

## Interventional Neurology—Recent Advances and New Applications

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### Abstract

Interventional neurology refers to endovascular, catheter-based techniques using fluoroscopy and angiography to diagnose and treat vascular disease of the central nervous system. This article provides an update on the recent advances and newer applications of diagnostic cerebral angiography, acute endovascular stroke treatment, revascularization of carotid and intracranial stenosis, as well as cerebral aneurysm treatment. More importantly, however, is demonstrating not only how diagnostic cerebral catheter angiography has been redefined, but also how the associated interventional procedures have transformed the therapeutic landscape for stroke patients.

### Keywords

Interventional neurology, cerebral angiography, endovascular stroke treatment, aneurysm coiling, intracranial stenosis

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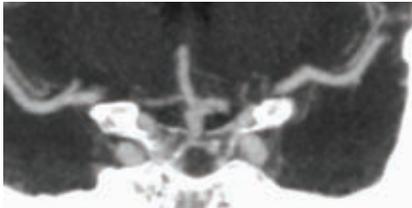
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Interventional neurology refers to endovascular, catheter-based techniques using fluoroscopy and angiography to diagnose and treat vascular disease of the central nervous system. These techniques were originally pioneered by a neurologist,<sup>1</sup> then the field was exclusively comprised of neuroradiologists. Recently, neurosurgeons and neurologists are increasingly seen as the majority. Not only are members of all three specialties enthusiastic stakeholders in this field, but each brings unique advantages to the field that may be best illustrated with the most common consultation.<sup>2</sup> When asked to perform a diagnostic angiogram, interventional neurologists are able to efficiently understand the salient clinical features of a case, tailoring the study to ensure the pertinent clinical questions are answered. The radiologist is trained not to let preconceived notions about a case bias their interpretation of the entire diagnostic study, thereby diminishing the chance that any abnormal finding is missed. The majority of diagnostic angiograms are still being requested by neurosurgeons, often for preoperative planning or embolization. In this case, information as it pertains to the technical aspects of the surgery, for example, obtaining oblique views replicating the views seen during craniotomy, may best be understood by a neurosurgeon performing the angiogram. The recent advances and applications in this field have as much to do with the practitioner and their role as with the advances in understanding pathology, imaging, and treatment options. This article will provide an update on the recent advances and newer applications of diagnostic cerebral angiography, acute endovascular stroke treatment, revascularization of carotid and intracranial stenosis, as well as cerebral aneurysm treatment. More important, though, is demonstrating not only how diagnostic cerebral catheter angiography has been redefined, but also how the associated interventional procedures have transformed the therapeutic landscape for stroke patients.

### Diagnostic Cerebral Catheter Angiography

Despite being the oldest of the primary *in vivo* brain vascular imaging modalities, the role of catheter angiography has undergone fascinating changes in light of the development of computed tomography angiography (CTA) and magnetic resonance angiography (MRA). Typical indications include the diagnosis of cerebral aneurysms, arteriovenous malformations, cerebral vasospasm, intracranial stenosis, arteriovenous fistula, or small vessel vasculopathy, including vasculitis. It is often performed just prior to a planned neurosurgical or neurointerventional procedure, as well as immediately after a neurosurgical case. Surveillance imaging is also performed to evaluate the durability of a prior vascular treatment. Fifi et al. evaluated over 72 months 3,636 diagnostic angiograms and found the range of clinical indications to be unruptured aneurysm (26.9 %), followed by subarachnoid hemorrhage (20.7 %), followed by arteriovenous malformation, other ischemic disease, and meningioma.<sup>3</sup> Intra-arterial digital subtraction angiography was once thought to be imminently obsolete, being replaced by CTA and MRA. Such noninvasive imaging modalities no longer exposed patients to the potential risks associated with intra-arterial catheterization and contrast injections and the possible neurologic deficits.<sup>4</sup> With increasing availability and use of improved noninvasive brain vascular imaging, including 3 Tesla MRA, and multidetector CTA, the indications for diagnostic catheter cerebral angiography as the initial brain vascular imaging study appear increasingly limited (see *Figures 1* and *2*). Concerns for the rare, but memorable, procedural complications that occur often factor into the decision-making among neurologists who may be considering such a study. In 2009, Fifi et al. evaluated over 3,500 diagnostic angiograms at a tertiary referral center and found a clinical complication rate, albeit self-reported, of 0.3%.<sup>3</sup> Despite alternative imaging modalities and safety concerns, the actual indications for catheter angiography have not significantly decreased

**Figure 1: Coronal View of Computed Tomography Angiography Maximum Intensity Projection Showing an Inferiorly Directed Anterior Communicating Artery Aneurysm**

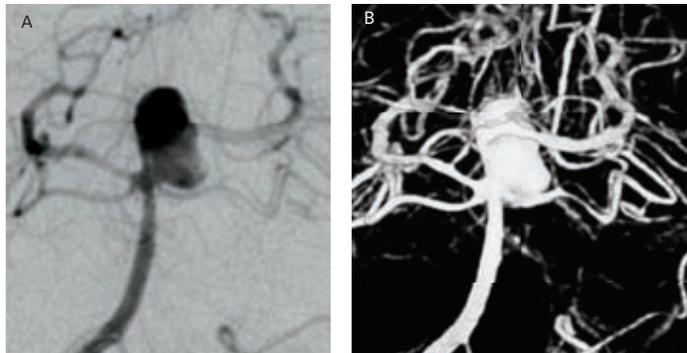


**Figure 2: Anteroposterior View of Catheter Angiogram**



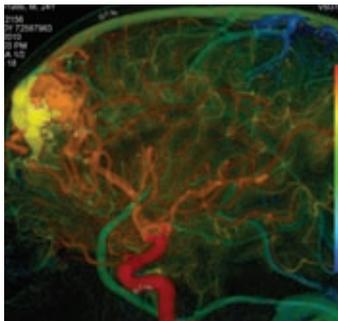
Showing, in better resolution, aspects of the aneurysm morphology, neck size, and relationship to anterior communicating artery complex.

**Figure 3: Limitations of Planar, Monochromatic Imaging**



A: Digital subtraction angiographic view of posterior circulation with aneurysms; B: 3D rotational reconstruction view of posterior circulation with aneurysm. The limitations of planar, monochromatic imaging are particularly noticeable here with understanding the relationship of the left P1 segment of the posterior cerebral artery and the distal basilar aneurysm. 3D rotational angiography allows for better visualization of this relationship, which has treatment implications.

**Figure 4: Angiography Color Map**



By measuring the time to maximum opacity for each pixel on a conventional catheter angiography run, a color map can then be generated, with variable intervals that are given chromatic designations, improving temporal resolution. This is particularly helpful with better understanding the components of a brain arteriovenous malformation, and possibly intracranial stenosis.

because of the increasing numbers of suspicious vascular findings seen on the very studies (CTA and MRA) thought to supplant it. Furthermore, since minimally invasive endovascular techniques have gained prominence and sometimes replaced open surgical techniques, catheter angiography remains an indispensable modern imaging modality. A development in the 1990s has been 3D rotational angiography, whereby a bolus of about 20–25 cc of contrast is injected over prespecified time intervals while a single C-arm rotates completely around the patient’s head twice, acquiring 120 digital subtraction images to then be used to generate a 3D model that allows evaluation of the opacified artery and its branches from any angle. The technique facilitates understanding of complex vascular anatomy and is a frequently used application in modern diagnostic as well as therapeutic neurovascular care (see Figure 3). Even though this method is well known for its superior spatial resolution, even newer applications aim to better quantify temporal resolution, or flow, during catheter angiography. Newer applications exploit the pre-existing physiologic information that is currently only subjectively, qualitatively, and in broad terms referred to as either high flow or low flow.<sup>4</sup> Strother et al.<sup>5</sup> discussed the strengths and limitations of this application in catheter angiography. They show that, rather than simply discriminating objects based on different shades of gray on a monochromatic image, color angiography allows discrimination based on the distribution of light wavelengths reflected to the eye. This provides yet another modality of conveying potentially important diagnostic information (see Figure 4).

**Endovascular Aspects of Acute Ischemic Stroke**

Despite the current availability of intravenous agents and intra-arterial devices to restore blood flow in an acute thromboembolic occlusion, there remains a frustrating discrepancy between the rate of recanalization and the rate of good functional outcomes.<sup>6</sup> Therefore, the interventional neurologist may be uniquely suited to help improve current strategies for patient selection, as well as design improved techniques and devices that optimize overall clinical efficacy while minimizing adverse events.

Smith et al. highlighted the importance of the term, ‘large vessel occlusion’ by evaluating brain CTA in 72 consecutive ischemic stroke patients. He found that intracranial large vessel occlusion, involving either the vertebral, basilar, middle cerebral artery, or carotid terminus, independently predicted a poor neurologic outcome at hospital discharge.<sup>7</sup> Most of the \$70 billion spent annually in the US on stroke care is for the severely disabled, who likely have large vessel occlusions. The only US Food and Drug Administration (FDA) approved therapy for acute ischemic stroke, namely intravenous thrombolysis, has been shown to lead to only modest recanalization rates for large vessel occlusions.<sup>8</sup> The Prolyse in acute cerebral thromboembolism (PROACT II) study represents the best study to date that evaluated intra-arterial stroke thrombolysis with primary clinical outcome measures that showed significantly improved clinical outcomes and recanalization rates among the treatment group.<sup>9</sup> Although not approved by the FDA for the treatment of acute ischemic stroke, various physician organizations have made qualified endorsements for intra-arterial stroke therapy with the belief that, “treating a suitable patient under appropriate clinical circumstances by means of intra-arterial thrombolysis is a responsible medical decision even in the absence of strict scientific guidelines.”<sup>10</sup> Consent is often obtained from family members or surrogates. Despite the desperate and traumatic situation, an efficient and effective discussion on stroke mechanism and treatment expectations

is necessary. Fifteen per cent of patients with a large vessel occlusion, without intra-arterial thrombolysis, may have a favorable functional outcome.<sup>7</sup> Risks of the procedure primarily concern symptomatic intracerebral hemorrhage, and consistently average around 10 %.<sup>9,10,11</sup> Recanalization rates consistently average around 75 %.<sup>11,12</sup> Recent data on the nuances of the technique highlight the unique needs of an acute ischemic stroke patient. In general, most anterior circulation strokes should perhaps be done without general anesthesia but with careful titration of sedatives with the help of the anesthesia team.<sup>13</sup> The first-line approach to recanalize a large vessel occlusion is mechanical thrombolysis. The Merci® Retrieval system (Concentric Medical, Mountain View) was the first FDA approved treatment option for embolectomy in cerebral arteries. This prospective, multicenter single-arm study with 177 patients demonstrated a combined 68 % recanalization rate, symptomatic hemorrhage rate of 9.8 %, with 36 % of patients achieving functional independence.<sup>11</sup> The Penumbra Stroke System (Penumbra, Alameda) was FDA approved in 2008 and is the most widely used thromboaspiration device in the US. This prospective, multicenter single-arm study with 125 patients demonstrated a combined 82 % recanalization rate, an 11 % symptomatic hemorrhage rate, but only 25 % of patients achieved functional independence at 90 days.<sup>12</sup> Analogous to recanalization of acute coronary occlusions, intracranial stent placement provides for rapid recanalization by entrapping the thrombus between the stent and vessel wall. The Solitaire flow restoration device with intention for thrombectomy (SWIFT) study aims to compare this closed cell, stent attached to a wire against the Merci Retrieval device with outcome measures evaluating both clinical outcomes and angiographic recanalization rates.<sup>14</sup> Many technical iterations have subsequently been reported using parts of the available tools in varying techniques tailored to the location and putative type of clot.<sup>15,16</sup>

### Endovascular Aspects of Secondary Stroke Prevention

Although less bold, the benefits of effective medical management strategies for secondary stroke prevention likely outweigh the benefits associated with interventional strategies. Such medical strategies include antiplatelet agents and medications to treat the risk factors associated with atherosclerosis, including hypertension, diabetes, and elevated lipids. Lifestyle changes, particularly smoking cessation, are equally important.<sup>17</sup>

### Carotid Artery Stenosis in the Neck

The North American carotid endarterectomy (NASCET) trial reported a 26 % risk of stroke at two years for patients with hemodynamically significant atherosclerosis at the origin of the internal carotid artery.<sup>18</sup> It is important to remember that the protocol for this often-referenced trial was created over 20 years ago, in 1987. Therefore, with current medical management, particularly with improvements in cholesterol and hypertension management strategies, the risk of recurrent stroke with such a lesion may in fact be less. Current surgical interventions to lower the risk of stroke among people with carotid artery stenosis include carotid endarterectomy (CEA) as well as carotid angioplasty and stent placement (CAS). A number of randomized clinical trials in Europe and North America have addressed the effectiveness of these procedures, which, when combined together, have mixed results. The two most recent large, randomized, sufficiently powered trials that addressed the clinically relevant safety and efficacy measures between CEA and CAS include the International carotid stenting study (ICSS) and the Carotid

revascularization endarterectomy versus stenting (CREST) trial. In ICSS, 1,713 patients from 50 mostly European academic centers showed a primary outcome of stroke, death, or procedural myocardial infarction (MI) at 120 days to be 8.5 and 5.2 % for CAS and CEA, respectively. There was a remarkably low 1.7 % rate of disabling stroke in both groups.<sup>19</sup> CREST is currently the largest trial to date comparing outcomes of both procedures in patients with >50 % carotid artery stenosis. In the trial, 2,502 patients from North America were randomized from 117 centers. Nearly all CAS procedures were done with embolic protection devices, a first.<sup>20</sup> Mean follow-up of 2.5 years showed for the primary endpoint of any stroke, MI, death, or post-procedure ipsilateral stroke to be 7.2 % for CAS and 6.8 % for CEA  $p=0.51$ . At 30 days, the incidence of stroke or death was 4.4 and 2.3 % for CAS and CEA, respectively. MI was significantly higher in the CEA group. No significant difference existed with subgroup analyses of either the symptomatic or asymptomatic groups. Therefore, the primary considerations in deciding the best management approach for secondary stroke prevention in a patient with carotid artery disease include several factors. The patient's age, the presence or absence of related cerebral ischemic symptoms; the presence, location, and morphology of the carotid artery lesions, the presence of intracranial occlusive lesions; the presence and severity of accompanying coronary artery disease; how well medical risk factors are controlled; and the experience and track record of the surgeons and interventionalists who would be chosen to perform the surgery or stenting. Also important is the patient's and family's preferences for open surgery or a radiologically monitored procedure that has no neck incision.<sup>21</sup> Both procedures entail considerable risk (for example, potentially disabling stroke), and the desired efficacy of the operations will not be achieved unless the perioperative morbidity and mortality are kept low.

### Intracranial Stenosis

Proof of clinical efficacy in using endovascular techniques, including angioplasty, balloon-mounted stents, and self-expanding stents alone or in combination is underway via randomized clinical trials. Both the Vitesse intracranial stent study for ischemic therapy (VISSIT) and Stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) trials may provide helpful data on whether endovascular revascularization confers any additional clinical benefit in secondary stroke prevention. The current literature has raised concerns for stent restenosis, as well as the significant variability in techniques, imaging protocols, and patient selection that current practice reflects. As a result, angioplasty and stent placement for the treatment of symptomatic ICAD should be performed on carefully selected patients at high-volume centers. Despite these concerns, use of angioplasty and stent placement for intracranial atherosclerosis has increased dramatically since FDA approval of Wingspan in 2005. The Wingspan Stent system involves the use of a noncompliant Gateway balloon for submaximal angioplasty followed by deployment of a self-expanding open cell nitinol stent that aims to sustain continuous outward radial force. Nearly 10,000 patients have undergone this procedure worldwide. Some of these concerns include the appropriateness and safety of a stent in the intracranial vessels, concurrent need for antiplatelet therapy, the costs, and the true impact in reducing the risk of recurrent stroke. In the extracranial carotid artery, stent-assisted angioplasty has been shown to have superior safety and efficacy compared with balloon angioplasty alone.<sup>22</sup> For symptomatic intracranial stenosis, Marks et al. published a series of over 120 patients treated with intracranial angioplasty alone. At

a mean follow-up of nearly four years, they found a future annual stroke rate, including periprocedural risks, to be between 3 and 4 %.<sup>23</sup>

Unfortunately, the current SAMMPRIS trial has excluded balloon angioplasty alone in its protocol, despite data from multiple prospective registries that suggest otherwise. Nevertheless, the data for angioplasty and stent placement, thus far, is far from conclusive. The National Institutes of Health Wingspan registry revealed a rate of stroke or death of 5 and 9 % at 24 hours and 30 days. Furthermore, at six months, 30 % of patients had in-stent stenosis of >50 %.<sup>24</sup> An unexpectedly negative finding was that in half of patients with restenosis, the new lesions were more extensive than the original lesion that had been treated.<sup>25</sup> Anecdotally, compliance with dual antiplatelet therapy in a patient with poor baseline medication compliance is a common clinical challenge. Noncompliance with dual antiplatelets after stent placement may very well be more dangerous than the original atherosclerotic lesion prior to stent placement. It seems as if stent placement may yield a host of additional potential problems that may further complicate the original problem. Lastly, the Wingspan stent alone costs approximately \$6,000 in the US, not including the overall costs of the procedure, additional adjunctive supplies, and hospitalization costs. Perhaps a more data-driven approach to the optimal management of intracranial stenosis is to consider balloon angioplasty alone. The Gateway balloon, a noncompliant balloon designed specifically for the treatment of intracranial atherosclerosis costs \$800 in the US and most recently, in a multicenter retrospective review of 74 patients at four institutions in the US, showed this approach to be a safe and effective approach to secondary stroke prevention in this patient cohort. The rate of stroke or death was 5 and 9 % at 24 hours and 30 days, respectively.<sup>26</sup> Although not yet published, the data safety monitoring board recommended halting further recruitment into the SAMMPRIS trial on April 5, 2011, whereby 451 subjects had been enrolled over two years and five months. They found that 14 % of those treated with stent placement developed stroke or death at 30 days compared to 5.8 % treated with medical therapy alone.

## Endovascular Aspects of Cerebral Aneurysm Management

Worldwide, endovascular strategies for anatomic aneurysm exclusion have become increasingly used. Long-term follow-up in the International subarachnoid aneurysm (ISAT) trial evaluating exclusively ruptured aneurysm, with a mean follow-up of nine years, has demonstrated the effectiveness of coil embolization in essentially eliminating the risk of future subarachnoid hemorrhage.<sup>27</sup> Management challenges have been focused on the ability of coil embolization to achieve the same level of durable and complete aneurysm exclusion that surgical aneurysm clipping yields. However, aneurysms greater than 1 cm and particularly those with wide necks have been shown to have relatively high rates of recurrence, all with unknown clinical ramifications leading to arbitrary re-treatments and serial imaging surveillance, sometimes over several years.<sup>28</sup> There is considerable controversy and uncertainty as to the best imaging protocol after endovascular coiling as well as what criteria should be used to determine whether re-treatment is beneficial.<sup>29</sup> Flexible, self-expanding, microcatheter-delivered, high-metal-surface-area coverage, stent-like devices often referred to as flow-diverters, represent a design change that addresses some of the limitations of current embolization strategies. These flow-diverting devices are designed to achieve aneurysm occlusion through the endoluminal reconstruction of the diseased segment of the parent artery that gives rise to the aneurysm. This approach promises a safer, more durable, and more cost-effective approach to large cerebral aneurysms.<sup>30</sup> Despite the lack of FDA approval, experience from Europe has demonstrated a considerable number of cases involving delayed post-treatment rupture. The proposed mechanism is that instead of cicatrization post flow-diverter deployment, there is aggressive thrombus-associated autolysis of the aneurysm wall possibly contributing to rupture.<sup>31</sup> A significant number of unruptured aneurysms continue to be treated. Much like the challenges associated with patient selection in acute ischemic stroke, similar work needs to be done to improve our understanding of aneurysm formation, growth, and rupture.<sup>32,33</sup> Such knowledge will likely play the largest role in finding the most effective and safe therapy. ■

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