12 Future Directions of Endovascular Neurosurgery

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12.1 INTRODUCTION

The major advances in endovascular neurosurgery over the past 15 years are reflections of the pioneering work of previous generations of enthusiastic, persistent, and optimistic physicians. Since the introduction of cerebral angiography by António
Egas Moniz in animal models in 1926 and subsequently in humans, the possibility of using a less invasive endovascular approach to treat cerebrovascular diseases was pursued.\textsuperscript{1–5} History unraveled many attempts by neurosurgeons searching for less invasive approaches to treating cerebrovascular diseases\textsuperscript{1–5} until Guido Guglielmi, an Italian neurosurgeon at the Medical Center of the University of California at Los Angeles, developed the platinum detachable coil as an effective and feasible treatment alternative to cerebral aneurysm clipping.\textsuperscript{6,7} This technology initiated the great advancements we see in endovascular neurosurgery today.

A second historical landmark was the publication in 2002 of the randomized International Subarachnoid Aneurysm Trial (ISAT) study comparing aneurysmal coiling and clipping.\textsuperscript{8} The study showed that the endovascular coil embolization of cerebral aneurysm is safe, feasible, and effective in comparison with open craniotomy and clipping. Despite the wide controversy surrounding the trial and its findings, it constituted another step in better defining the role of coiling and its long-term efficacy in aneurysm therapy based on scientific background.

Unfortunately, endovascular therapy for arteriovenous malformation (AVM) has not undergone a similar rapid pace of achievement. Newer flow directed microcatheters to facilitate closer access to the AVM nidus were introduced\textsuperscript{9} and AVM embolic agents are under investigation in the search for the ideal embolic agent.\textsuperscript{10–13} These advances may provide a more effective adjunctive or even curative role for endovascular AVM therapy.

The catheter-based treatment of atherosclerotic carotid disease is rapidly evolving despite the disappointing early clinical trials.\textsuperscript{14} The results may be related to the use of older generation stents. Biodegradable and biocompatible materials and drug coatings have been incorporated in contemporary stent designs to provide better trackability, flexibility, conformability, and compressibility and prevent restenosis.\textsuperscript{14–16}

Interventional acute stroke therapy is rapidly evolving, with newer pharmacological agents that may be administered locally into clots via the intra-arterial route in combination with intravenous administration or with mechanical microdevices to achieve clot disruption.\textsuperscript{17–20}

The pace and the dynamic evolution of endovascular therapy advances have escalated rapidly over the past 10 years. The potential exists for further advances and the only limitation is imagination. The minimally invasive treatment of vascular neurosurgical diseases is the desired approach of the future. Keeping up with clinical advancements in interventional and catheter-based technologies is the key factor for improving clinical outcomes. The future is going to be marked by constant changes and the development of more minimally invasive techniques to treat central nervous system (CNS) diseases.

The core of advances in treating different CNS vascular diseases lies in refining existing techniques and tools and developing more biocompatible ones. The current management strategies and approaches may also evolve over time and be replaced by techniques tailored to specific vascular anomalies.

Materials are becoming more bioactive and less irritating or toxic to vascular structures. They are designed with the different anatomical and structural variations of the vascular diseases in mind. New tools are being designed to lessen the complication rates during or following endovascular interventions. Future developments
involve all aspects of endovascular neurosurgery. This chapter will provide an overview of recent developments and future directions of endovascular neurosurgical approaches for treating various CNS diseases.

12.2 CEREBRAL ANEURYSMS

The rate of cerebral aneurysm treatment via nonconventional endovascular therapy (rather than surgical clipping) is steadily increasing. The endovascular approach is accomplished by filling aneurysm lumens with balloons, Guglielmi detachable coils (GDC), or liquid polymers.6–8,21–26 The recent publication of the prospective and randomized ISAT is considered a significant step in providing clinical evidence of endovascular aneurysm coiling. The study showed a 6.9% absolute risk reduction in functional outcomes in patients with ruptured aneurysms treated with GDC when compared to surgical clipping.8

Although the study results provoked wide controversies, they influenced the treatment approach to ruptured cerebral aneurysms in many institutions worldwide. Further studies in North America are on the way and may define better the exact future role of endovascular therapy.

In addition to clinical advances, technology is constantly evolving and the pace of improvement may be hastened by the spread of endovascular approaches. The standard platinum-based GDC has been improved by the addition of 3-dimensional shapes and the use of new biologically compatible polymer-coated Matrix® detachable coils (Boston Scientific, Fremont, CA).28–31 Different detachable coil shapes, materials, coatings, and designs under development may allow better conformation to the shape of an aneurysm and improve healing, fibrosis, endothelialization, and obliteration of the aneurysm lumen.

Several technical and design aspects of endovascular treatment of cerebral aneurysms are being refined to enhance trackability, ease of deployment, and biological activity in promoting aneurysmal neck neoendothelialization. The aneurysm coil-coating compositions are made mainly from biodegradable lactose or cellulose copolymer derivatives.28–31 Molecular biology and translational basic research are becoming the bases for developing newer coil designs.32,33 Those advances are summarized in Table 12.1 and discussed next.

12.2.1 SURFACE MODIFICATION OF GDC EMBOLIZATION

Biological material-based coatings intended to achieve complete luminal filling are being developed to enhance the efficacy of the newer generation of aneurysm coils. Coating with bioactive materials would make GDC more biocompatible and could stimulate clot organization with aneurysm fibrosis and neck endothelialization. Matrix 2- and 3-dimensional coils composed of 75% bioabsorbable polyglycolic/poly-L-lactic acid copolymer outer coats and 25% platinum cores are currently in use.28 In preclinical studies, Matrix detachable coils were shown to accelerate the formation of intra-aneurysmal connective tissue, fibrosis, endothelialization with increased aneurysmal neck thickness, and reduced aneurysm size over a shorter
period of follow-up when compared to standard GDC.28 The copolymer was hypoth-
esized to enhance the inflammatory response to coil deployment and hasten aneu-
rysms healing. As a stronger neck forms, the biological material is degraded and
absorbed, leaving the platinum core and promoting shrinkage of the aneurysm.28

Fibroblast cells and growth factors are some of the other materials used to coat
GDC in aneurysm animal models in an aim to improve the rate of luminal fibrosis
and neck closure.32,33 Fibroblast allograft delivery via deployed coils was shown to
be safe and feasible in animal studies.33 After 2 weeks of the fibroblast allograft
coated coil deployment, the fibroblasts remained viable and contained within the
aneurysm lumen, with cellular proliferation and fibrosis versus unorganized thrombi
in the control aneurysms.33 Other radiological and histological studies involving
collagen, protein, ion-implantation, and polyester coating showed variable success
rates of aneurysm occlusion and neck endothelialization.32,33 Current modifications
to GDC coils are in their early phases. The Matrix coated detachable coils are the
first available for clinical use. Follow-up data on long-term efficacy of the Matrix
may be available in the next few years. Other modified GDC or complete biologically
active coils are expected to become available in the near future.

The Hydrocoil® (Microvention, Aliso Viejo, CA) is another recently released
polymer-coated coil. The product has a pH-activated hydrogel coating that expands
over a period of several minutes after hydration. Modification of the polymer coating
allows for a high percentage of aneurysm filling with coils and may ultimately reduce
the recanalization rate due to coil compaction. Other companies are also attempting
to develop polymer-based coils that can completely fill an aneurysm and increase
the healing response to seal the aneurysm neck.

<table>
<thead>
<tr>
<th>TABLE 12.1</th>
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<tbody>
<tr>
<td><strong>Overview of Future Aneurysmal Endovascular Neurosurgical Therapy</strong></td>
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<tr>
<td>Advances</td>
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<tr>
<td><strong>Surface-Modified Aneurysmal Coils</strong></td>
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<tr>
<td>Polyglycolic acid bioabsorable polymeric coating</td>
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<tr>
<td>Polyglycolic acid</td>
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<tr>
<td>Polyglycolic/poly-L-lactic acid copolymer</td>
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<td>Fibroblast tissue allograft</td>
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<td><strong>Others</strong></td>
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<tr>
<td>Smooth muscle, growth factor, and ion implantation</td>
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<tr>
<td>Collagen coating</td>
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<tr>
<td>Polyurethane, Gelfoam, Dacron, and Fibronectin implants</td>
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<td><strong>New Techniques</strong></td>
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<tr>
<td>Balloon remodeling, stent-assisted coiling, double catheters, 3-D coils,</td>
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<tr>
<td>liquid polymers (Onyx, cyanoacrylate, cellulose acetate, etc.)</td>
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<tr>
<td><strong>Comments</strong></td>
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<tr>
<td>Theoretical advantage: improves intra-aneurysmal fibrosis</td>
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<tr>
<td>Neointima formation across aneurysm neck</td>
</tr>
<tr>
<td>Promotes tissue reaction and fibrosis; fibroblast proliferation and</td>
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| aneurysm obliteration; fibroblasts rapidly proliferate, are immunologi-
| cally inert                                                              |

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12.2.2 New Techniques: 3-D Coils, Balloons, and Stent-Assisted Coiling

Aneurysm coiling is best suited for small aneurysms with narrow necks (dome-to-neck ratio greater than 1.5). Aneurysms with irregular shapes and wide necks and those that have been partially clipped are usually approached with innovative endovascular techniques. Balloon remodeling was devised to protect the parent vessel lumen from coil herniation by inflating the balloon across the aneurysm neck after placing a microcatheter into the aneurysm lumen. More recently, flexible and small intracranial stents (e.g., Boston Scientific’s Neuroform) have become available. They can be used to protect parent vessels with wide neck or irregularly shaped aneurysms.

Other techniques include the double-catheter approach. Two microcatheters are placed in the aneurysm lumen prior to detaching the two coils. The interventionalist can then test the positioning of the two coils. If deployment is satisfactory, the result is basket protection formed by deploying two coils simultaneously. Finally, the availability of 3-D coils has made it safe and feasible to deploy and detach coils in irregularly shaped aneurysms with wider necks.

Flexible stents covered with polyethylene terephthalate may be used to treat spontaneous, traumatic, or postsurgical pseudoaneurysms, where no significant branches of the parent vessels exist. The Symbiot-covered stent (Boston Scientific/SCIMED, Minneapolis, MN) has been used in a few reported cases to cross a pseudoaneurysm neck and effectively treat pseudoaneurysms of the internal carotid arteries.

12.2.3 Liquid Polymers

The use of liquid materials to embolize cerebral aneurysms has emerged again despite the controversy, increased risk of procedural complications, and past failures to obtain perfect luminal obliteration. Liquid material may indeed provide an advantage in that it can conform to the shape of an aneurysm and may enhance and promote intraluminal fibrosis. However, it also carries high potential risks of protrusion into the parent vessel lumen with distal migration and inability to stimulate endothelialization across the aneurysm neck. The latter risk makes the currently available liquid embolic agents unfavorable first choices to embolize cerebral aneurysms. Such limitations may be lessened with the use of protective devices such as balloons or stents or in combinations with coils.

One liquid polymer currently undergoing clinical trials and in use in humans is Onyx® (Micro Therapeutic Inc., Irvine, CA). Onyx is an ethylene–vinyl alcohol (EVGOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and mixed with micronized tantalum powder to achieve the appropriate radio-opacity. Onyx is a nonadhesive biocompatible polymer that allows slow delivery and complete filling of an aneurysm, but requires a balloon or other protective device to contain the delivered material in place.

A study by Muramaya et al. revealed that despite the improvement in liquid leakage to the parent vessel lumen, such a complication remained a difficult
challenge even with the use of protective devices to contain the liquid polymer inside the aneurysm lumen.\textsuperscript{23} They used 12\% Onyx: (1) alone, (2) in combination with GDC, (3) proximal, (4) across the aneurysm protective balloon, and (5) with neck stenting. The study was limited in the design and sample size (five to ten patients per group), but showed that the use of Onyx combined with protective devices provided more complete filling, with migration rates into the parent vessels ranging from 9 to 33\%, but with no significant differences among the groups.

Cyanoacrylate embolization with GDC coil protection in an animal model of carotid bifurcation aneurysm revealed a better filling rate at 3-month follow-up.\textsuperscript{24} Unfortunately, the cyanoacrylate escape rate to the parent blood vessel remained high (25\%).\textsuperscript{25} Other liquid polymers used \textit{in vitro} and \textit{in vivo} are iodinized cellulose mixed esters that provided good results in aneurysm models in sheep.\textsuperscript{26} These embolic agents need further modifications of solvent concentrations to become less toxic prior to use on a larger scale in human subjects.\textsuperscript{26}

12.3 ARTERIOVENOUS MALFORMATION AND ARTERIOVENOUS FISTULA

Arteriovenous malformations (AVM) and arteriovenous fistulae (AVF) are congenital lesions that can present at any age, although they are most common in the third and fourth decades of life. The main presenting symptoms are related to headache, seizure, and intracranial bleeding. AVM and AVF may be also found via magnetic resonance imaging (MRI) and angiography. The risk of bleeding may range from 3 to 4\% per year. The risk of chronic neurological disability or death following intracranial bleeding ranges from 20 to 50\%. The mainstay of AVM therapy depends on the clinical and imaging grade of the condition that closely correlates with postoperative complications and predicts surgical outcome. To reduce surgical risk, presurgical endovascular embolization is usually attempted. In addition, endovascular therapy may be implemented to reduce AVM volume prior to surgical resection or radiosurgery treatment. Recent endovascular advances may define better the adjunctive and occasionally curative role of local AVM embolization (Table 12.2).

12.3.1 DEVELOPMENT OF NEW EMBOLIZATION MATERIALS: GLUES AND POLYMERS

Endovascular AVM therapy is progressing at a slower rate than aneurysm therapy because it involves different obstacles. The current endovascular neurosurgical therapeutic approach to AVM remains adjunctive rather than curative. It is used to aid gamma knife radiosurgery of eloquent and large AVM and conventional surgical resection for smaller noneloquent AVM.

Obstacles in achieving an important milestone in treating AVM via endovascular therapy include the lack of ideal materials for embolization of the AVM, the need to access and embolize all the feeders, and the ability to deal with hemodynamic changes upon abruptly occluding large amounts of inflow or outflow to the AVM. The current complications rate remains around 2 to 15\% due to inadvertent embolization of an arterial branch supplying an important functional brain region.
Embolizing materials include Onyx, cyanoacrylate (n-butyl cyanoacrylate or n-BCA), Ethibloc, polyvinyl alcohol (PVA), GDC, and other agents including silastic or latex balloons, gelfoam powder, cellulose, fibrin glue, silicone spheres, calcium alginate, surgical silk thread, and microhydrogel spheres.\textsuperscript{9–13,39–41} The most common embolic agent is n-BCA,\textsuperscript{10} which solidifies immediately on contact with free hydrogen ions in the blood; the casting effect is permanent.\textsuperscript{10} The n-BCA is dissolved in lipiodol, and injected via a flow-directed microcatheter. The risks with n-BCA include escape of the agent to the venous side or normal arteries, possibly leading to cerebral infarction, and adhesion of the catheter to the wall of the blood vessel due to back-reflux of the n-BCA. Adhesion prevents reuse of microcatheters. Each catheter should be withdrawn immediately as soon as the injection is completed.\textsuperscript{10}

Ethibloc is a solution of ethanol and zein, a corn protein (210 mg zein/ml ethanol) in an aqueous solution. The ethanol dissolves and the zein precipitates.\textsuperscript{9} Ethibloc provides an advantage over n-BCA in that it is less adhesive and allows re-use of flow-directed microcatheters rather than removing the catheters immediately after a single use, as required with n-BCA. Unfortunately, Ethibloc must be infused via a microcatheter with an outer diameter of 1.8 French; otherwise it could cause rupture of the microcatheter.

Both ethibloc and n-BCA are mixed with lipid-based oil before injection.\textsuperscript{9} Other agents used include PVA with different particle sizes: small (50 to 150 \(\mu\)m), medium (250 to 450 \(\mu\)m), and large (500 to 750 \(\mu\)m). The PVA is used mainly for preoperative embolization of tumors and AVMs due to the increased incidence of recanalization.\textsuperscript{39–41} Another treatment strategy is use of an embolic agent in combination with GDC coils or using the coils alone to close some of the AVM feeders.\textsuperscript{13,42} Balloon protection and assisted closure with trispan devices may also be used.\textsuperscript{42}

\begin{table}
\centering
\caption{Advances in Arteriovenous Malformation Endovascular Therapy}
\begin{tabular}{|l|p{5in}|}
\hline
\textbf{Embolic Agents} & \textbf{Comments} \\
\hline
n-BCA & Immediate solidification; risk of escape of the agent; microcatheter adhesions; microcatheters can be used only once \\
Ethibloc & Slow solidification; microcatheters can be used up to four times; risk of rupture of microcatheter \\
PVA & Several particle sizes: 150 to 1000 \(\mu\)m; temporary occlusion; mainly used preoperatively \\
\hline
\textbf{Others} & Onyx, GDC, gelfoam, silastic or latex balloon, fibrin silicon, hydrogel glue, calcium alginate, etc. \\
\hline
\end{tabular}
\end{table}
Technical advances in AVM endovascular therapy involve reemergence of the transvenous approach and induced systemic hypotension during such therapy. The rationale is to lessen the hemodynamic effect of abrupt occlusion of the AVM outflow. Induced systemic hypotension to 70 to 80 mm Hg mean arterial blood pressure during the AVM transvenous embolization procedure via systemic vasodilators or adenosine-induced cardiac pause could be performed successfully without complications. These studies may reopen the door to AVM therapy via the transvenous approach in combination with induced hypotension.

12.3.2 Arteriovenous Fistula

Carotid-cavernous fistulae (CCF) are of four types: type A (fast flow) and slow flow types B, C, and D. Treatment is achieved via venous or arterial approaches. Success has been variable, ranging from 50 to 80%. The current methods include embolizing the fistulae with liquid embolic agents such as n-BCA or microparticles, balloon occlusions, GDC, and hydrocoils. Inflatable detachable balloons and hydrocoils are usually used for type A fast flow post-traumatic CCF via arterial or venous approaches through the inferior petrosal sinus. Type B dural shunts receive slow flows via meningeal branches of the internal carotid arteries and endovascular surgery usually is not feasible. Type D dural arteriovenous shunts receive contributions via the meningeal branches of the external or internal carotid arteries. Types C and D are usually treated via embolization with liquid agents to external carotid artery feeders.

12.4 Stenting for Atherosclerotic Disease

The carotid endarterectomy remains the gold standard for treating patients with carotid disease to prevent future neurological deficit and stroke. Carotid endarterectomy is more effective in preventing stroke and death than medical therapy alone in symptomatic patients with carotid artery stenosis measuring more than 50%, if the surgical complication rate is less than or equal to 1.5% according to several studies.

Earlier studies comparing endovascular therapy with endarterectomy failed to show significant differences in favor of carotid angioplasty or stenting (CAS) due to high periprocedural complication rates reaching 10%. The early Wallstent® study was terminated because of a high event rate in the CAS arm. Results of further studies designed with advanced techniques and protective embolic devices (Carotid Revascularization Endarterectomy versus Stent Trial [CREST]; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [SAPHIRE]) are still pending. Despite recent advances in endovascular stenting and angioplasty, several hurdles must be overcome. Increased rates of restenosis and periprocedural complications due to distal embolization and stroke following CAS remained important factors that limit widespread clinical application.

Current and future technical advances are focused on improving the restenosis and neurological complication rates after CAS. Recent developments in carotid stent design and clinical CAS trials are making use of drug-coated stents, embolic...
TABLE 12.3
Areas of Focus and Advances in Stent Development

<table>
<thead>
<tr>
<th>Advances</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent design</td>
<td>Different links and shapes; tight versus loose cells; covered versus uncovered; porous versus nonporous</td>
</tr>
<tr>
<td>Stent composition to decrease restenosis rate and thrombogenicity</td>
<td>Traditional stainless steel, nitinol, gold, titanium, tantalum, cobalt chromium alloy stents, etc.; total biodegradable or combined metallics and copolymers</td>
</tr>
<tr>
<td>Drug-coated and drug-eluting stents</td>
<td>Heparin, hirudin, iloprost, abciximab, prednisone, methotrexate, rapamycin, paclitaxel, collagen or polylactic acid incorporating adenovirus gene-loaded vector, radioactive stent, polytetrafluoroethylene</td>
</tr>
<tr>
<td>Embolic protection devices</td>
<td>PercuSurge, Angioguard filter, PAEC, and FilterWire-EX EPD</td>
</tr>
<tr>
<td>Adjunctive medical therapy</td>
<td>Clopidogrel, aspirin, heparin, parenteral GP IIb/IIIb inhibitors (abciximab, eptifibatide, tirofiban, lamifiban), oral GP IIb/IIIa inhibitors (orbofiban, sibrafiban), neuroprotective agents (nimodipine, citicholine, labulazole, etc.)</td>
</tr>
</tbody>
</table>

Intracranial angioplasty and stenting present additional technical challenges. The flexibility of the stent and its interference with the small arterial perforators originating at stenotic lesions are of paramount significance in designing an intracranial stent that will attain good results and achieve low morbidity and mortality.

12.4.1 DRUG-COATED AND DRUG-ELUTING STENTS

The pathophysiology of atherosclerotic disease involves inflammatory changes incited by intimal wall injury, with leukocyte activation and secretion of prostacyclins and cytokines. Platelet activation follows, with subsequent adhesion, aggregation, and thrombus formation. In addition to the atherosclerotic process when deploying an intraluminal stent, the tension and stress on the intima may stimulate growth factors and lead to intimal hyperplasia and subsequent peri- or within-stent restenosis.14,15,52–54 These pathophysiological changes now serve as the basis for developing a newer generation of drug-coated stents.50,51 Impregnating stents with heparin, iloprost, hirudin, or a combination of these drugs may help decrease thrombotic responses and prevent intimal hyperplasia.14,15,52–54

Drug-eluting stents with abciximab,55 prednisone, methotrexate, paclitaxel, rapamycin, or angiopeptin may also provide some protection against restenosis by inhibiting inflammatory response, intimal proliferation, and thrombosis. Current data on drug-coated stents for coronary intervention indicate that antimitotic agents such as sirolimus and paclitaxel are promising in preventing neointimal hyperplasia and restenosis.15,52,53 These studies should be duplicated in CAS, particularly because it
involves a different pathophysiology and vessel caliber from coronary atherosclerosis. Coating the stents with radioactive substances provides an additional method for preventing restenosis by inhibiting intimal hyperplasia. One drawback of the radioactive approach may be related to less radiation delivery at the periphery of the stent due to penumbral effects that may lead to peri-stent restenosis.15,52,53

12.4.2 Surface-Modified and Biocompatible Stents

Surface modifications to stents are performed to achieve increased biocompatibility, better conformation to blood vessel shape by wall opposition, and ability to withstand external crush forces. The new expandable stents provide better physical fit to a narrowed arterial lumen. These stents are mainly made of nitinol — a four-atom biocompatible composite of nickel and titanium. Nitinol changes its crystal structure upon contact with human blood and reverts to its original austenite crystals with high elastic properties at body temperature. This provides a stent with better hemodynamic resilience, conformability, and wall opposition.15

Other biocompatible stent modifications include collagen polymer coatings to reduce neointimal hyperplasia and electrochemical polishing of the stent surface that decreases thrombogenic reactions when stents are deployed in the arterial lumen.14,15 More recently, biochemical and tissue engineering techniques are being applied in animal studies seeking the ideal stent design, particularly a “living stent.” Fibrin-, nitric oxide-, and phosphorylcholine-coated stents try to mimic living vascular wall tissue (with its physiological function and antiproliferative feedback mechanism) to lessen atherosclerosis and intimal hyperplasia.14,15,56,57 Surface modification of stents is still in its early phases, and further studies promise to delineate better their role in managing patients with high risks of carotid artery peri-stent and in-stent restenosis.

12.4.3 Vector-Coated Stents

While the Human Genome Project unravels the genetic code sequences for humans, gene therapy to inhibit local atherosclerosis and plaque formation presents a real potential therapeutic alternative. Coating metallic stents with biologically active materials and hydrogels, such as lactic acid derivatives and gelatin macromers, allows incorporation of different drugs and gene therapies in stents and local delivery to nearby arterial walls.56,57 Coating stents with specific gene-carrying vectors that may inhibit expression of known growth factors or act on platelet aggregation and smooth muscle growth factors are also undergoing testing.

Theoretically, delivering these agents to arterial walls would prevent neointimal formation and proliferation and halt the restenosis process and progression of carotid atherosclerosis.56,57 Vector-coated stents were tested in rabbit carotid arteries in vivo.56 After the stents were coated with adenovirus vectors expressing bacterial beta-galactosidase, the genetic material was transmitted to the vascular wall. Gene expression was altered within 3 weeks of the bioactive stent deployment and the adenovirus vector indeed induced production of beta-galactosidase in the vascular wall near the stent.56 This study indicates the feasibility and potential of this technique to be applied with an effective gene therapy to halt the progression of or reverse carotid and intracranial atherosclerosis.
12.4.4 Embolic Protective Strategies

The risks associated with carotid stent deployment from transcranial ultrasound studies are known to occur early; they are associated with microembolic phenomena, often leading to neurological deficits. To minimize such risks, several studies are investigating embolic protective devices (EPDs) during CAS, including flow reversal devices, filters, umbrellas, and other membranous devices.58–60

In one study, three types of EPDs were used on 30 high-risk surgical patients during CAS. The CAS with pre-EPD placement was found to be safe and feasible. Only one patient suffered a major periprocedural stroke, making the complication rate equal to 3%.59 Another small study of 36 CAS procedures used a FilterWire-EX EPD consisting of a 0.014-inch guide wire with an integrated expandable distal nitinol loop attached to a thin microporous polyurethane filter. The procedures were performed successfully without any permanent neurological deficits at 30 days.60

Transient neurological deficits lasting 30 minutes without residual effects were noted in two patients (5.7%).60 In the cardiac literature and in a multicenter study, a total of 801 stents have been deployed. Cases were randomly assigned stents with PercuSurge EPDs or stents without EPDs. The study showed a significant reduction in periprocedural cardiac complications, decreasing from 14.7% in the control group to 8.6% in the PercuSurge EPD group (\(p = 0.008\)).58

Large, randomized studies to better delineate optimal EPDs and proper patient selection are underway (CREST and SAPHIRE), and results should be forthcoming in the next few years.50,51 The risk of distal embolization persists due to lack of protection from EPD malfunction during the diagnostic segment of the CAS or during placement of the EPD.

12.4.5 Adjunctive Medical Therapy

The routine use of antiplatelet therapy before or during CAS is mainly derived from cardiac literature protocols. The evidence for such therapy during CAS is based solely on anecdotal evidence or case series.61 Current practice is to load patients with 300 mg of clopidogrel on the day preceding the CAS, use heparin to extend activated clotting time above 250 seconds during the CAS, and continue both aspirin and clopidogrel for 6 weeks followed by use of one agent only.

The use of different types of intravenous glycoproteins IIb and IIIa has not been well delineated. They are currently used in cases of emergency CAS that do not involve large areas of cerebral infarction, as documented by neurological examination or imaging studies, to avoid the risk of intracerebral hemorrhage.61 The glycoprotein IIb and IIIa inhibitors available in the United States are abciximab (ReoPro®, Centocor Inc., Malvern, PA; Eli Lilly & Company, Indianapolis, IN), eptifibatide (Integrilin®, Cor Therapeutics Inc., South San Francisco, CA; Key Pharmaceuticals Inc., Kenilworth, NJ), and tirofiban (Aggrastat®, Merck & Co. Inc., Whitehouse Station, NJ).

These agents have been used sporadically in CAS and the rationale for their use is derived from anecdotal experience or small published case series.61,62 Randomized clinical trials to define their exact role in CAS are needed, although the systemic
glycoprotein may be used in urgent or emergency CAS and oral versions may be
used for elective CAS. Meanwhile, additional data can be expected from ongoing
studies comparing CAS to endarterectomy.

The area of adjunctive medical therapy in CAS is still in its early stages: defining
the role of periprocedural medications to prevent neurological complications and
stent restenosis. Another potential adjunctive medical therapy is the use of neuro-
protective agents to halt ischemic cascades in acute stroke patients. Because stroke
risk may be high during CAS, a neuroprotective agent with a high safety profile
may be administered before and during the CAS or even immediately after the onset
of neurological symptoms.

12.5 ENDOVASCULAR STROKE TREATMENT

In June 1996, the U.S. Food and Drug Administration (FDA) approved intravenous
(IV) therapy of recombinant tissue plasminogen activator (rtPA) for use in acute
ischemic stroke patients within 180 minutes of symptom onset. This approval
followed publication by the National Institute of Neurological Disorders and Stroke
(NINDS) of improved 3-month outcomes in patients who received 0.9 mg/kg within
3 hours of symptom onset, compared with a placebo, based on the modified Rankin
disability scale. The narrow time window for treatment (within 3 hours) and lack
of public awareness preclude offering this therapy to large number of patients.

Questions remain about the effectiveness of IV therapy and how the proportion
of treated patients can be increased. Moreover, IV rtPA efficacy may be marginal
because of low-drug concentration delivered to the clot, given the stagnation and
slow blood flow surrounding the blocked artery. The risk of symptomatic intracere-
bral hemorrhage (ICH) is about 6.4% in the NINDS group, although 40% had no
disabilities at 3 months. Although this is better than placebo results, 60% retained
different degrees of disabilities at 90 days.

The ideal goal of future intervention would be to improve the proportion of
patients with better outcomes and have fewer patients with ICHs. Hence, endovas-
cular, local administration of thrombolytics or mechanical clot retrieval devices is
appealing. Several studies have shown the efficacy of intra-arterial administration
of rtPA in various types of vessel occlusions. In the prolyse in acute cerebral thromboembolism (PROACT) study, pro-urokinase was administered to the horizontal portion of the middle cerebral artery with good recanalization rate and improved clinical outcomes at 3 months, but at the expense of an increase in ICH rate to about 10%.

The main obstacles to intra-arterial thrombolytic therapy for acute ischemic
stroke are the narrow therapeutic time window (6 hours from symptom onset) and
the lack of public awareness of the emergency nature of stroke treatment. In acute
ischemic stroke, the marginal benefit of thrombolytic agents more than 6 hours after
symptom onset is outweighed by the incremental risk of ICH as time passes. An
additional obstacle is the efficacy of clot lysis following administration of currently
available thrombolytic agents. The complete recanalization rate is modest, even when
treatment is administered early. Intra-arterial therapy may provide a higher recanal-
ization rate, but at the expense of increased risk of bleeding. To try to improve the
rate of recanalization, a combination strategy of administering IV followed by intra-arterial thrombolytics has been implemented in many tertiary care centers. The vessel patency rate improved slightly, but the risk of ICH was as high as or higher (10 to 15%) than intra-arterial therapy alone.

To improve patency rates after administration of thrombolytics, second, third, and fourth generations of rtPA have been introduced. The newer generations were developed by altering the terminal N units of rtPA and include tenecteplase (TNK), reteplase, alteplase, monteplase, lanoteplase, and pamiteplase. The modification may have improved the plasma half-life from 4 minutes to 40 minutes on average, but clinical trials in cardiology showed only marginal benefits over rtPA in achieving vessel patency. TNK is a mutant rtPA with higher fibrin specificity and longer plasma half-life due to slower clearance. Staphylokinase, a non-rtPA derivative produced by Staphylococcus aureus, has extreme fibrin specificity and a 6-minute plasma half-life, in comparison to 3 to 4 minutes for rtPA. Specificity to fibrin is thought to correspond to drug efficacy and lower incidence of hemorrhagic complications.

In addition to fibrinolytic agents, the availability of a new generation of parenteral glycoprotein IIb and IIIa antagonists will provide stroke victims with alternative therapeutic options. The preliminary results of the study of abciximab in acute ischemic stroke are encouraging, and the risk of hemorrhage does not seem to be higher than the risk with IV rtPA. A Phase I safety study of rtPA plus tirofiban showed that the combination is safe and feasible.

Although the pharmacological advances for acute interventional stroke therapy are still improving, several conclusions may be drawn:

1. The recanalization rate using IV rtPA is less than intra-arterial therapy, and the latter seems to be less with combined therapy.
2. Even with the best strategy, the current pharmacological agents provide modest vessel patency rates and are time consuming to administer.
3. Increasing the doses of therapeutic agents or combining different anti-platelet and fibrinolytic drugs may only lead to increased risk of ICH in stroke patients.

This leads us to contemporary microendovascular device designs and innovative techniques that may provide significant advantages over pharmacological approaches. Endovascular approaches with mechanical devices ideally would offer stroke patients faster recanalization and more effective flow reconstitution, possibly make blood clots more amenable to lower doses of thrombolytics or anti-platelet agents, and reduce the risk of ICH. Several devices are available and have undergone Phase I trials or have been reported in case series format in the literature and await large-scale Phase III trials. Clot retrieval devices have been developed to physically capture clots and remove them from the body via a microcatheter.

The Microsnare is a simple primitive design reported to capture or disrupt blood clots, but it can be associated with vessel dissection, perforation, or distal clot migration. The Concentric Thrombus Retriever (Concentric Medical, Mountain View, CA) is a more advanced design to retrieve clots from the intracranial circulation. The
nitiol corkscrew-like tip on the microwire can be pulled back to an inflated balloon at the tip of a microcatheter when the clot is captured. Ideally, the blood clot, the tips of the microwire, and the microcatheter should be engulfed by the end balloon and should be pulled out as one unit. Initial studies of nine vessels in swine models showed good retrieval and no dissection or perforation. A Phase I trial of mechanical embolus removal in cerebral ischemia (MERCI) within 3 to 8 hours of symptom onset using this device is ongoing.

Another device also in Phase I trials is the new generation basket-like Neuronet endovascular snare (Guidant Corporation, Indianapolis, IN). A European trial known as the Neuronet evaluation in embolic stroke disease (NEED) is currently being conducted. Thrombus obliteration devices including the AngioJet (Possis Medical, Inc., Minneapolis, MN) and the X-ciser (Endicor Medical, Inc., San Clemente, CA), are being tested in pilot safety and feasibility studies. The AngioJet uses a vacuum created by a high-pressure saline solution jet to aspirate clots. It is currently being tested within 6 hours of stroke onset in a trial known as TIME (thrombectomy in middle cerebral artery embolism). The X-ciser uses a dual lumen microcathether with rotating blades within a central hollow core and vacuum simultaneously to aspirate the debris of a clot. Several other devices are in development, including a catheter with several wires that form a basket when the catheter tip is placed in the clot.

One other contemporary design is the EKOS catheter (EKOS Corporation, Bothell, WA) — a 2.5-French drug infusion catheter with a 2.1-mm distal ultrasound transducer. The rationale behind this design is that the use of transcranial and endovascular ultrasound has been shown to intensify the effects of thrombolysis therapy in animal models and early human studies. The catheter is placed proximal to the clot and ideally the transducer is embedded in the clot. A total of 14 ischemic stroke patients were treated in the North American EKOS trial without any complications and with a 57% recanalization rate using the thrombolysis-in-myocardial infarction (TIMI 2–3) scale.

Lasers are also thought to produce clot emulsification by transforming photoenergy into acoustic energy. Two laser emitting catheters are being tested in a Phase I trial. The intra-arterial endovascular photo acoustic recanalization (EPAR) laser system trial enrolled 26 patients within 6 hours of symptoms onset. A total of 31 vessels were treated with 48% recanalization rate (TIMI 2–3), although 2 vessels were perforated during microcathether placement and before laser therapy. Endovascular stroke therapy is summarized in Table 12.4.

12.6 OTHER ENDOVASCULAR APPLICATIONS

12.6.1 NEOPLASTIC DISEASES

Vascular tumors such as meningiomas and hemangioblastomas are currently treated preoperatively with embolization of the vascular tumor bed. Embolic materials similar to those used for AVM and AVF therapies may be used to embolize tumor feeders. With enhancement of microbioengineering technology, new microcatheters, wires, and particles will lead to more effective adjunctive tumor embolotherapy.
Endovascular neurosurgery would be an effective and direct means of administering chemotherapeutic agents to brain tumors locally with fewer unwanted side effects from systemic administration. As the molecular biologies and bases of neoplastic diseases are being uncovered, the endovascular approach may be the choice in some cases to deliver gene therapy or newer and more effective antimitotic agents.

12.6.2 Degenerative Diseases

Newer disease-modifying drugs for both genetic and degenerative neurological diseases would be probably safer, less toxic, and more effective when applied directly to the affected areas rather than systemically. The current microcatheter technology allows selective catheterization of small arterial branches to deliver higher concentrations of therapeutic agents directly to the affected neuronal tissues. As the genetic codes unfold, the endovascular approach may become the preferred method of administering gene therapy to combat various genetic and degenerative diseases.

12.7 Conclusions

The field of endovascular neurosurgery is evolving rapidly. Newer and more biocompatible devices are becoming increasingly available and the interests of physicians and industry will hasten the progress even further. In the field of endovascular intracranial aneurysm therapy, the first and largest randomized control study (ISAT) comparing coiling to clipping was completed and published with positive results. North American trials are being designed and funded. When completed, they are
expected to clarify the exact role of aneurysm coiling, taking into account the fact that U.S. practice strategies are different from those in Europe where ISAT was initiated.\textsuperscript{74}

Newer coil materials and compositions, with more emphasis on biocompatibility and bioactive substances, are currently available. Advances in microwire, microcatheter, and guide catheter technology are also imperative to safer and more successful coiling. Angiography equipment in many endovascular suites includes three-dimensional rotational capability that allows better delineation of small vessels, aneurysmal origins, and aneurysmal neck and provides better endovascular guidance.\textsuperscript{75,76} Newer, more flexible stents for intracranial deployment now allow endovascular neurosurgeons to secure wide neck aneurysms with better coil packing and less residual filling.

Endovascular microangioscopy or aneurysmoscopy is still in its infancy, but may become the future imaging technique for cerebral aneurysms and AVMs.\textsuperscript{77} AVM endovascular therapy is now more effective. Flow-directed microcatheters allow access to more feeders and a user can get closer to the nidus. New nonadhesive embolic agents such as Onyx and Ethibloc allow reuse of microcatheters with fewer complications. The field of CAS expanded further with the development of specific, self-expansible extracranial and intracranial flexible stents. Several embolic protection devices that may reduce periprocedural neurological complications are available. Drug-coating and drug-eluting technologies to reduce rates of stenosis are in development. For example, rapamycin-eluting stents are associated with remarkable reductions in rates of restenosis in coronary vessels and may prove as effective in the carotid and intracranial blood vessels.\textsuperscript{78}

New stroke therapies with intra-arterial thrombolytic agents and combination therapies are also available. Endovascular nonpharmacological means of clot removal and recanalization including the AngioJet, Microsnare, and ultrasound and laser catheters with or without thrombolytic therapies are currently in Phase I trials. The role of near real-time magnetic resonance angiography (MRA) is not well defined yet, and remains to be explored when instant and fluoroscopic real-time MR capability with its compatible catheters, devices, and patient accessibility becomes available.\textsuperscript{79,80} The future of endovascular neurosurgery will continue to see dynamic and constant changes over the next decade, with wider applications and enhanced techniques, devices, and imaging capabilities.

REFERENCES


