral angiography has been mastered in the fourth year, the endovascular skill set could be well developed, along with the open microsurgical skills, with focused fifth and sixth years. Throughout the fourth through sixth years, the resident should continue to take general neurosurgery call. The chief year would provide an opportunity to operate on general neurosurgery cases and refine the resident's particular area of interest.

The model described above is but one concept of how residency could be revised for more efficient training of the cerebrovascular specialist. In Japan, in the case of subarachnoid hemorrhage (SAH), the first-year neurosurgery resident is expected to evaluate the patient in the emergency room, intubate the patient as necessary, perform cerebral angiography, and then transport the patient to the operating room, often managing the anesthesia and critical care; in addition, all postoperative management is handled by the neurosurgical service (Inoue T, Nakatomi H, Endo T, Yamamoto J, personal communication, May 2006). In the United States, the Japanese model seems extreme, but it is not without merit that all residents perform angiography. Most United States neurosurgeons who are now in their sixties often performed angiography and myelography during their training. This skill set informs the training requirements for both open and endovascular treatment of cerebrovascular disease. As mentioned earlier, today's neurosurgery graduate has mastered many of the nuances of spinal instrumentation. Twenty years ago, this subspecialization was reserved for select training programs. Particularly challenging spine cases, such as fixation for craniocervical junction instability, extensive reconstruction for tumor resection defect, and correction of scoliotic deformity, currently remain the realm of the dedicated spine surgeon. As neurosurgical treatment strategies change, so should the training. Paralleling this development, it could be envisioned that, a generation from now, the graduating neurosurgery resident will be capable of performing cerebral angiography, straightforward carotid artery stenting, intra-arterial stroke intervention, and possibly even clipping and/or coiling a simple unruptured aneurysm, whereas complex intravascular

reconstruction will remain the purview of dedicated cerebrovascular specialists.

CENTERS OF EXCELLENCE

A genre of study in the neurosurgical literature has compared patient outcomes at "high-volume" and "low-volume" centers for neurosurgical diseases including supratentorial brain tumors, meningiomas, pediatric brain tumors, metastatic brain tumors, hydrocephalus, transsphenoidal pituitary tumors, cerebral aneurysms, acoustic neuromas, and trigeminal neuralgia (5–8, 12, 20, 22). Although not directly leading to a determination of the number of cases necessary for mastery of a particular skill, all of these studies have suggested that outcomes are superior and costs are better controlled at large-volume centers of excellence. Surgeons participating in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) were vetted, and a minimum of 30 endarterectomies had to be performed annually to achieve the NASCET results of a perioperative rate of stroke and death of less than 6% (14). Standards have been established in other surgical fields. According to a 1999 review on transplant volume and mortality at liver transplantation centers, those centers performing 20 or fewer transplants had significantly higher mortality rates (13).

The concept of high-volume centers or centers of excellence is important for two reasons relevant to training. First, not all of the 95 accredited neurosurgery training programs (3) have sufficient volume to teach the fundamentals of open and endovascular techniques to the interested resident. Existent asymmetries will need to be addressed by both the individual and the institution, with more time allocated to cadaver laboratory and virtual training, as well as away-rotations or post-residency training. Simulation-based learning is becoming a reality. The second-generation cerebral angiography and carotid stenting simulators provide realistic haptics and visuals. Cerebral aneurysm models are in the process of development. The Barrow Neurological Institute has designed drill manipulation and virtual anatomy software that is visually impressive (4, 9), but currently there is no virtual surgical environment to support these applications.

Second, it is clear that patients with complex vascular conditions requiring multimodality treatment or prolonged intensive care, such as poor-grade SAH patients, are best served at a high-volume center. So, what of the aforementioned concept of training programs in which most graduating neurosurgical residents will be capable of performing angiography, carotid stenting, or simple aneurysm coiling? In a healthcare system with diverse payers and patients, such as in the United States, it will be impossible to centralize all care for all cerebrovascular patients. Local surgical volume, practice makeup, and outcome assessment should determine practice patterns. There have been previous publications on small-volume aneurysm centers with thoughtful physicians having excellent results when a cross-specialty approach has been undertaken (26). Other practitioners of neurosurgery choose those spine, tumor, and general cases with which they are comfortable and refer other cases to outside centers. Similarly, at a practice where 30 to 50 patients with aneurysms are seen annually, a single well-trained endovascular neurosurgeon could treat the straightforward cases and refer others elsewhere.

PREVIOUS WORKFORCE ESTIMATES AND STROKE MANAGEMENT

Workforce estimates are, by their nature, economically, temporally, and politically constrained. Cloft et al. (11) have published the only study (to our knowledge) that addresses workforce needs in interventional neuroradiology. Their overall argument is that the growth phase of endovascular neurosurgery is over and is now plateauing. By their estimates, the workforce of interventional neuroradiologists will soon likely outstrip the needs of the country. We disagree. It is our contention that neurosurgeons' role in endovascular therapeutics is in its infancy—at this time, there are only approximately 50 endovascular neurosurgeons. More than 80% of the 700,000 strokes occurring annually in the United States are ischemic (31); of these, 25% are major vessel occlusions amenable to endovascular techniques, yielding between 200,000 and 400,000 cases a year. The future of stroke is difficult to predict. However, with new techniques to broaden the therapeutic window and with better technology, we will need a large, multidisciplinary endovascular workforce to deal with acute stroke, and interventional neurosurgery, cardiology, radiology, and neurology will undoubtedly play a role. More than 150,000 carotid endarterectomies are performed each year (28). With approval from the Centers for Medicare and Medicaid Services (CMS) and Medicare funding for carotid artery stenting, the 4000 interventional cardiologists working in the United States will perform these surgeries unless neurosurgeons continue to be trained in stenting techniques. According to the results of the Asymptomatic Carotid Surgery Trial (ACST) (19), surgery clearly benefits patients with asymptomatic stenosis, even with modern medical management. As morbidity and mortality rates associated with endovascular therapy become lower with improved technology, better patient selection, and greater operator experience, the number of patients receiving treatment for carotid artery stenosis will grow significantly, possibly to 300,000 or more cases per year. An estimated 2 to 4% of the population harbors an intracranial aneurysm (29). Approximately 30,000 patients experience SAH annually and more than 10,000 patients are hospitalized each year with unruptured intracranial aneurysms (29). More than 50% of these patients are now being treated by endovascular techniques at major centers. As noninvasive diagnostic tests improve and procedural risks decline further, many more aneurysms will be diagnosed and treated with endovascular techniques. Combining 700,000 patients with stroke, 150,000 to 300,000 patients with occlusive carotid artery disease, and 40,000 patients with cerebral aneurysms with the rest of patients with cerebrovascular disease, it is clear that neurosur-

geons cannot accommodate every patient. Well-trained neuroradiologists, neurologists, cardiologists, vascular surgeons, and peripheral interventionists all give unique perspective and will continue to be valuable members of the team, but this should not be at the expense of training our own residents.

The workforce needs for endovascular therapeutics in neurosurgery will ultimately be defined by two groups: our patients and organized neurosurgery. One recent look at general neurosurgical workforce needs demonstrated a doubling of the positions needed in both private practice and academia in conjunction with a shrinking pool of board-certified neurosurgeons (17). Minimally invasive techniques for treating cerebrovascular disease will continue to be refined and developed, improving both efficacy and safety. Patients will demand these techniques and will find practitioners able to provide their treatment. Every neurosurgical training program needs at least two neurosurgeons competent in endovascular techniques to cover the on-call burden. Neurosurgeons need to continue to pursue endovascular training, and organized neurosurgery needs to develop efficient training pathways. As the treatment strategies change for neurosurgical diseases, we should not defer to other specialties, but rather integrate the new techniques and adapt the training program. If neurosurgery does not embrace endovascular surgery, we risk losing a large swath of patients with cerebrovascular disorders to cross-trained neuroradiologists, peripheral interventionists, cardiologists, vascular surgeons, neurologists, and others who do not even need to be asked.

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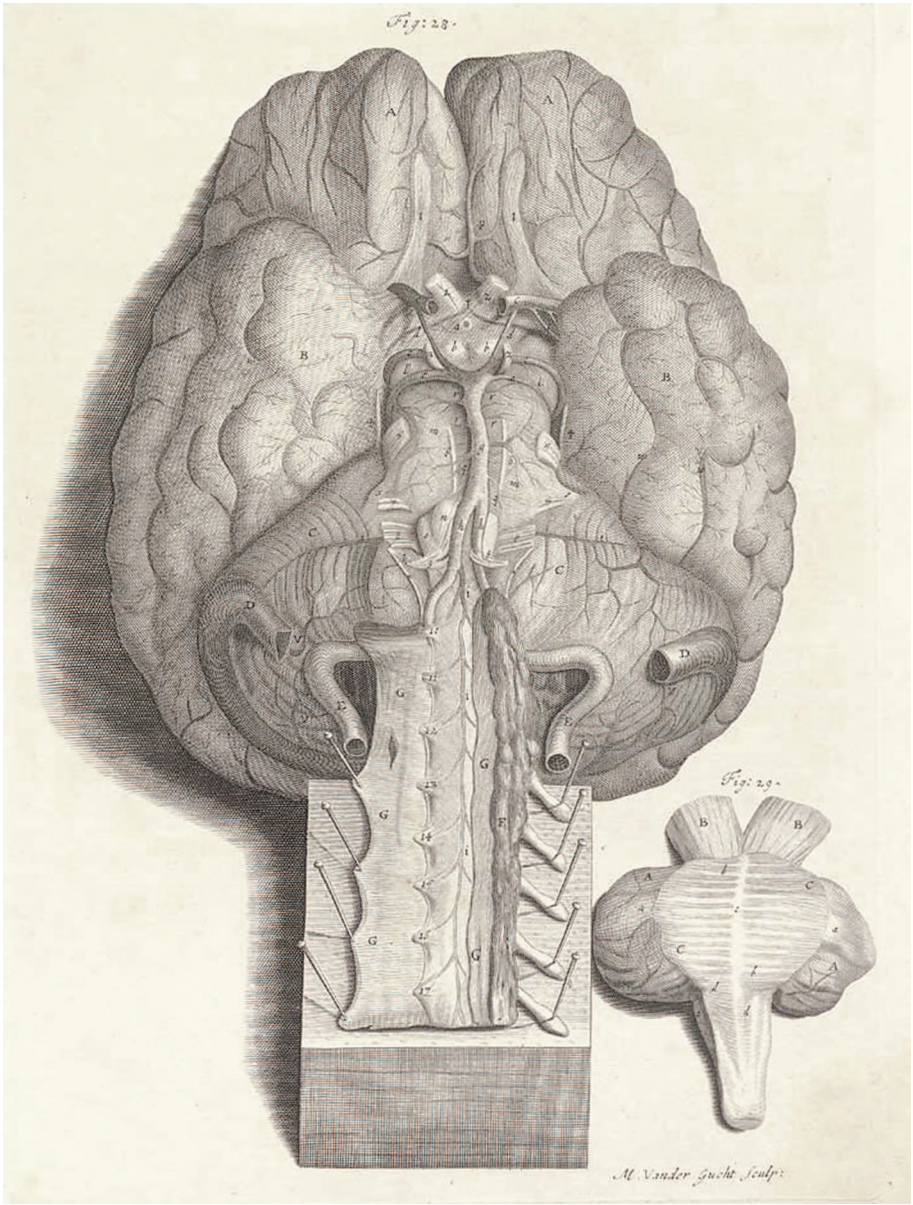

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TRAINING RESIDENTS IN ENDOVASCULAR NEUROSURGERY

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NEUROSURGEONS HAVE A long history of treating cerebrovascular disease. Understanding the vascular anatomy and physiology of the nervous system and management of patients with abnormalities of theses vascular structures are vitally important aspects of neurosurgery resident training. Over the past decade, the treatment of cerebrovascular disease has been evolving toward endovascular strategies for many patients. Interventional neuroradiologists were the pioneers in developing this area of therapy, but the number of neurosurgical trainees in neuroendovascular treatment is increasing, and other specialties, including neurology, vascular surgery, and cardiology, are now entering the field of neuroendovascular treatment. The purpose of this article is to review the current credentialing guidelines for neurosurgeons to use endovascular techniques in the treatment of cerebrovascular disease and to consider options for resident training in the rapidly evolving field of endovascular neurosurgery.

KEY WORDS: Cerebrovascular disease, Endovascular neurosurgery, Endovascular surgical neuroradiology, Endovascular treatment, Interventional neuroradiology, Neurosurgical trainees, Neuroendovascular treatment

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Interventional neuroradiology, endovascular neurosurgery (ENS), and endovascular surgical neuroradiology are some designations for specialties dealing with the endovascular treatment of cerebrovascular disease. The fact that three different titles refer to the same subspecialty field indicates the fluid nature of this rapidly progressing area of clinical activity. Neuroendovascular treatment began as a hybrid of traditional neurosurgical and neuroradiological approaches. Because of their clinical training and experience with management of critically ill patients with cerebrovascular disease, neurosurgeons have, in general, had a superior understanding of the pathophysiology, the indications and contraindications for treatment, and the medical management of patients with cerebrovascular disease. Neuroradiologists, on the other hand, have had more expertise in diagnostic imaging and catheter skills. The collaborative efforts of endovascular neurosurgeons and interventional neuroradiologists have resulted in improving the practice of neuroendovascular practitioners from both disciplines and in developing neuroendovascular specialists who possess expertise in both neurosurgical and neuroradiological areas.

One accomplishment of the collaboration between neuroradiologists and neurosurgeons has been the Accreditation Council for Graduate Medical Education (ACGME) accredited specialty of endovascular surgical neuroradiology. This has become an established medical subspecialty with program requirements for fellowship training set forth by the ACGME (1). These requirements, along with training standard guidelines recommended by the Executive Committees of the Cerebrovascular Section and the American Society of Interventional and Therapeutic Neuroradiology (4), were designed to make the endovascular neurosurgeon a hybrid of traditional neurosurgical and radiological training.

As noted above, this agreement was a great accomplishment when it was forged. However, the field of neuroendovascular treatment is evolving so rapidly that this agreement may no longer be the best strategy to follow. At present, neuroendovascular procedures are being performed by neurosurgeons, neuroradiologists, neurologists, interventional radiologists, vascular surgeons, and cardiologists. We question whether the ACGME fellowship model is now ideal or even appropriate for the coming generation of neurosurgical trainees. We will argue that endovascular training should become a standard part of neurosurgery residency training, at least in those pro-

grams that offer adequate experience in this technique for dealing with cerebrovascular disease. Furthermore, we think that residents finishing an American Board of Neurological Surgery (ABNS)- approved residency program in which adequate endovascular training has been received should be credentialed to perform endovascular neurosurgical procedures. The efforts toward this end at Penn State Hershey Medical Center will be reviewed.

ACGME REQUIREMENTS FOR ENDOVASCULAR SURGICAL NEURORADIOLOGY

The ACGME requirements for an endovascular surgical neuroradiology training program include: 1) performing a neurological examination; 2) recognizing the clinical signs and symptoms and the neuroimaging manifestations of cerebrovascular disease; 3) understanding the pathophysiology and natural history of cerebrovascular disease; 4) recognizing the therapeutic options available for management of patients with cerebrovascular disease and the indications for these options; 5) demonstrating opportunities for basic or clinical research; 6) understanding the periprocedural management of patients; 7) understanding radiation physics, radiation biology, and radiation safety; and 8) performing endovascular procedures. It is obvious from a review of this list that neurosurgery residency training already addresses items one through six and that item seven can readily be obtained through didactic courses. I think that, if a neurosurgery residency allows residents to perform an adequate number of endovascular procedures, the residents finishing that program should be credentialed for endovascular capabilities without additional training. We need to treat ENS the same way we treat spinal instrumentation, image guided surgery, and radiosurgery, as techniques within the armamentarium of neurosurgery. We need to see the angiography suite as an operating room and catheters as flexible scalpels. If we continue to set ENS aside as the enclave of a small number of fellowship-trained neurosurgeons, neurosurgery will lose the entire field of cerebrovascular disease treatment to non-neurological catheter-based specialties.

RESIDENCY TRAINING IN ENDOVASCULAR NEUROSURGERY

In this article, we will use the term ENS for the sake of convenience. However, we think that a better term is *endovascular techniques in neurovascular surgery*, and that we must view catheter-based treatment as another option to be used by neurosurgeons to treat neurosurgical patients with vascular disease. Catheter techniques should be an integral part of neurosurgery, not a small enclave set apart. Much as cranial base surgical approaches can be used to treat patients with vascular disease and tumors, catheter-based surgical approaches can be used to treat neurosurgical patients with, for example, vascular disease and vertebral compression fractures.

As for any other technique in neurosurgery, residency training in ENS must take place in an environment dedicated to teaching the core competencies of neurosurgical practice. For ENS, this will include didactic teaching of the anatomy, physiology, pathology, and pharmacology critical to endovascular neurosurgical procedures. Conference time must also be devoted to teaching the basics of radiation physics, radiation safety, and radiation biology. In addition, neurosurgery residency training must provide sufficient exposure to the spectrum of diseases treatable by endovascular techniques and to a wide variety of endovascular procedures. Residents must have the opportunity to perform preprocedural examinations of patients, evaluate preliminary diagnostic studies, and formulate treatment plans. They must also be given the opportunity to perform diagnostic and interventional procedures and generate reports in the endovascular suite just as they do in the operating room. Finally, residents must also participate in the inpatient and outpatient postprocedural management of endovascularly treated patients to assure that they are familiar with the short- and long-term complications of ENS.

Of major importance for resident training is access to adequate case material that encompasses the range of cerebrovascular disease. The question arises as to how we are to determine what is adequate. The Cerebrovascular Section and American Society of Interventional and Therapeutic Neuroradiology have recommended 100 diagnostic angiograms before starting training in endovascular procedures, such as embolization of aneurysms, arteriovenous malformations and tumors, angioplasty and stenting for the treatment of intracranial and extracranial occlusive cerebrovascular disease, and the performance of invasive functional testing (2, 3).

We find this number of concern. First, such numbers are almost always arbitrary. As for any other surgical procedure, some residents or fellows are ready to perform procedures quickly, and some need many more repetitions before gaining competence. This is certainly the case for other neurosurgical procedures and for any other type of learned manual activity. Are endovascular procedures different from all other manual procedures?

Second, as noninvasive methods of imaging the cerebral vasculature improve, the indications for diagnostic angiography decrease, making it increasingly difficult to obtain the designated number of 100 diagnostic angiograms before being involved in any neuroendovascular treatment procedure. The use of arbitrary numbers makes it more difficult for people to enter the field of ENS. This, we think, is the real reason such numbers have been recommended.

Third, endovascular simulators now offer an alternative for developing catheter skills before doing any procedure on a patient. In speaking to endovascular specialists who have used these simulators, they have been enthusiastic in their endorsement of the realism of these simulators and their value in teaching catheter techniques. A technically facile neurosur-

gery resident should be able to develop considerable catheter skills using such simulators.

Finally, ENS is the only neurosurgical subspecialty in which we expect those who perform any procedure to be competent to perform all procedures. In all other subspecialty areas, we expect every neurosurgeon to be able to do some procedures but not necessarily all procedures. However, for ENS, those deemed competent to perform intra-arterial thrombolysis must also be trained to stent and coil a wide-necked aneurysm and embolize a complex arteriovenous malformation. Why should ENS be treated differently than all other techniques in neurosurgery?

THE AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS ENDOVASCULAR TASK FORCE

I cochaired (RH) (with L.N. Hopkins, M.D.) the American Association of Neurological Surgeons Endovascular Task Force. This task force was charged by then- American Association of Neurological Surgeons President, Roberto Heros, with generating ideas for increasing the number of endovascularly trained neurosurgeons and determining "what we can do, as organized neurosurgery, to ensure that endovascular surgery becomes a mainstream discipline within neurosurgery." Other members of the task force, in addition to Drs. Hopkins and Heros, included Drs. Robert Rosenwasser, Ralph Dacey, and Lee Guterman. Some of the findings of this task force are germane to the present discussion. These are outlined below:

1) The challenge to neurosurgery from other specialties in regard to the care of patients with cerebrovascular disease is, in many ways, analogous to the challenge from orthopedic surgery in regard to the treatment of patients with spine disease. Although significant differences exist between the two situations, they are similar enough that the neurosurgical response to the orthopedic challenge can be used as a starting point for the neurosurgical response to the challenge of other specialties using endovascular therapy in the treatment of cerebrovascular disease.
2) A mandate from the ABNS and the Residency Review Committee for Neurosurgery requiring exposure to endovascular neurosurgical techniques, although burdensome for neurosurgery residency program directors, would be helpful for introducing neurosurgery residents to endovascular techniques and helping neurosurgeons obtain access to angiography suites.
3) It is in the best interests of our patients and our specialty to continue to work closely with interventional neuroradiology. Organized neurosurgery has no desire to exclude interventional neuroradiologists from the marketplace. These findings and conclusions will be elaborated upon below.

THE ANALOGY WITH SPINAL SURGERY

When neurosurgeons were faced with the possibility of losing spine surgery to orthopedics, they fought back aggressively by developing spine fellowships, offering training courses, and garnering industry support for training neurosurgeons to perform spinal instrumentation. A similar approach may work for ENS, but will be more difficult. In the case of spinal instrumentation, neurosurgeons were familiar with the operating room environment, and spinal instrumentation cases were not dramatically different from other procedures. Neurosurgeons used the same basic techniques as were used for other procedures and simply added a layer of expertise. To do endovascular procedures, neurosurgeons need to have access to digital angiographic imaging and to become familiar with a set of tools, such as catheters, stents, coils, balloons, and thrombolytic agents, that they have never used before.

The ACGME-approved 2-year fellowship presently available to neurosurgery residents is working in the same way spine fellowships worked, by developing a cadre of fully trained endovascular neurosurgeons who can do any neuroendovascular procedure. If there were no time constraints and no non-neurologically trained neuroendovascular specialists, this slow addition of endovascular neurosurgeons would be adequate to assure that neurosurgery remains active in the endovascular treatment of cerebrovascular disease.

THE COMPETITION FROM OTHER SPECIALTIES

Unfortunately, there is a time constraint, and there are other competitors. Specialty societies in vascular surgery and cardiology have developed short courses of instruction to allow their diplomates to perform neuroendovascular procedures. This has had the effect of rapidly increasing the number of physicians who have been trained to perform neuroendovascular procedures, often with little or no understanding of the nervous system or cerebrovascular anatomy and pathophysiology. The greatest threat is from interventional cardiologists who exist in large numbers, possess catheter skills, have access to angiographic imaging, have demonstrated a desire to do procedures, and who have the infrastructure for patient access and follow-up. Cardiologists already perform the majority of carotid stenting procedures in the United States, and they have no plans to stop at the cranial base. Protests from other specialties about cardiologists' inadequate training to perform neuroendovascular procedures will be ignored by cardiologists and by hospitals without interventional neuroradiologists or endovascular neurosurgeons.

LEVELS OF EXPERTISE

ENS, because it is relatively new, is being treated differently than every other subspecialty area in neurosurgery. In other

subspecialty areas, such as tumor, spine, peripheral nerve, vascular, stereotactic, and functional and pediatric neurosurgery, we recognize that there are varying levels of difficulty of procedures and corresponding levels of expertise needed to perform them. For instance, we do not expect every neurosurgeon who can do a carpal tunnel release to be competent to perform a brachial plexus reconstruction or that every neurosurgeon who treats tumor patients should be able to remove a clivus meningioma.

It is only in ENS that we require full fellowship training to do any procedure. This is particularly concerning because the procedures used for the treatment of ischemic stroke will be the largest potential market and will require the least endovascular expertise. Neurosurgery needs a strategy that significantly speeds up the production of endovascular neurosurgeons, as was the case with spinal neurosurgeons trained to do instrumentation. Full fellowship training was available for neurosurgeons who wanted to be able to do any and all spinal instrumentation cases, but in a relatively short time, spinal instrumentation became a routine part of neurosurgical resident training. I think the same process should occur for ENS.

NEUROSURGERY RESIDENT TRAINING OPTIONS?

We see three options for training neurosurgery residents in endovascular techniques in cerebrovascular surgery. One would be to require all neurosurgeons who wish to perform any neuroendovascular procedure to complete an ACGME-defined fellowship. This was a reasonable approach when the joint training agreement was being developed, but I do not think that it is the best strategy for neurosurgery at present. Training in endovascular techniques is now readily available in some neurosurgery residency programs, and a steadily increasing percentage of patients with neurovascular disease are being treated endovascularly. Other specialties with no neurological expertise are eager to treat these patients. Adherence to the ACGME fellowship training approach could have disastrous consequences for neurosurgical training and for patients with neurovascular disease who end up being treated by endovascular specialists with little or no understanding of cerebrovascular disease.

A second approach would be for the ABNS to require competence in endovascular techniques for successful completion of training in all neurosurgery training programs. With this approach, all ABNS-eligible or certified neurosurgeons would automatically be certified in endovascular techniques. This requirement would put an intolerable burden on many neurosurgery resident training programs, and otherwise good programs might not be able to meet this requirement. Furthermore, many residents might be inadequately trained, but certified to use endovascular techniques, resulting in poorer quality of care for their patients.

We think a third option should be considered. This option would require exposure to endovascular techniques as part of all neurosurgical resident training programs and recognize some programs as supplying adequate training in the use of endovascular techniques. Competence to perform neuroendovascular procedures would be determined by performance criteria determined by the ABNS and Residency Review Committee for Neurosurgery with a certificate of added qualification in endovascular techniques awarded at the completion of resident training for those residents who meet the criteria. This would increase the supply of well-trained endovascular neurosurgeons and avoid the adverse effects on other programs.

THE RELATIONSHIP WITH INTERVENTIONAL NEURORADIOLOGY AND OTHER SPECIALTIES

The field of endovascular treatment of cerebrovascular disease has benefited from the collaboration between interventional neuroradiology and vascular neurosurgery. Through the efforts of the Cerebrovascular Section and American Society of Interventional and Therapeutic Neuroradiology, we should continue to work in a collegial and collaborative fashion. It must be clear that our efforts to train endovascular neurosurgeons are not done to exclude our interventional neuroradiology colleagues from the marketplace but to augment the number of endovascular practitioners with expertise and training in caring for patients with neurological disease. Closer collaboration between interventional neuroradiologists and endovascular neurosurgeons will benefit both groups. Interventional neuroradiologists often have much more in common with vascular neurosurgeons than they do with other radiologists. Joining departments of neurosurgery would give them immediate access to outpatient and inpatient clinical infrastructure that most radiology departments do not have.

THE PENN STATE EXPERIENCE

The Departments of Neurosurgery and Radiology at the Penn State Hershey Medical Center have developed what we think is a unique approach for training radiology and neurosurgery residents in interventional neuroradiology/ENS. Two faculty members, one interventional neuroradiologist and one endovascular neurosurgeon, have been jointly hired by the Departments of Neurosurgery and Radiology. Each department is responsible for 50% of the faculty members' salary, fringe benefits, and other expenses. The neuroendovascular specialists each have academic appointments in neurosurgery and radiology and attend both departments' faculty meetings. Fifty percent of all revenue generated by each faculty member go to each department. For example, if the interventional neuroradiologist interprets a diagnostic study, 50% of that revenue goes to neurosurgery. If the neurosurgeon operates on an acute subdural hematoma, 50% of that revenue goes to radiology. This equal sharing of expenses and revenue has effectively removed financial incentives for a "turf war."

Both physicians see outpatients in the neurosurgery clinic with the neurosurgery residents, and both have their endovascular procedures scheduled by the Department of Neurosurgery. Diagnostic procedures are scheduled through the Department of Radiology. Both faculty members have admitting privileges, and all postprocedural patients who require admission are admitted to the neurosurgery service and are cared for by neurosurgery residents. Emergency neuroendovascular calls are shared equally between the two faculty members. Radiology and neurosurgery residents have equal access to the neuroendovascular suite, but the neurosurgery residents have shown much more interest in developing neuroendovascular skills.

Each resident receives his or her own set of lead protective garments when starting the residency program. The neurosurgery residents are required to cover neuroendovascular procedures in the same way they cover neurosurgical procedures in the operating room or radiosurgical facility. They are instructed to consider the neuroangiography suite as an operating room and to learn to use a catheter as they would learn to use a scalpel or ionizing radiation. This is expected whether the endovascular neurosurgeon or the interventional neuroradiologist is doing the procedures. Our neurosurgery residents, starting in their first year, gain experience in endovascular techniques just as they gain experience in other neurosurgery techniques. It should be noted that we have had facile first year residents successfully coil intracranial aneurysms. Neurosurgery residents with good manual dexterity, a knowledge of neuroanatomy and neurophysiology, and the commitment to excellence that comes with a decision to pursue a career in neurosurgery are fertile ground for growing neuroendovascular skills quickly.

One of our residents who is finishing resident training this year is fully capable of using the entire spectrum of neuroendovascular techniques for treating patients with cerebrovascular disease. This resident recognized that he wanted to be a cerebrovascular surgeon and that endovascular techniques were an increasingly important part of cerebrovascular surgery. He availed himself of every opportunity to gain endovascular experience during his residency, including a 6-month elective in neuroendovascular surgery and an enfolded fellowship year on the neuroendovascular service at Penn State. As of March 31, 2006, he had performed 220 diagnostic and 317 interventional neuroendovascular procedures and had cared for hundreds of patients with cerebrovascular disease in clinic, on the wards, and in the neurointensive care unit. We think that he is perfectly competent to use endovascular techniques in treating patients with cerebrovascular disease at the time he finishes his residency.

CONCLUSION

Endovascular techniques for treating patients with cerebrovascular disease are evolving rapidly. The ACGME has recognized a 2-year fellowship training standard for accreditation in endovascular surgical neuroradiology. However, as neuroendovascular availability in neurosurgical training programs increases, and competition from other specialty societies grows; last year's solution may be this year's problem. We think it is time for neurosurgeons to start training residents in ENS in the same way we train neurosurgeons in every other neurosurgical discipline.

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TRAINING IN CEREBROVASCULAR DISEASE: DO WE NEED TO CHANGE THE WAY WE TRAIN RESIDENTS?

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WITH THE ONGOING development of endovascular techniques and technologies, treatment of cerebrovascular disease is evolving at a fast pace. For neurosurgery to maintain a leadership role in the treatment of these disorders, modifications in neurosurgical training programs are essential. In this article, we discuss the changes perceived to enable residents to acquire the multifaceted understanding and skill set necessary to meet the new clinical reality and prepare to become the leaders of tomorrow in the management of cerebrovascular disease.

KEY WORDS: Cerebrovascular disease, Endovascular surgery, Neurosurgical training programs

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"The biggest obstacle to innovation is thinking it can be done the old way."

—Jim Wetherbe

Cerebrovascular surgery is at a unique crossroad: the clinical reality of the future will be molded by the determination of neurosurgeons to adapt and by their enthusiasm to broaden the definition of this field by including and integrating knowledge of endovascular therapeutics into their practice. In the past, a neurosurgeon armed with a microscope, agile hands, and a scalpel could function effectively in the world of aneurysms, arteriovenous malformations (AVMs), and cerebrovascular occlusive disease. Now, to be successful in the field, neurosurgeons should possess additional skills and collaborate with other specialists. Endovascular and radiosurgery therapists, although viewed as opposing forces by some, should be welcomed as essential allies. The goal of organized neurosurgery should be to learn, to develop, and to maintain a leadership role in the treatment of cerebrovascular disorders, not by opposition, but rather by an evolution aimed to meet the present reality (i.e., the best defense is a good offense).

Neurosurgical training programs currently focus on clinical and surgical skills—neurology, neuroradiology, neuropathology rotations—and basic science and research exposure. These training programs should permit the transition from a resident neurosurgeon to a fully trained neurosurgeon without substantial change in the performance of the individual or the expectations of his or her patients. Newly trained neurosurgeons should possess the cognitive and psychomotor skills necessary to deal with the pathological conditions for which they will be consulted by their colleagues in other specialties. Is the trainee of today obtaining the appropriate background to manage and provide the continuum of care for patients with cerebrovascular disease? No, residency training needs to be changed. Trainees should realize that each person is responsible for his or her own career. Pursuing the best and most appropriate training is important for anyone who is receiving training in neurosurgery. A proactive, rather than a reactive, attitude should be encouraged. Our objective in this article is to increase awareness that neurosurgical training programs should evolve to meet the clinical reality. Residency training needs to change so that the neurosurgeon's role in cerebrovascular disease is not limited to a cognitive aspect and to ensure that neurosurgery has a leading influence in the global management and treatment of patients with such disease.

LOOKING AT THE REALITY TO BETTER EVALUATE THE NEED FOR CHANGE

A paradigm represents a way of looking at the world within a framework of assumptions. It enables one to predict or understand behavior. Paradigms have a powerful effect on in-

dividuals and on society because an individual's perception of the world is determined by his or her set of associated assumptions. The paradigm effect may cause people to be blind to what is happening around them, such that they may overlook the potential in a new application of technology. In being faced with the invention of the telegraph, the first reaction of the Pony Express was to buy faster horses. When that failed, they attempted to hire better riders. They did not realize that the world had changed and, consequently, they went out of business. The world of neurovascular surgery is changing, and modern neurosurgeons should strive to understand the innovations, seek appropriate training, and develop appropriate training approaches. Neurosurgeons need to change their approach to the management of patients with cerebrovascular disease and embrace the paradigm shift to less-invasive surgical treatment options. Neurosurgeons have always been considered leaders in the provision of health care in the realm of cerebrovascular disease. To remain at the forefront of evaluating, caring for, and treating patients with cerebrovascular disease, vascular neurosurgery has to evolve toward a specialty, mastering the knife as well as the catheter.

INTRACRANIAL ANEURYSMS

Initially seen as a suboptimal treatment modality, aneurysm coiling has progressively emerged as a valuable technique in selected cases since the publication of the results of the first randomized study comparing coiling and clipping in 1999 (22). Publication of the International Subarachnoid Aneurysm Trial results in 2002 (15) led to an increase in the performance of endovascular procedures for aneurysms. The results of this trial have encouraged many clinicians to consider endovascular coiling as an alternative to surgical clipping of intracranial aneurysms. Neurosurgeons who perceive catheter-based intervention as a nonsurgical modality have been confronted with the increasing role of endovascular treatment in the management strategy for patients with intracranial aneurysms. With the development of new devices and drugs, in conjunction with improvements in the effectiveness and safety of the technique, the proportion of patients treated with this approach is expected to grow. At some medical centers in North America, more than half the patients with intracranial aneurysms are already treated with coil embolization; in Europe, this proportion has reached 80% and above. These changes in practice cannot be denied, and, even if surgical clipping remains the modality of choice for some cases (for example, for those with mass effect associated with intracranial hematoma), the overall volume of surgical cases is expected to decrease overall. At present, patient selection is the challenge, and a good working knowledge of both modalities, including the difficulties and limitations of each, is key.

ARTERIOVENOUS MALFORMATIONS

Microsurgical resection, endovascular embolization, and stereotactic radiosurgery are the three effective modalities currently available for the treatment of AVMs. During the past decade, rapid changes have occurred in the field. The number of patients undergoing radiosurgery over the past decades has increased. Rates of AVM obliteration between 70 and 90% and low morbidity have been reported (18). With respect to high Spetzler-Martin grade AVMs, radiosurgery has surpassed microsurgery with or without previous endovascular embolization (24). To provide the best care for patients, multimodality planning with consideration of resection, embolization, and radiosurgery should be performed as part of the total management plan for the eradication of an AVM. Embolization alone rarely represents a curative treatment. However, a reduction in the size of the nidus or flow to the AVM can enable the performance of radiosurgery or facilitate surgical removal (6, 8, 11, 25). Combination therapy is aimed at reducing the overall risk of therapy and providing protection against AVM hemorrhage. To choose an appropriate treatment plan, an underlying knowledge of the inherent risks and benefits expected from each modality is necessary. Appropriate knowledge of these therapies to formulate the best treatment strategy for each case and to better guide the patient in his or her decision-making should be the aim of the neurosurgical trainee (16).

CEREBROVASCULAR OCCLUSIVE DISEASE

Carotid artery stenting has an established role as a minimally invasive therapeutic alternative for the management of extracranial carotid occlusive disease in the high-risk population (i.e., patients with recurrent stenosis, severe medical comorbid conditions, radiation-induced carotid stenosis, or surgically difficult-to-access lesions, such as those located above the C2 level, below the clavicle) (23, 26). The 30-day stroke and death rates reported for a broad-risk population of patients with carotid stenosis enrolled in a Phase I clinical trial suggest that carotid stenting (with distal embolic protection) is equivalent to standard carotid endarterectomy (1, 2). Lower-risk patients are currently being randomized in other trials.

Recent improvements in technique and technology have permitted endoluminal revascularization procedures to become a clinical reality for the treatment of atherosclerotic occlusive disease in intracranial vessels. With the poor natural history of this disease and the recent results of the Warfarin-Aspirin Symptomatic Intracranial Disease trial, which demonstrated no benefit for warfarin compared with aspirin in patients with symptomatic intracranial stenosis (4), endovascular revascularization has become an appealing modality (13, 14). Balloon dilation and subsequent deployment of a self-expandable stent for the treatment of symptomatic intracranial arterial stenosis seems to afford clinically effective and technically safe treatment of these frequently challenging lesions (10). Neurosurgeons should broaden their procedural inventory by incorporating endovascular techniques for the treatment of cerebrovascular occlusive disease into their practice and obtaining adequate training for proficiency in these approaches. Surgical bypass procedures may regain favor in select cases (20). A newer cerebral revascularization technique

includes the Excimer laser-assisted nonocclusive anastomosis for extracranial-to-intracranial and intracranial-to-intracranial bypass. Interest and training in potential endovascular and open surgical treatment solutions for cerebrovascular occlusive disease are certainly to be encouraged.

OBTAIN APPROPRIATE TRAINING TO SECURE A BETTER POSITION

"Leaders establish the vision for the future and set the strategy for getting there."

—John Kotter

Neurosurgeons are often considered to be technical masters who are accomplished in the performance of demanding surgical procedures. Nevertheless, technical skills are but one aspect of the neurosurgeon's expertise. Surgery is more than cutting and sewing. Neurosurgery residents in training should be inspired and motivated to learn new methods for the treatment of vascular disease. Without question, no physician is as experienced, qualified, and comfortable in dealing with neurological emergencies as the neurosurgeon. A logical extension of these attributes is that neurosurgeons should be capable of performing endovascular interventions in emergency situations (e.g., institution of pharmacological or mechanical thrombolysis in the setting of an acute stroke). Neurosurgeons are experts in dealing with the initial diagnosis and management of an acute neurological illness and should be able to complete the patient's care without the need for rescue by an interventionist in acute situations. We should retain the concept of training technically-oriented individuals, but strive to train disease-oriented physicians. Such expertise ensures continuity of care and may afford reassurance to patients and their families as they are confronted by a major, and frequently unexpected, illness.

For neurosurgery trainees pursuing a quest for technical excellence in vascular disease, the acquisition of catheter skills should be seen as a prerequisite. The neurosurgeon's hands are the primary tools of his or her craft, whether they manipulate a catheter or a scalpel. Trainees should participate in a wide breadth of opportunities, including early exposure to related fields (e.g., neuroradiology, otolaryngology, vascular surgery, neurology, intensive or critical care medicine, and cardiology). Collaboration with other specialties is key to appropriate and adequate cognitive and technical training. Interaction should be encouraged early on. Comprehensive training in catheter skills should be seen as a first step toward attaining endovascular competency. These skills should be acquired during the training period and refined as the trainee gains experience. Proficiency and experience are essential for the safe performance of any procedure that confers risks to patients. Adequate procedural training with repetition is essential to ensure proper outcome.

One training goal for the neurosurgery resident should be to perform and interpret a significant number of brachiocephalic angiograms under appropriate supervision, as recommended by the Neurovascular Coalition Writing Group (5). Attainment of this goal seems reasonable considering that the most recent Medicare data show that at least 92,000 cervicocerebral angiograms were performed in 2002 (3). Nevertheless, given the reality that opportunities to learn the psychomotor technical skills of diagnostic angiography may decrease because of the increased use of noninvasive studies, new training adjuncts and opportunities should be welcomed to overcome this limitation. The neurosurgical residency program in Japan serves as a training model in this regard. In Japan, endovascular surgery is performed by neurosurgeons. Trainees learn how to perform cerebral angiography and interpret angiographic images early in their training. Proficiency acquired during subsequent program years not only improves the resident's knowledge of intracranial vascular anatomy, but also benefits his or her surgical acumen. Rotation training in neurointervention, or in interventional cardiology, could facilitate the acquisition of fundamental catheter skills. Exchange programs and in-training visits to other neurosurgical departments within the United States and abroad, along with visiting professors from elsewhere to the resident's own department, represent further opportunities to expand the perspective, knowledge base, and skills of the trainees. Basic endovascular procedures could eventually become an inherent part of the core curriculum for the neurosurgical resident. Acquiring this knowledge would be beneficial, and trainees who are interested in the vascular area should be encouraged to acquire supplemental experience, just as trainees who are interested in spine or another particular field should be encouraged to pursue additional experience in their area of focus. Although difficult to imagine now, cerebral angiography, and perhaps even other endovascular procedures, may be assimilated into the program curriculum of the future, as was the case with spinal instrumentation techniques. Of major importance, organized neurosurgery should become the governing body to integrate endovascular techniques into neurosurgical training before the recognition of endovascular competency becomes the purview of and is validated by other organizations.

In vitro and animal laboratories and computer simulation-based learning could also augment opportunities for endovascular training. The resident's research rotation or elective time could be used to increase the level of confidence with techniques for obtaining vessel access and skills in wielding wires, catheters, and other endovascular devices. These tools would provide an early introduction to some psychomotor skills for which practice and early acquisition, as well as repetition, are the basis of efficiency. An experimental stroke model suitable for testing the selective infusion of thrombolytic agents has been described (17). The swine rete mirabile for embolic agent testing, first reported by Lee et al. (12), could serve as a useful training adjunct. Other animal models have been developed to evaluate stents, coils, and other embolic materials for application in aneurysm treatment (7, 21). Also noteworthy, computer simulation, although undergoing development and refinement, allows the operator to perform the technical aspects of the case with a variety of endovascular devices. A full spec-

trum of cases could be programmed into the simulator, allowing for a gradual and progressive learning experience. Psychometric analysis of performance could be used to point out areas of difficulty or deficiency. Computer simulation-based training represents an appealing option for increasing the resident's exposure to neurointerventional procedures and the overall efficiency of the residency program experience. The development of more realistic systems will narrow the gap between computer-based simulation and the clinical setting. Training in other high-skill professions, such as aviation, already involves virtual reality. The efficacy of simulation-based learning has been demonstrated in the surgical field. Two randomized, double-blinded studies have demonstrated that residents who were trained using even a low-fidelity virtual reality simulator made significantly fewer intraoperative errors than a standardly trained group while performing laparoscopic cholecystectomies (9, 19). Quicker procedural time, decreased learning curve, and even performance approximating that of an experienced attending surgeon were reported.

PATIENT AND PHYSICIAN SATISFACTION

By adapting training programs to a disease-oriented rather than a technically oriented mode, neurosurgery as a specialty will see its referral base broadened. The neurosurgeons of tomorrow will be better prepared to guide patients to their best interest, to discuss appropriate treatment options, and to decrease the anxiety associated with changing physicians, thereby increasing contact and rapport. Appropriate, comprehensive follow-up is ensured, and patient and physician satisfaction are likely to be increased.

CONCLUSION

Spinal instrumentation and stereotactic radiosurgery have already necessitated a shift in the neurosurgical treatment paradigm, and neurosurgeons have adapted by modifying their practices and providing a sound educational foundation in these areas. A global thrust in medicine today is to manage disease in a less-invasive manner. Endovascular therapy, initially seen as a limited arsenal, has emerged as a highly efficient weapon in the battleground of cerebrovascular disease. Patients seeking care for complex cerebrovascular disorders are unique. They often present with minimal or no symptoms, but with underlying disease processes capable of causing major disability or death. More importantly, the inherent risks associated with treatment of these diseases are significant (i.e., a "normal" patient preoperatively may be neurologically devastated by the treatment itself). Patients should be able to visit one unbiased surgeon who understands the disease from both the endovascular as well as the surgical prospective, ideally, one surgeon who can treat the disease either way or as a completely unbiased member of a multidisciplinary team. Neurosurgeons should acquire the knowledge and skills of endovascular therapeutics so they can be cognizant of endovascular indications, techniques, and appropriate follow-up evaluation. An active role should be promoted to increase the energy in this field and to fortify the position of our specialty in this area. Endovascular surgery should become an inherent rotation for the neurosurgery resident, enhancing the comprehension of endovascular skills among the neurosurgical practitioners of tomorrow and ensuring a continuum of care for patients with cerebrovascular disease.

"The future has several names. For the weak, it is 'Impossible.'
For the fainthearted, it is the 'Unknown.'
For the thoughtful and valiant, it is 'Ideal.'"

—Victor Hugo

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