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Tzu Chi Medical Journal

Review Article

Current Status of Interventional Neuroradiology (Neurointerventional Surgery)

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Article info

Article history:
Received: September 20, 2007
Revised: October 9, 2007
Accepted: November 1, 2007

Keywords:
Aneurysm
Arteriovenous malformation
Fistulae
Interventional
Intracranial atherosclerosis

Abstract

This article provides an overview of different neurointerventional procedures by reviewing important papers relevant to neurovascular disease and the latest concept of endovascular treatment. The focus was on studies that dealt with cerebral aneurysm, arteriovenous malformation, direct carotid-cavernous fistula, dural arteriovenous fistula, intracranial atherosclerosis, and acute symptomatic intracranial arterial occlusion. Studies on extracranial atherosclerosis and other nonvascular part were excluded. Interventional neuroradiology is a well-developed subspecialty that mainly treats neurovascular disease in a less invasive way. Advances in new technology and knowledge will make it an important method to treat different disorders in future. (*Tzu Chi Med J* 2008;20(3):177–187)

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1. Introduction

Interventional neuroradiology is one of the latest well-developed subspecialties that focus on treatment of disorders of the nervous system and related issues. It is also known as endovascular neurosurgery, intravascular neurosurgery, and interventional and therapeutic neuroradiology (ITN). Worldwide, two of the largest organizations in this field are the World Federation of ITN (WFITN) and the American Society of ITN (ASITN). However, during the 4th annual meeting of the ASITN from July 30 to August 3, 2007, the society decided to change their name to the Society of Neuro-Interventional Surgery (SNIS).

Over the last 20 years, interventional neuroradiology has been a less invasive modality compared to open neurosurgery for the treatment of a wide range of neurovascular disorders. Refinements in technique, advances in knowledge of neurovascular anatomy, and improvements in the design of microcatheters, guidewires and embolic materials, as well as the production of high quality X-ray fluoroscopic systems, have yielded superior clinical outcomes and provided an impetus to treat more often using interventional neuroradiology. The dramatic evolution of interventional neuroradiology has secured its primary role in the treatment of many vascular lesions, such as intracranial aneurysms, painful compression fractures of vertebrae, dural and venous sinus thromboses, some arteriovenous malformations, post-traumatic bleeding and fistulae, and many dural arteriovenous fistulae. It is also an effective alternative to surgery in those with premorbid medical conditions such as extracranial and intracranial atherosclerotic diseases, and is

a valuable adjunct to neurosurgery or other therapies in the treatment of arteriovenous malformations, some complex giant aneurysms and skull base tumors. We can foresee that, in the near future, interventional neuroradiology will increasingly play an important role in the management of acute ischemic stroke and intracerebral hemorrhage (ICH). In this review, well-developed endovascular treatment will be discussed.

2. Cerebral aneurysms

Surgical clipping or endovascular coiling are the two major methods of treatment for cerebral aneurysms. There is much controversy about the pros and cons of both treatments. However, after the two publications of the International Subarachnoid Aneurysm Trial (ISAT) [1,2], the concept of intracranial aneurysm treatment was at least clarified in some basic terms. In these two papers, neurosurgery was compared with endovascular treatment of ruptured aneurysms, and a 24% relative and 7.4% absolute reduction in death or dependency at 1 year was demonstrated in favor of endovascular coiling. The overall procedure-related morbidity was 9–10% and mortality for endovascular coiling was 1–2%. Procedural complications included aneurysm rupture (2–5%), symptomatic thromboembolic events (5–9%), parent vessel occlusion (2.5%) and coil migration (0.5%). All the data suggested that endovascular coiling is better than surgical clipping for the treatment of cerebral aneurysms, though the turf war is still ongoing.

Aneurysm occlusion relates to the size of the aneurysm and its neck. Larger aneurysms with wide necks are more difficult to occlude completely. In ISAT [2], 66% of aneurysms were completely occluded at follow-up, 26% were subtotally occluded (neck remnant), and 8% were incompletely occluded. However, most aneurysms bleed from the dome or body and only 2% from the neck, and it seems logical that a small stable neck remnant is safe. Neurosurgical clipping does not guarantee occlusion [2,3]. Post-clip angiography shows that 4% of aneurysms are completely unclipped and another 4% show major remnants. With the use of early endovascular coiling, the rate of angiographic obliteration was significantly lower for aneurysms with a fundus-to-neck ratio of less than 2 [4–6]. This led to the development of balloon-assisted coil embolization techniques that were successful in swine aneurysm models as early as 1994. Moret et al [7] and others [8–11] have described the clinical use of this technique in humans, and have achieved excellent obliteration rates for wide-neck aneurysms with balloon-assisted coil embolization. However, this technique is associated with an increased risk of thromboembolic events as high as 18% [12] and a higher risk of hemorrhagic complications because of increased pressure at the aneurysm neck with balloon inflation [8]. The development of a self-expanding flexible stent designed to navigate the tortuous intracranial vasculature has revolutionized endovascular management of wide neck aneurysms. The Neuroform stent is a nitinol stent delivered over a guidewire enclosed within a microcatheter that expands with limited radial force on the vessel. Data [13,14] with the first-generation Neuroform stent demonstrated complete occlusion in 73% of patients and a complication rate of 10.7%, mainly involving thromboembolic events. Other centers [15,16] have demonstrated similar results with improved technical stent success and delivery with a newer design, whereas procedural morbidity and mortality remains at 11%. Another problem with the stent-assisted method is the risk of thromboembolic events and the potential for long-term development of in-stent stenosis [17].

Aneurysm recanalization may occur because the aneurysm lumen is only partially filled with coils. According to an experiment, a completely occluded aneurysm contains 25–35% of its volume in coils; the rest is thrombus. The body's natural thrombolytic processes and coil compaction, more likely in a wide neck, may cause this recanalization and it is estimated that about 10% of coiled aneurysms will require a second treatment to ensure stability. The risk of rebleeding has been documented to be 0.2% per patient-year with a follow-up of 1 to 8 years (mean, 4) [2]. This is similar to the rebleeding rate after neurosurgical clipping.

To achieve safer, more durable treatment, and less coil compaction and recanalization of aneurysms after coiling, several modifications to the bare platinum coils have increased the formation of thrombus within the aneurysm, thus reducing risk of recanalization. They include bioactive coils, hydrogel coils and radioactive coils. The bioactive coils, such as Matrix coil (Boston Scientific), are coated with polyglycolic-polylactic acid to enhance thrombus formation and organization, and accelerate aneurysm fibrosis and neointima formation with increased neck tissue thickness but no parent artery stenosis [18,19]. The hydrogel coils are platinum coils coated with a polymeric hydrogel that swells when in contact with blood. They occupy more space by increasing coil volume from threefold to ninefold within the aneurysm, and achieve greater packing density to reduce recurrence rates and also stimulate a healing cellular response. The radioactive coils are implanted with P-32 emitting beta radiation and the local beta emission can prevent recanalization, probably by increasing neointima formation and other unknown mechanisms. Early data involving the hydrogel coil and the Matrix coil suggest equivalent or inferior periprocedural outcomes and recanalization rates, respectively [20–22]. Some trials are underway or are being designed to test the efficacy of some of these developments. The future

of bioactive endovascular technology will likely involve delivery of growth factors, including vascular endothelial growth factor, transforming growth factor-β and fibroblast growth factor, as well as gene therapy or cellular substrates within the aneurysm that will regenerate or remodel an endothelial wall layer across the aneurysm neck.

Final techniques for treatment of aneurysms depend on the experience of the neurosurgeons and neurointerventionalists at each center. In the treatment of unruptured intracranial aneurysms, there is still more controversy. The main patient and aneurysm risk factors for rupture of intracranial aneurysms are older age, female gender, larger size, location of the aneurysm at the posterior circulation and symptoms caused by the aneurysm. If there are no contraindications and patients have no serious preexisting diseases, treatment should be considered for all unruptured aneurysms in patients aged <50 to 60 years (open surgery), as well as perhaps for aneurysms of >7 mm in diameter in older patients. Patients with symptomatic aneurysms should be candidates for treatment irrespective of age and symptoms.

3. Cerebral arteriovenous malformations (AVM)

Therapeutic options for cerebral AVMs include neurosurgery, embolization and stereotactic radiosurgery, in any combination, or no treatment at all if the risks of treatment are considered worse than the natural history. The aim of treatment usually is to obliterate the AVM completely, to eliminate the risk of hemorrhage and, less frequently, to reduce the effects of steal or venous congestion. 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 with an understanding of the natural history of the lesion, as well as the morbidity and mortality associated with various treatments. The overall lifetime risk of hemorrhage is estimated at 40–42% [23,24]. Having said that, most estimates approximate a 2–4% per year risk of hemorrhage [23,25]. In the year immediately after a symptomatic hemorrhage, the rebleeding risk is generally thought to be considerably higher, in the order of 6–18% per year, gradually returning toward the 2–4% baseline with time [25–28]. AVM-related factors representing a higher or high bleeding risk, such as previous hemorrhage, intranidal aneurysms and singular or even impaired venous drainage, will have high priority.

For the resection of Grade I and II AVMs (<1%), and Grade III AVMs (<3%), the morbidity and mortality rates are subjectively very low in neurosurgical treatment. However, much higher morbidity rates were observed for Grade IV and V AVMs, reaching 31% and 50%, respectively, in the early postoperative period. They subsequently improved to 22% and 17%, respectively, at the time of the follow-up examination [29,30]. Since the surgical resection of Grade IV and V AVMs is generally associated with a risk of operative morbidity and mortality, and there is a relatively low risk of hemorrhage in these patients (1% per year) [31], no treatment for most patients in this group is advised.

The goals of preoperative embolization may be to generally reduce the degree of arteriovenous shunting and total blood flow through the nidus, in an effort to reduce blood loss during surgical excision. Alternatively, the goal may be more directive, such as embolizing the deep feeders to obliterate the section of the AVM that is more difficult to resect. Jafar et al [32] 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. DeMeritt et al [33] reported similar results with preoperative embolization of large AVMs, reporting improved postsurgical outcomes in comparison with a control group of smaller AVMs that were not embolized. However, in patients with Grade IV and V AVMs after partial treatment, Han et al [31] observed a hemorrhage rate of 10.4%, compared with a 1% risk in patients with no previous treatment. Another report [34] found an annual risk of hemorrhage of 14.6% in patients who underwent palliative treatment of cerebral AVMs. Wikholm et al [35] observed an increased rate of hemorrhage and death in patients undergoing partial treatment that resulted in less than 90% nidus obliteration. When an unresectable AVM hemorrhages one or more times, targeted partial treatment with endovascular exploration for an intranidal aneurysm and other risk factors, to reduce the risk of bleeding or to reduce the effects of steal, represents a reasonable strategy. Although the reported rates of complete endovascular obliteration of cerebral AVMs vary, most series estimates are in the range of 10% [36–40], though some have achieved 22% [41] and 40% [42].

Currently, N-butyl cyanoacrylate (NBCA) is the choice for AVM embolization. NBCA is radiolucent and must be mixed with a radio-opaque agent, typically ethiodized oil (e.g. lipiodol, ethiodol) in a 1.5:1 to 3:1 (oil-to-NBCA) mixture for most applications. After solidifying, the cyanoacrylates (if a sufficient volume has been injected) create an immediate occlusion of the embolized pedicle.

Onyx (EVOH copolymer-DMSO solvent) is mechanically occlusive but nonadhesive, inert and less inflammatory than NBCA, soft and compressible, easier to operate, more controllable and more predictable, and allows better surgical handling. Very slow controlled injections allow permeation of the Onyx through the various AVM compartments via interconnecting vascular channels. Tantalum powder must be mixed with

the agent to provide radio-opacity. Jahan et al (43) reported no recanalization in a small number of patients imaged up to 20 months after embolization. Murayama et al (44) demonstrated no recanalization in swine after 6 months of follow-up. Long-term follow-up is necessary to prove that Onyx is a better embolic material for cerebral AVM.

The complication rates of AVM embolization vary from 3% to 35% and are obviously higher for higher grade AVMs, which may require multiple embolizations and are located in or close to eloquent cortex. Many are transient, but minor permanent deficits occur in 10% and major in 8%, and mortality is around 1–2% (24,37,38,40,45–47). Complications may be thromboembolic or relate to venous occlusion, arterial perforation or pressure breakthrough bleeding.

In Taiwan, stereotactic radiosurgery is very popular for the treatment of cerebral AVMs. In our institute, we consider that radiosurgery should be applied to AVMs in patients with no evidence of previous bleeding at the location of eloquent or deep-seated regions, with the longest diameter less than 3 cm or the whole volume less than 27 mL. Though there are many papers that mention that size is of no matter in radiosurgery, the total obliteration rate is definitely decreased as size increases. We combine embolization with radiosurgery for the purpose of reducing the volume of the AVM, and eradicating the dural supply and AV shunting inside the nidus, which are resistant to radiotherapy. So far, there have been no large series reports about the outcome of combination treatment of embolization and radiosurgery for brain AVMs.

4. Direct carotid cavernous fistulae (CCF)

Direct CCFs may be spontaneous or acquired lesions. The most common clinical signs include cavernous cranial nerve palsies, proptosis, chemosis, pain and reduced visual acuity. Retinal perfusion pressure can be compromised to the extent of inducing permanent blindness (48). Usually, the aim is to preserve the internal carotid artery (ICA), so using transarterial balloon embolization with detachable balloons passed through the fistula and into the cavernous sinus to occlude the tear in the ICA is the first choice of treatment. If transarterial balloon occlusion is not feasible, transvenous embolization may be performed using a microcatheter positioned in the cavernous sinus via the inferior petrosal sinus. Even when the inferior petrosal sinus cannot be visualized angiographically, a channel can usually be found by probing with a steerable guidewire in up to 75% of cases (49–52). The embolic material can be a balloon, coils or even NBCA, depending on different scenarios. Recently, there have been reports of placing a covered stent across the fistula and/or stent-assisted coil embolization (53–56). The outcome of management of direct CCFs is usually excellent (57,58). The patient's proptosis rapidly regresses and the eye may be completely normal 1 week later. Visual acuity and ophthalmoplegia may take longer to resolve, and can be exacerbated in the short-term by thrombosis and associated swelling within the cavernous sinus (59). In a review of 87 patients with direct CCFs, detachable balloon embolization allowed ICA preservation: during the mean follow-up period of 10 years, diplopia improved in all patients and there was no recurrence of bruit, chemosis, proptosis or conjunctival edema (57).

5. Dural arteriovenous fistulae (DAVF)

DAVFs are acquired lesions, thought to originate from an insult to a dural venous sinus that stimulates an inflammatory response with subsequent neovascularization, angiogenesis and development of pathological shunts at the arteriolar level. The initial insult may be thrombophlebitis, trauma, intracranial surgery or dural venous thrombosis. Alternatively, the fistula could be the initial event, with turbulent arterialized blood flow in the dural venous sinus inciting a process of thrombosis, stenosis and occlusion (60).

The most common presentation is in perimenopausal women and is least common in men (27%), suggesting an underlying hormonal influence (61–64). The transverse and sigmoid sinuses are most commonly involved, followed by the cavernous sinus, the latter also referred to as indirect cavernous sinus dural arteriovenous fistulae (CSDAVF). In Asian countries, including Taiwan, Japan and Korea, the incidence of CSDAVF seems to be higher than elsewhere. In our institute, CSDAVF constitute about 45% of all DAVF, followed by DAVF in the transverse and sigmoid sinus (35%).

Some authors believe that the pathophysiological changes of persistent arteriovenous fistulae result in venous stenoses and sinus occlusions that develop in cases of low-risk fistulae, which then can transform into higher risk lesions. Any change in the patient's symptoms, such as worsening headaches or change in the quality of pulsatile tinnitus, may indicate alteration in the venous drainage pattern and risk of hemorrhage (65). In our experience, this is extremely rare in CSDAVF but can occur in other DAVF.

The classification that was proposed by Merland et al (66) is perhaps the most widely accepted among the various classification systems for DAVF. This classification indicates that the risk of intracranial hemorrhage is related to the venous drainage pattern. Low-risk fistulae exhibit antegrade venous drainage into a venous sinus, whereas high-risk fistulae exhibit reflux into a cortical vein(s) from the dural venous sinus or direct drainage into a cortical vein when the adjacent sinus is occluded. The cortical veins develop

tortuosity, stenoses and venous aneurysms that are potential sites of hemorrhage. Cognard et al's classification (67) is a modification of Merland et al's classification and also useful in risk assessment. Cognard et al classify five main types of venous drainage in DAVF: type I includes DAVF that drain into a sinus with normal antegrade flow; type II DAVF drain into a sinus but there is insufficient antegrade flow because of sinus stenosis/occlusion or high flow and there is reflux into either venous sinuses (IIa), cortical veins (IIb) or both (IIa+b); type III fistulae drain into cortical veins without venous distension; type IV fistulae drain into cortical veins with venous ectasia; type V fistulae drain into spinal perimedullary veins. Some may add a type VI that drain into bilateral cerebral hemispheres with stasis of venous ectasia.

In patients with low-risk fistulae (usually types I and IIa), the lesions may be discovered incidentally during angiography, or present with pulsatile tinnitus chemosis or headache. Spontaneous resolution of angiographically-proven DAVF has been reported to occur in 5–10% of cases. Aggressive features are present in about 37% of type IIa and these relate to elevated intracranial pressure. Patients with type I or type IIa DAVF are not at risk from ICH (67). For type I lesions, conservative treatment, carotid-jugular compression or particulate transarterial embolization will usually relieve the symptoms. The treatment of choice for type IIa is arterial embolization of the external carotid artery (ECA) feeders using polyvinyl alcohol (PVA) particles, repeated as necessary to diminish flow and intracranial hypertension. However, this achieves angiographic cure in only a small number; recanalization occurs and there is often recruitment of other feeding arteries.

High-risk fistulae (other than types I and IIa) may present with hemorrhage into the subarachnoid space or brain parenchyma resulting in focal neurological deficits or death. In those with type IIb fistulae, 30% have aggressive symptoms, with ICH and intracranial hypertension. In type IIa+b, aggressive features are present in two-thirds, in three-quarters of type III and nearly all of type IV. Half of those with perimedullary venous drainage have progressive myelopathy and most of the others have subarachnoid hemorrhage (SAH). Cortical venous drainage associated with venous hypertension is a well-known cause of neurological deficit and severe headache (68). In type VI, patients usually present with dementia or severe neurological deficits. The outcome is usually poor but occasional case reports with good outcomes have been noted. High-risk DAVF, therefore, warrant aggressive therapy, either endovascular or surgical, whereas low-risk fistulae can undergo palliative treatment if symptoms, such as pulsatile tinnitus, are troublesome (67).

For CSDAVF, carotid-jugular compression can be performed in those cases incidentally found or in patients who refuse aggressive treatment. Carotid-jugular compression involves compression of the ipsilateral common carotid artery with the contralateral hand for 10 seconds per compression, 4–6 times each waking hour. The compression time may be gradually increased to 30 seconds, with the neck moderately hyperextended to allow adequate compression, and performed for 4–6 weeks. This procedure should be supervised at first by a clinician to ensure that the patient does not experience a vasovagal attack or cerebral ischemia. If properly performed, it causes simultaneous compression of both the carotid artery and internal jugular vein, so reducing arterial flow and raising venous pressure. Cure may be achievable in approximately 34% of patients (69). This form of treatment is contraindicated in patients with carotid artery atherosclerosis, for fear of embolic events, those with hypercoagulable states and patients with cortical venous drainage, ICH or visual deterioration in whom more aggressive treatment is indicated. In low-flow CSDAVF (type B), presentation is less acute, and signs and symptoms may be both nonspecific and subtle. The patient may complain of retro-orbital headaches due to stretching of the dural lining of the distended cavernous sinus, or spontaneous thrombosis at the fistula site or draining veins. Most type B CSDAVF are associated with low morbidity and up to 50% may spontaneously resolve (70). Since they do not usually produce major neurological deficits and are not life-threatening, a minimally invasive form of therapy is desirable. Treatment should be focused on the patient's symptoms and not necessarily complete angiographic cure.

ECA feeders may be embolized, preferentially using PVA particles (>120 microns), achieving complete cure in 70–78% and improvement in 20–30%, with a complication rate of 5% (71–73). Recanalization, however, may occur and in these cases repeated transarterial particulate embolization or transvenous coil occlusion of the cavernous sinus, either through the jugular vein and inferior petrosal sinus or through the superior ophthalmic vein, is indicated if the condition persists or deteriorates. Transvenous coil occlusion of the cavernous sinus achieves cure in most patients, with a 6% complication rate.

In transvenous embolization of DAVF in other locations, coils are deposited at the site of arteriovenous shunting. If this is possible, it can result in cure without having to involve the myriad of feeding arteries. When transvenous access is prevented by occlusion of the recipient venous sinus, the site of shunting can be occasionally accessed transarterially or via a cortical draining vein. The venous approach includes: transcranial embolization after limited craniotomy and direct venous sinus catheterization (74); direct puncture through the superior orbital fissure (75); transvenous access to the cavernous sinus via the facial

and superficial temporal veins [76]. Although detachable coils have the advantage of being able to be repositioned or removed if placement is unsatisfactory, they are significantly more expensive and less thrombogenic than pushable fibered coils. A combination of the two types may be placed as a compromise. If the sinus is thrombosed on both sides of the DAVF, then there are a few options besides surgical operation and access may be gained either through the thrombosed portion [77], directly into the isolated portion of the sinus via a small craniotomy [78] or by careful transarterial embolization with low concentration NBCA [79].

Types III and IV are very aggressive, and partial obliteration will not adequately protect against hemorrhage. The goal of treatment must be complete occlusion. In cases where the DAVF drains into a cortical vein, endovascular occlusion of the draining vein itself using coils may occlude the fistula preserving dural sinuses.

Chemosis and proptosis typically improve rapidly after successful obliteration of CSDAVF. Visual acuity and ophthalmoplegia may take longer to resolve and can be exacerbated in the short-term by thrombosis and associated swelling within the cavernous sinus [59]. In a retrospective review of 135 patients with indirect endovascularly-treated CSDAVF, 121 (90%) patients were clinically cured after a mean follow-up period of 56 months, and a good clinical recovery (modified Rankin Scale score of 1–2) was demonstrated in more than 97% of the population at long-term follow-up examination [80]. In nine patients in whom transvenous coil embolization was performed for CSDAVF, two patients suffered temporary deterioration of ocular motor function [81]. There is some evidence that this effect may be limited by the use of corticosteroid agents or heparin in the postoperative period [82]. In a recent study of 135 patients in whom endovascular treatment was conducted for intracranial DAVF, cure was achieved in 74 patients and significant improvement in 54 [83]. In another series of 11 patients with DAVF of the transverse and sigmoid sinuses, preoperative transarterial embolization was undertaken in seven patients. Endovascular cure was achieved in one of four patients who underwent transvenous embolization, and AV communication was significantly reduced in the remaining three patients [51].

6. Intracranial atherosclerosis

For patients with transient ischemic attack (TIA) or stroke due to intracranial atherosclerosis and who require medical treatment, the question remains as to what constitutes the best regimen. There have been many trials but all have failed to demonstrate that medication is the best choice for prevention of TIA or stroke in intracranial atherosclerosis. Both the *Management of Atherothrombosis with Clopidogrel in High-risk Patients* trial and the recent *Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance* trial have demonstrated no benefits from the combination of aspirin and clopidogrel, and an associated increase in the risk of bleeding [84,85]. The *European Stroke Prevention Study* demonstrated the efficacy of dipyridamole plus aspirin versus aspirin alone [85]. The *Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events* trial demonstrated a slight benefit for clopidogrel compared to aspirin [86]. Certainly, on the basis of the *Warfarin-Aspirin Symptomatic Intracranial Disease* study results, warfarin is not better than aspirin and there is an associated increase in the risk of bleeding too [87]. Judicious use of high-dose aspirin, clopidogrel or dipyridamole as a single agent is likely the 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.

For those patients who failed to respond to aggressive medical treatment, the incidence of recurrent stroke was as high as 50% in the Stanford study. Most of the studies on angioplasty were small and results are not convincing when compared with the natural history of this disease. The results of intracranial angioplasty and stenting performed between 1999 and 2002 were reported in 10 series consisting of 89 patients [88]. Technical success rates ranging from 64% to 100% were reported, with major complication rates ranging from 0% to 36%. Recently, three clinical series on intracranial stenting have been reported. They are the *Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries* (SSYLVIA) study [89], the consecutive series of angioplasty and stenting for M1 stenoses reported by Jiang et al [90], and the HDE (*Human Devices Exemption*) Wingspan study [91]; all are important additions to the literature. The first two studies used balloon-expanding stents, while the Wingspan study used self-expandable stents. The perioperative mobility rate, mortality rate and 12-month stroke rate demonstrated that the Wingspan system seems to have a better safety profile and lower restenosis rate than other systems to date. Since these reports have taken place within 3 years, long-term results are not yet available. From our own limited experience, within 3 years, no patient was found to have symptomatic restenosis in a series of 32 patients, and about 25% of patients have asymptomatic stenosis (<50%) either inside the stent or at the margin of the stent.

Since intracranial stenting is a high-risk procedure, we selected patients who have failed to improve with aggressive medical treatment for 3 months and have poor cerebrovascular reserve capacity. According to

the experience from coronary arteries, drug-eluting stents have more in-stent stenosis and the problems with the balloon-expandable bare stents are the same: the study on such stents was very small.

7. Acute symptomatic intracranial arterial occlusion

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA), given to selected patients within 3 hours of ictus, remains the only approved treatment for acute symptomatic intracranial arterial occlusion [92]. Unfortunately, less than 5% of the eligible population receives this treatment in most countries. Additionally, strict adherence to this time window precludes many patients who might benefit from thrombolytic treatment and includes those who are unlikely to benefit. For example, those with internal carotid artery and main trunk middle cerebral artery (MCA) (M1) occlusions (if a proximal artery is occluded, insufficient IV drug reaches the thrombus), and those in whom the embolus has already dissipated (20–25%). Despite this advance in treatment, results with IV thrombolysis remain suboptimal and several randomized studies have failed to demonstrate significant benefits [93–99]. More recently, intra-arterial (IA) thrombolysis has been found to be safe and effective for the treatment of acute, anterior-circulation occlusion if instituted within 6 hours of symptom onset [100,101]. Nevertheless, reocclusion has been found to occur relatively frequently during IA thrombolysis for ischemic stroke and seems to be associated with poor clinical outcomes [102,103]. 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.

IA thrombolysis involves the direct infusion of the thrombolytic into the occluding thrombus, achieving higher local concentration of the drug, lower systemic concentration and fewer extracranial hemorrhagic complications. Faster and more complete recanalization may be achieved, particularly with proximal MCA occlusions. This allows a longer time window of 3–6 hours or longer if perfusion studies are favorable. Cerebral angiography allows direct visualization of the occluding thrombus and directly monitors thrombus dissolution.

Additionally, mechanical means may also be applied to disrupt the clot using the micro-guidewire and this may facilitate the action of the thrombolytic agent. Clot retrieval devices are now available that may actually extract the thrombus from the occluded artery, achieving reperfusion much more readily. Mechanical thrombolysis is obviously invaluable if the clot is resistant to IA rt-PA. The recently Food and Drug Administration (FDA)-approved Merci retriever thrombectomy device (Concentric Medical Inc., Mountain View, CA, USA) and stent-assisted recanalization are steps toward the future [104–111]. Pharmacological IA thrombolysis fails to recanalize vessels in approximately 50% of patients [109,112,113]. This is largely attributable to underlying atherosclerotic disease and "hard clot" [100,101]. Part I of the *Mechanical Embolus Removal in Cerebral Ischemia* (MERCI) trial was completed in 2004. It demonstrated *Thrombolysis in Myocardial Infarction/Thrombolysis in Cerebral Infarction* (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 [105]. The results of both parts of this trial [111] documented recanalization rates of 33% without thrombolytics versus 51% with additional thrombolytics. Another study done with the Merci device (L5) consisted of patients ineligible for IV t-PA or those in whom recanalization had failed after IV t-PA thrombolysis [114]. In this study, subsequent passes could be made with the Merci device. Adjuvant therapy with IA t-PA was allowed after attempts had been made with the retriever. 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. Good neurological outcome (modified Rankin scale score of ≤ 2) was achieved in 32% of the population treated.

Stenting is an appealing alternative that has been useful in achieving recanalization in acute intracranial vessel occlusion. Self-expanding and balloon-mounted stent-assisted recanalization of embolic occlusions has been tested *in vivo* in a canine model [115]. Recanalization of 90% of vessels acutely occluded with either soft or hard clot was achieved. Buttressing of the clot by the stent is likely to be the main mechanism involved. A clinical study done on intracranial stent implantation with coronary balloon-expandable stents after failed pharmacological and/or mechanical thrombolysis found reestablished 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. Self-expandable stent implantation also seems to have potential, as shown in recent reports [104,110,116].

Another mechanical thrombolysis trial used ultrasound. In the phase II *Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA* trial, 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) [117].

In a recent report of IA therapy in 168 patients with acute stroke, the combination of IV GP IIb/IIIa inhibitors and IA thrombolytics (t-PA or urokinase) in the setting of multimodal therapy was an independent predictor for recanalization of occluded vessels ($p<0.048$) [106]. Many trials on IV plus IA chemical thrombolysis for the treatment of acute arterial occlusion are still ongoing.

Vertebrobasilar occlusion is usually associated with a poor prognosis, with overall mortality rates of 70–80%. There are no randomized studies but many cases of thrombolysis have been reported in the literature using local IA infusions of urokinase or rt-PA [118]. Successful recanalization, either partial or complete, has been achieved in 70% of cases over a median infusion time of 120 minutes, resulting in survival rates of 55–70%. Survival rates in untreated or persistent occlusion were 0–10%. All survivors in the untreated group were at least moderately disabled. Two-thirds of those treated aggressively had good outcomes. Distal occlusions are probably due to emboli and not surprisingly are easier to lyse than proximal occlusions, which are more likely to be the result of a thrombus superimposed on an atherosclerotic plaque. The latter often requires adjuvant treatment with angioplasty and/or stenting. Paradoxically, these may have generated collaterals so the time window is extended. It seems to be that more aggressive treatment to posterior circulation acute arterial occlusion is reasonable.

From an analysis [119] of the mortality and outcomes of 1117 patients from 27 reports between 1998 and 2006, reviewers found considerable variability and lack of evidence for a net improvement in outcome after IA therapy relative to predicted natural history, substantiating the need for a prospective comparison with best medical therapy. Better outcomes were found in those reports related to: lower doses of urokinase; use of fixed dose thrombolytic without regard for success or extent of recanalization; recanalization achieving better results than non-recanalization. The MERCI mechanical thrombectomy trial was the eighth worst study among the 27 reports. The authors concluded that aggressive recanalization should not be the only goal of IA thrombolytic treatment of acute ischemic stroke. For those patients who do not readily recanalize, more aggressive efforts may actually have had harmful effects.

In our institute, if a thrombus is superimposed upon a stenosis, it may be necessary to undertake angioplasty or stent the lesion. Mechanical thrombolysis may also be considered if pharmacological thrombolysis is contraindicated. In the posterior circulation, we will extend the therapeutic window to 12 hours. Clearly, in all treatment options, prompt diagnosis and treatment are paramount to good outcomes. Advances in neuroimaging techniques have also improved the selection of candidates for acute stroke revascularization. Recently, we have used perfusion computed tomography (CT) and signal intensity CT angiography (CTA) for evaluation of penumbra. We shall use the concept of image-therapeutic-window instead of time-therapeutic-window when we select a candidate for intracranial thrombolysis in the near future.

In conclusion, further development of better devices, and new molecular and cellular regimens will be targets in the treatment of many neurovascular diseases. Interventional neuroradiology will play an important role in such treatment for its unique skill trained and the vast experience in treating different neurovascular diseases.

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