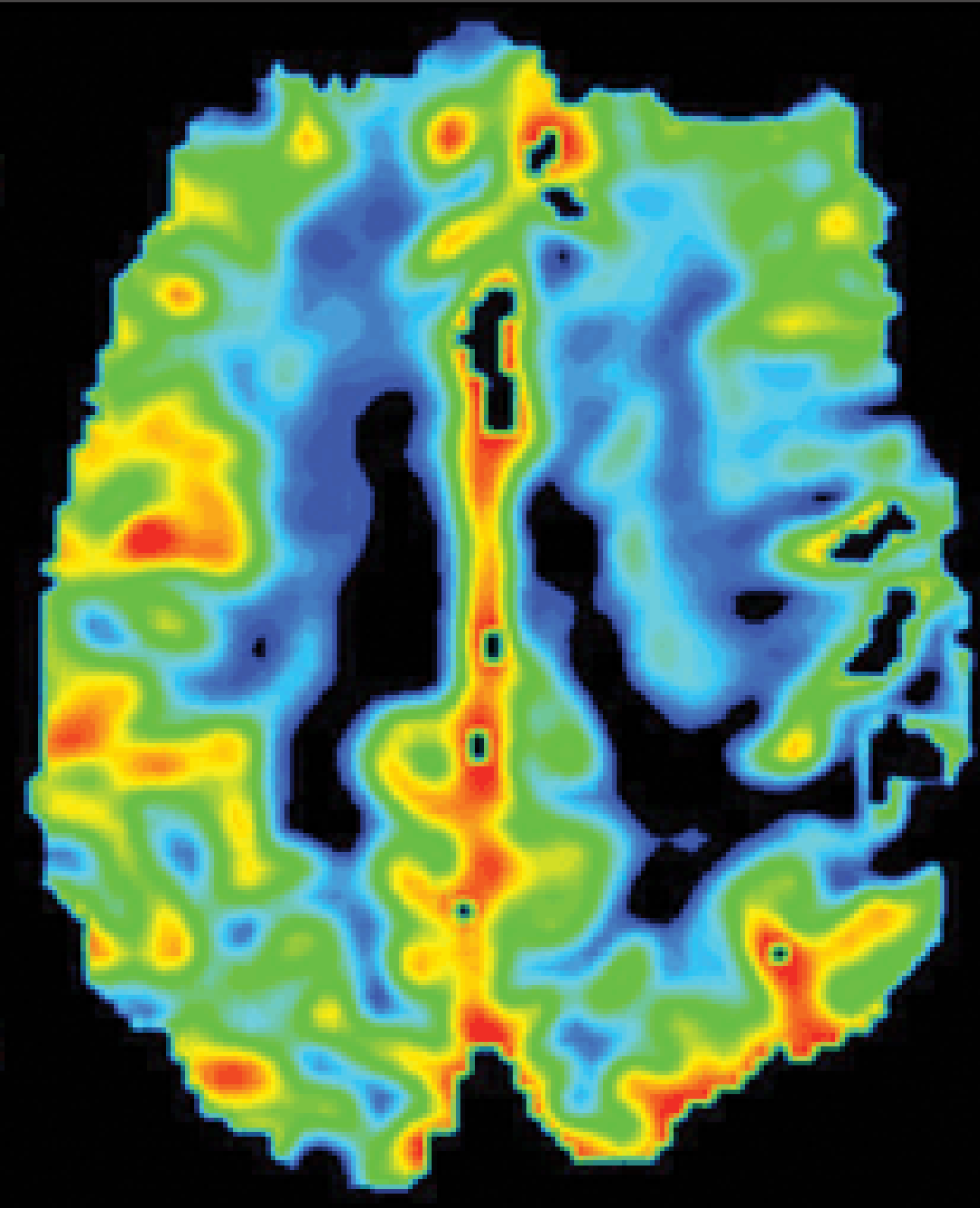

Introduction

Stroke in the new millenium

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We entered the 21st century with great optimism that cerebrovascular disease, both ischemic and hemorrhagic, would fall off the radar as a major public health issue. There was a generalized sentiment that open surgery would dwindle in importance and be replaced almost completely by minimally invasive and endovascular techniques. Neither of these predictions has come to pass. Hemorrhagic stroke continues to afflict high numbers of people earlier in life, in general, than ischemic stroke and the incidence is actually increasing in many centers as a result of the newer blood-thinning cardiac medications. Our public awareness efforts have improved regional triage networks, and more and more patients are presenting with acute cerebral ischemia within the critical therapeutic windows. On the technical side, numerous new device advances have occurred for the delivery of highly complex endovascular interventions. And the same is true on the open surgical side, with very creative new revascularization techniques becoming mainstream in all of the major centers.

This issue of *Neurosurgical Focus* provides a potpourri of offerings ranging from new information regarding the natural history of ischemic and hemorrhagic states, advanced imaging as it relates to evolving case selection criteria, evidenced-based results for medical and surgical therapies, and updates on when more traditional endovascular and surgical strategies should be utilized. The editors hope that these papers are informative to the readership and help improve outcomes from these often disastrous conditions. *(DOI: 10.3171/2011.4.FOCUS1199)*

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Evidence-based review of primary and secondary ischemic stroke prevention in adults: a neurosurgical perspective

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In this paper, the authors' aim is to provide an evidence-based review of primary and secondary ischemic stroke prevention guidelines covering most of the common risk factors and stroke etiologies for the practicing neurosurgeon. The key to stroke prevention is in the identification and treatment of the major risk factors for stroke. These include hypertension, heart disease, diabetes mellitus, dyslipidemia, and tobacco smoking. An updated approach to secondary prevention of stroke in the setting of intracranial and extracranial large vessel atherosclerosis and cardioembolism is provided along with a brief overview of pertinent clinical trials. Novel pharmacological options for prevention of cardioembolic strokes, such as new alternatives to warfarin, are addressed with recommendations for interruption of therapy for elective surgical procedures. In addition, the authors have reviewed the anticoagulation guidelines and the risk of thromboembolic complications of such therapies in the perioperative period, which is an invaluable piece of information for neurosurgeons. Less common etiologies such as arterial dissections and patent foramen ovale are also briefly discussed. Finally, the authors have outlined the quality measures in the Medicare Physician Quality Reporting System and essential guidelines for Primary Stroke Center certification, which have implications for day-to-day neurosurgical practice. *(DOI: 10.3171/2011.2.FOCUS1164)*

Key Words • evidence-based study • stroke prevention • clinical trial • CHADS2 • Physician Quality Reporting System

Across the world, stroke is considered the second leading cause of death, responsible for 4.4 million (9%) of the total 50.5 million deaths each year. According to the US National Center for Health Statistics, stroke mortality has improved, and it is now the fourth leading cause of death behind heart disease, cancer, and chronic respiratory diseases but remains the leading cause of disability among adults in the US.[63] Each year, about 55,000 more women than men have a stroke among a total of 795,000 strokes occurring each year, or about 1 stroke every 40 seconds. The prevalence of stroke in people 20 years of age and older is around 2.9% across the US population. The direct and indirect costs associated with stroke for 2010 are projected to total $7.3 billion.[63] Likewise, the prevalence of asymptomatic carotid artery stenosis greater than 50% is approximately 5%–9% in patients 65 years of age and older, which amounts to 1.3–2.4 million patients, more among men than women.[34,49] Symptomatic carotid artery stenosis with TIA occurs in 4.9 million patients, 36% of whom have moderate to severe stenosis.[40,66] In 2010, a new definition for TIA was introduced as a transient episode of focal neurological signs and symptoms not resulting in evidence of brain injury on neuroimages. This reflects the fact that many transient episodes lasting hours are associated with evidence of tissue infarction on imaging (CT or MR imaging) and are actually a stroke. As the best treatment of stroke is preventing the stroke, this article focuses on the evidence-based guidelines for primary and secondary ischemic stroke prevention with key messages important to the practicing neurosurgeon.

Abbreviations used in this paper: CAS = carotid artery stenting; CEA = carotid endarterectomy; CHD = coronary heart disease; EC-IC = extracranial-intracranial; HR = hazard ratio; ICA = internal carotid artery; INR = international normalized ratio; MCA = middle cerebral artery; MI = myocardial infarction; PFO = patent foramen ovale; PQRS = Physician Quality Reporting System; PSC = Primary Stroke Center; TIA = transient ischemic attack.

Why is an Understanding of Ischemic Stroke Subtypes Important?

For patients who have had a TIA or ischemic stroke, understanding the underlying mechanism is critical in developing an appropriate management plan. There are many classification schemes but the best is the TOAST criteria, which was developed for the Trial of ORG 10172 in Acute Stroke Treatment. ORG 10172 was an antithrombin tested

for the treatment of acute stroke.[2] The trial, evaluating low-molecular-weight heparin for acute ischemic stroke, was negative, but the classification scheme has stood the test of time. The 5 major subtypes are as follows: large artery atherosclerosis, including large artery thrombosis and artery-to-artery embolism; cardioembolism; lacunar small artery occlusion; stroke of other determined cause or determined etiology; and stroke of undetermined cause due either to an inadequate evaluation or more than one cause being identified by risk factor profiles, clinical features, and results of diagnostic tests (Table 1).

Large Artery Atherosclerosis

Patients with TIA or ischemic stroke due to large artery atherosclerosis affecting the cervicocephalic or intracranial vessels represent approximately 15% of all patients with TIA/strokes but are at highest risk for early stroke progression or recurrent ischemic stroke and are also at high risk for vascular death, largely due to cardiovascular disease. Treatment options for stroke prevention include aggressive medical management, revascularization surgeries, and endovascular revascularization with angioplasty and stenting.

Carotid Revascularization Procedures. Introduced in 1953, CEA has been established by multiple randomized clinical trials as the superior option for stroke prevention for many patients with symptomatic carotid artery stenosis (Table 2).[9,10,13,27,51] The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Stenosis Trial (ECST) are the landmark studies that demonstrated the superior efficacy of CEA with medical therapy over medical therapy alone in patients with severe symptomatic carotid artery stenosis.[27,51] After only 2 years of follow-up, the risk of ipsilateral stroke and stroke or death in patients with 70%–99% carotid artery stenosis was significantly reduced from 26%–32.3% in patients with medical therapy alone to 9%–15.8% in patients receiving both CEA and medical therapy. The risk of perioperative stroke (within 30 days of surgery) or death was 5.8%–6.7% for combined CEA and medical therapy versus 2.5%–3.3% for medical therapy alone. A lesser degree of benefit was seen for patients with 50%–69% stenosis, but this was statistically significant at 5 years of follow-up.

For asymptomatic carotid artery stenosis, the trial results are less concordant. For selected patients with significant (> 60%–80%) carotid artery stenosis, CEA can reduce the risk of perioperative stroke over medical therapy alone, but patient selection is crucial. Data from the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) reported that over the ensuing 5 years, the risk of a periprocedural stroke and death was reduced by half, from 11%–11.7% with medical therapy alone to 5.1%–6.4% with early CEA.[53] As the benefits of surgery are influenced by periprocedural risks, endarterectomy is recommended when the procedure can be performed with a perioperative risk of less than 6% for symptomatic patients and less than 3% for asymptomatic patients.[31]

Emerging in 1994, CAS offers an alternative treatment for highly selected patients with carotid artery stenosis. Several randomized trials of CAS, such as the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS)–CEA, Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), and Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), have not demonstrated superiority or noninferiority over CEA for patients eligible for both procedures.[53] However, some patients are not candidates for CEA, and for them CAS still fills an important role. The Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy (SAPPHIRE) Trial is notable for introducing several unique aspects including focusing on high-risk patients, requiring the use of an emboli-protection device, adding major adverse cardiac events to the primary end point of stroke and death, and requiring a triumvirate of a surgeon, stenting proceduralist, and neurologist to agree on patient selection.[53] Protected CAS was noninferior to CEA for patients with either a ≥ 50% symptomatic or ≥ 80% asymptomatic carotid artery stenosis, but there was a significant reduction in secondary end points of associated cranial nerve palsy, revascularizations, and length of hospital stay, which were lower among the endovascular cohort. However, these data are specific to high-risk medical and surgical patients and did not address low-to-moderate risk patients. The EVA-3S trial was prematurely terminated due to safety concerns and a futility analysis.[28] The SPACE study was also prematurely terminated after a futility analysis but identified a significant increased risk with CAS of complications in patients older than 68 years and a higher rate of in-stent restenosis as defined by ultrasonography.[31]

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) offers the most recent and comprehensive assessment of stenting versus endarterectomy

TABLE 1: Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria*

Condition	Criteria
LAA	requires >50% stenosis or occlusion of ipsilat cervicocephalic or intracranial artery, CE excluded, infarcts usually >1.5 cm
CE	infarcts usually >1.5 cm, LAA excluded; high risk: AF, prosthetic heart valve, clot, recent MI, infective endocarditis, dilated cardiomyopathy; possible: PFO, atrial septal aneurysm, mitral valve prolapse, low ejection fraction
lacunar infarct	traditional syndrome, infarct <1.5 cm, CE & LAA excluded, usually in the setting of risk factors such as hypertension & DM
other determined etiology	dissection, other vasculopathy, infection, hematological, drugs; CE & LAA excluded
undetermined etiology	no cause identified (cryptogenic) or evaluation incomplete; uncertain w/ multiple potential causes identified

* AF = atrial fibrillation; CE = cardiac embolism; DM = diabetes mellitus; LAA = large artery atherosclerosis.

TABLE 2: Summary of randomized controlled trials of surgical or endovascular interventions with best medical therapy in patients with carotid artery stenosis*

Study & Year	No. of Pts	% CA Stenosis	Symptomatic vs Asymptomatic	Study Results	Benefit From Surgical or Endo Intervention w/ Best Medical Tx
NASCET, 1991	659	70–99	symptomatic	stenosis 70–99% showed most significant reduction in ipsilat stroke risk; ipsilat stroke risk significantly decreased in pts w/ 50–69% stenosis undergoing CEA; no benefit in pts w/ <50% stenosis	yes
	858	50–69	symptomatic		yes
ECST, 1998	646	70–99	symptomatic	11.6% benefit from op after 3 yrs in pts w/ stenosis >80% (w/ variations in age & sex)	yes
	429	50–69	symptomatic		yes
VACSP, 1991	444	50–99	asymptomatic	at 11.9 mos mean FU, there was significant reduction in stroke or crescendo TIA in pts undergoing CEA (7.7%) compared w/ nonsurgical pts (19.4%); benefits were more pronounced in stenosis >70%	yes
ACAS, 1995	1662	60–99	asymptomatic	aggregate risk for ipsilat stroke, any periop stroke, or death was estimated to be 5.1% for surgical pts & 11.0% for pts treated medically	yes
ACST, 2008	3120	60–99	asymptomatic	comparing all pts randomized to immediate CEA vs all patients randomized to deferral, net 5-yr stroke risks were 6.4% vs 11.8% for all & 3.5% vs 6.1% for fatal or disabling strokes and 2.1% vs 4.2% for only fatal strokes	yes
CAVATAS, 2001	504	50–99	symptomatic	w/in 30 days of treatment (randomly assigned to endovascular vs surgical), there were more minor strokes that lasted <7 days in the endovascular group, but the no. of other strokes in any territory or death was the same; more CN palsies in the endarterectomy group than in the endovascular group; more pts had stroke during FU in the endovascular group than in the surgical group, but the rate of ipsilat non-periop stroke was low in both groups & none of the differences in the stroke outcome measures was significant	no
SAPPHIRE, 2004	334	50–99	both	at 36 mos the incidence of stroke was virtually identical for both CAS & CEA, indicating that CAS is not inferior to CEA; 3-yr incidence of stroke across the CAS treatment group members had only an average increase of 4.0% over the 30-day stroke rate	noninferior
SPACE, 2008	1200	50–99	symptomatic	in contrast to CEA the periprocedural risk of the CAS cohort seems to be dependent upon the timing of intervention, having a higher risk w/ early treatment; hence, for pts w/ symptomatic CA stenosis that can be treated early, CEA seems to be the safer method, most likely due to plaque stabilization	no
EVA-3S, 2006	527	60–99	symptomatic	30-day risk of stroke or mortality was significantly increased in the stenting group compared w/ the endarterectomy group; stenting showed a significantly lower risk for CN injury & a beneficial trend for systemic complications but a much higher risk for major local complications & TIA	no
ICSS, 2010	1713	50–99	symptomatic	incidence of stroke, death, or procedural MI was 8.5% in the stenting group compared w/ 5.2% in the endarterectomy group; risks of any stroke & all-cause death were higher in the stenting group than in the endarterectomy group	no
CREST, 2010	2502	50–99	both	among pts w/ symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, MI, or death did not differ significantly in the group undergoing CAS and the group undergoing CEA; during the periprocedural period, there was a higher risk of stroke w/ stenting & a higher risk of MI w/ endarterectomy	equivalent
COSS, 2011	191	symptomatic ICA occlusion		early termination after futility analysis of 139 pts after 2-yr FU; despite excellent graft patency & improved cerebral hemodynamics, EC-IC bypass surgery failed to provide an overall benefit on 2-yr stroke recurrence due to the much better than expected recurrence rate in the nonsurgical group	no

* CA = carotid artery; CN = cranial nerve; Endo = endovascular; FU = follow-up; Pts = patients. Studies are as follows: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CAVATAS = Carotid and Vertebral Transluminal Angioplasty Study; COSS = Carotid Occlusion Surgery Study; CREST = Carotid Revascularization Endarterectomy vs Stenting Trial; ECST = European Carotid Surgery Trial; EVA-3S = Endarterectomy Versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis; ICSS (CAVATAS-2) = International Carotid Stenting Study; NASCET = North American Symptomatic Carotid Endarterectomy Trial; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy; SPACE = Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy; VACSP = Veterans Affairs Cooperative Studies Program.

for treatment of carotid artery stenosis.[53] Comprising more than 2500 individuals with symptomatic and asymptomatic extracranial carotid stenosis and over 108 centers in the US and Canada, the primary end point studied was the composite of any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization. Over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary end point between the stenting and endarterectomy cohorts (7.2% and 6.8%, respectively; HR with stenting 1.11 [95% CI 0.81–1.51; p = 0.51]). There was no discernible treatment effect with regard to the primary end point according to symptomatic status (p = 0.84) or sex (p = 0.34), but the 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (HR 1.50; p = 0.03). In contrast, the rates among symptomatic patients were 8.0% and 6.4% (HR 1.37; p = 0.14), and the rates among asymptomatic patients were 4.5% and 2.7% (HR 1.86; p = 0.07), respectively. After this initial period, the rates of ipsilateral stroke with CAS and CEA were nonsignificant (2.0% and 2.4%, respectively; p = 0.85). In general, outcomes were slightly better after CAS in patients younger than 70 years old and better after CEA for patients older than 70 years old. The risks of stroke and death were found to be significantly higher for CAS versus CEA in symptomatic patients (6.0% vs 3.2%; HR 1.89, 95% CI 1.11–3.21) but not for asymptomatic patients (2.5% vs 1.4%; HR 1.88, 95% CI 0.79–4.42). However, the rate of periprocedural MI was higher in CEA versus CAS (1.1% vs 2.3%, p = 0.032).[9,10,31]

In the ICSS (International Carotid Stenting Study), 1713 patients were enrolled and randomized from 50 mostly European academic centers for the study, allowing a variety of stents and emboli-protection devices in 72% of CAS-treated patients, possibly more accurately reflecting the practice in the broader medical community.[31] The mean time intervals from the most recent time-to-treatment were 35 days for CAS and 40 days for CEA. The main safety end points (stroke, death, or procedural MI at 120 days) was 8.5% and 5.2% for CAS and CEA, respectively (HR 1.69; p = 0.006) At 30 days, the incidence of disabling stroke was the same in both groups (1.7%), but the incidence of fatal and nondisabling stroke was significantly higher in CAS-treated patients. Seventy-four percent of CAS-treated patients and 44% of CEA-treated patients had periprocedural strokes that occurred on the day of the procedure. Whether most strokes in the CAS-treated patients were intraprocedural could not be ascertained on the basis of this report. The incidence of procedural MI was less than 0.6% in both treatment groups, but 3 of 8 MIs were fatal. Electrocardiography and biomarkers such as creatine kinase and troponin were not required at set times before and after the procedure, suggesting that the incidence of MI was underestimated in this study. The high proportion of fatal MI, nearly 40%, is probably accounted for by an assessment that includes only extreme presentations of MI. The 30-day incidence of stroke or death in the CEA-treated group is among the best ever reported for symptomatic patients, and the results of the CAS group are in the same range as those for CEA in NASCET. The aggregate 30-day risk of stroke, death, or MI was 7.4% for CAS and 4.0% for CEA. As in other CAS versus CEA studies, more cranial nerve palsies occurred in the CEA-treated group. The frequency of severe hematoma, another finding with possible implications for morbidity, length of hospital stay, and cost are significantly higher in CEA-treated patients.[13,17,64] The investigators concluded that CEA remains the treatment of choice for symptomatic patients with severe carotid artery stenosis who are suitable candidates for surgery.[31]

Extracranial-Intracranial Bypass Surgery for Carotid Artery Occlusion. Alexis Carrel (1873–1944), a French surgeon, pioneered revascularization surgery in the early 1900s. In 1961, Pool and Potts[54] reported the first documented EC-IC bypass surgery using a plastic tube as a conduit. Concurrent advancements in surgical magnification and microsurgery paved the way for M. Gazi Yaşargil[65] to perform the first successful EC-IC bypass in 1967 for an occluded ICA in Zurich. In 1972, Yaşargil performed the first EC-IC bypass for moyamoya disease in a 4-year-old boy with right hemiplegia and anarthria.[22]

Extracranial-intracranial bypass for atherosclerotic disease was initially envisioned as an analogous procedure to coronary artery bypass surgery for cerebrovascular ischemic and occlusive disease, and the majority of bypasses in the early period were performed for vascular stenosis or occlusion. However, few data existed that directly compared outcomes with medical management against medical management and surgery. The EC/IC Bypass Study Group began a trial in 1977 to assess the efficacy of EC-IC bypass in stroke prevention for patients with stenosis or occlusion of the ICA above the level of C-2 or in the MCA. The results, published in 1985, did not show a benefit for surgery.[24] Indeed, bypass for MCA stenosis fared particularly poorly. Several limitations in this major study were cited, including the inability to stratify patients based on the extent of hemodynamic insufficiency. The smaller Japanese EC-IC Bypass Trial (JET) in 2006 noted a reduction in stroke rate in patients undergoing bypass without an overall survival benefit.[52]

A recent meta-analysis of EC-IC bypass against best medical management for symptomatic carotid artery occlusion demonstrated neither superiority nor inferiority of EC-IC bypass when compared with medical therapy alone.[30] The meta-analysis included 2 randomized controlled trials (EC-IC bypass trial and JET) and 19 nonrandom studies with a total of 2591 patients. No benefit with regard to stroke or death and dependency was found, although a trend toward benefit for surgery with regard to ischemic stroke was noted in a meta-analysis of the 2 randomized controlled trials. However, the majority of studies included patients without evaluation of their cerebral hemodynamics, limiting the utility of the analysis.

Powers and colleagues designed the carotid occlusion surgery study (COSS), which sought to randomize patients with symptomatic carotid artery occlusion defined by recent stroke and evidence of hemodynamic insufficiency by ^{15}O PET.[36,55] Based on the St. Louis Carotid Occlusion Study,[55] a stroke rate of 40% was expected in the medical arm at 2 years. An anticipated stroke rate of 24% at 2 years was expected in the surgical arm. The first patient was enrolled in 2002. With 372 randomized

patients, data collection was stopped early in June 2010 as the preliminary results of the medical arm fared much better than expected. A stroke rate of 23% at 2 years was seen in the medical arm compared with 21% in the surgical arm ($p = 0.88$). Of note, graft patency was 98% at 30 days and 96% at last follow-up.[55]

Incorporating these data from COSS with the previously published EC-IC studies, the current data demonstrate neither superiority nor inferiority of EC-IC bypass compared with medical therapy. Table 3 lists the hypotheses and outcomes of the various completed EC-IC bypass trials.

Cardiac Embolism. The classic causes of cardiac embolism include atrial fibrillation, valvular heart disease, heart failure, and recent myocardial infarction and account for approximately 20% of ischemic strokes as well as a common medical comorbidity with elderly neurosurgical patients.

Atrial Fibrillation. The projected figures might actually be larger since some patients initially diagnosed as cryptogenic will be determined to have paroxysmal atrial fibrillation at a follow-up medical evaluation or after an extended period of portable cardiac monitoring. Atrial fibrillation is the most common arrhythmia in the elderly, claiming well over 2 million American lives. This number is bound to increase as the population ages. The most important risk factor for stroke with atrial fibrillation is prior TIA or stroke; other risk factors include age older than 75 years, history of heart failure, hypertension, and diabetes.[56,57] For the majority of patients with atrial fibrillation, anticoagulation therapy is the standard of care. Multiple randomized studies have proven the superiority of anticoagulation with warfarin for preventing stroke with an overall relative risk reduction of 68%, from 4.5% in patients with placebo or aspirin compared with 1.4% in treated patients.[38] The ideal INR for these patients is 2.5 with a therapeutic range from 2.0 to 3.0. There is no evidence to support increasing the target INR because patients who have suffered a stroke have better outcomes while in the therapeutic range.

In early clinical trials, warfarin therapy was generally found to be safe with an annual major bleeding risk of 1.4% compared with 1% for placebo or aspirin. Many patients and doctors are opposed to long-term warfarin therapy, largely fueled by the fear of bleeding or requirements for monitoring. As an alternative to long-term warfarin therapy for atrial fibrillation, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) study reported a reduction in stroke risk with aspirin plus clopidogrel at 2.4% compared with 3.3% with aspirin alone in patients refusing or thought to be too high risk for anticoagulation therapy.[1] However, major bleeding was significantly greater (2% vs 1.3%) and similar to the bleeding risk with warfarin in other studies.[1]

Other anticoagulants are emerging as an alternative to warfarin therapy. Dabigatran, a direct thrombin inhibitor, was the first to receive FDA approval in September 2010. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial randomized 18,113 patients with nonvalvular atrial fibrillation and determined that the 150 mg twice daily dose of dabigatran was superior and the 110 mg twice daily dose of dabigatran was noninferior to standard warfarin therapy in the prevention of stroke (including hemorrhagic stroke) and systemic embolism. The risk of major bleeding was similar to that of warfarin at the higher dosage but less than that for warfarin at the lower dosage, and the rates of hemorrhagic stroke were

TABLE 3: Overview of the completed EC-IC bypass trials*

Study & Year	Hypothesis	Outcome
EC/IC Bypass Study, 1985	to determine whether anastomosis of STA-MCA decreases the rate of stroke & stroke-related death among pts w/ symptomatic disease of the ICA & MCA	nonfatal & fatal stroke occurred more frequently & earlier in pts who underwent op; patients w/ severe MCA stenosis & those w/ persistence of ischemic symptoms after ICA occlusion fared substantially worse in the surgical group
St. Louis Carotid Occlusion Study, 1998	evaluates prognostic abilities of hemodynamic factors for pts w/ CA occlusion	ipsilat stroke rate at 2 yrs in asymptomatic pts had a lower frequency of hemodynamic abnormalities compared w/ similar symptomatic pts w/ baseline risk factors
Cost-effectiveness Analysis of Therapy for Symptomatic Carotid Occlusion, 2002	PET screening before selective EC-IC vs medical treatment	PET screening of the cohort followed by EC-IC bypass yielded 23.2 additional QALYs (at $20,000/QALY) compared w/ medical treatment alone
JET-1, 2006	Stage II hemodynamic compromise improves w/ bypass	EC-IC bypass surgery significantly reduced the frequency of recurrent stroke for pts w/ Stage II ischemia compared w/ strict medical therapy
JET-1 subanalysis	EC-IC bypass changes brain volume & hemodynamics	EC-IC bypass increased the affected/unaffected % regional cerebral blood flow ratio
COSS, 2003	to determine whether surgical STA-to-MCA anastomoses in conjunction w/ the best medical therapy can reduce the incidence of ipsilat ischemic stroke by ≥40% in pts w/ symptomatic ICA occlusion	study concluded on June 24, 2010, based on futility analysis of 139 pts who had completed a 2-yr FU; despite well patent grafts & improved cerebral hemodynamics, EC-IC bypass surgery did not provide an overall benefit in terms of 2-yr ischemic stroke recurrence

* JET-1 = Japanese EC-IC Bypass Trial; QALY = quality-adjusted life year; STA = superficial temporal artery.

lower with dabigatran (0.10%–0.12% per year) compared with warfarin (0.38% per year).[16] Dabigatran is an attractive alternative to warfarin since it is not impacted by diet or drug interactions and requires no laboratory monitoring. However, the lack of routine laboratory monitoring is a blessing and a curse because its anticoagulant effect is not accurately reflected in routine laboratory studies such as the prothrombin time and the activated partial thromboplastin time and requires a validated thrombin time. Although short acting and requiring twice-a-day dosing, it accumulates in patients with renal failure and has no specific antidote for reversal of effect. The interconversion of warfarin, dabigatran, and heparin are performed at our institution based on the guidelines listed in Table 4.

On the horizon are several oral factor Xa inhibitors including rivaroxaban and apixaban. These agents will also be attractive alternatives to warfarin in terms of limited drug interactions and reduced bleeding risk, but they also have no routine laboratory assay or antidote.

Interrupting Anticoagulation Therapy and Risk of Thromboembolism. Deciding to interrupt anticoagulation therapy to perform an invasive procedure or surgery can be difficult. The risk of a thromboembolic event during interruption of therapy is often a factor that weighs heavily on that decision and should be guided by an understanding of patient-specific factors to stratify risk as high, moderate, or low (Table 5).[18] A more difficult situation from a neurosurgical standpoint is the treatment of patients with intracranial or intraspinal hemorrhage who have underlying conditions requiring anticoagulation, such as mechanical heart valves or chronic atrial fibrillation. In the acute setting of intracranial, subdural, or subarachnoid hemorrhages, the current practice is to discontinue all anticoagulants and antiplatelets for 1–2 weeks; however, in cases at high risk for ischemic stroke, warfarin is restarted after 7–10 days of hemorrhage due to compelling indications. Factors that would allow resuming anticoagulation in such patients include a hypertension-related hemorrhage (given that the blood pressure is well controlled), the need for secondary prevention, atrial fibrillation with a high CHADS2 score, the presence of a mechanical valve, or a hypercoagulable state. On the other hand, if there is any evidence of cerebral angiopathy or mircohemorrhages on gradient echo MR imaging or if primary prevention is only sought in the setting of atrial fibrillation with a low CHADS2 score, then anticoagulation should not be resumed immediately.

Small Artery Occlusion and Lacunar Infarcts

Small artery occlusion can present in a wide variety of lacunar syndromes. Patients in these cases do not have any evidence of cortical involvement. Imaging usually reveals a brainstem or subcortical hemispheric infarct smaller than 1.5 cm.[2,42] Such lesions occur most frequently in the putamen, basis pontis, thalamus, posterior limb of the internal capsule, and caudate nucleus. The etiology of these lacunar infarcts is attributed to hypertension, hyperlipidemia, diabetes mellitus, tobacco smoking, or a combination of these risk factors in addition to other less frequently emphasized (or addressed) risk factors such as alcohol consumption, obesity and physical inactivity, metabolic syndrome, obstructive sleep apnea, and restless leg syndrome. It is thought that these risk factors are directly or indirectly responsible for inflicting detrimental structural changes to small penetrating arteries through arterial hypertension. These changes commonly involve fibrinoid angiopathy, lipohyalinosis, and mircoraneurysm formation.[8] Other sources of cerebral ischemia such as large-vessel atherosclerosis or cardioembolism are absent. Hypertension and diabetes mellitus play a major role in small vessel ischemic disease. In fact, lacunar disease is rarely found at autopsy without a history of diabetes or hypertension.[11]

Other Determined Causes

Arterial Dissections. Carotid and vertebral artery dissections are relatively common causes of TIA and stroke, particularly among young patients, either due to head and neck trauma or occurring spontaneously.[44,60] Connective tissue disorders are known risk factors for spontaneous dissection, including fibromuscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome (Type IV), and osteogenesis imperfecta. Currently, there is no substantial available medical treatment for the aforelisted conditions. Computed tomography angiography or MR imaging and MR angiography with fat saturation protocols are used to diagnose extracranial dissection, and conventional angiography is the gold standard for the diagnosis of intracranial dissection.

Although most ischemic strokes due to dissection are a result of early thromboembolism, a minority are attributed to hemodynamic compromise.[50] Rather infrequently, these dissections can lead to formation of a dissecting aneurysm, which can also serve as a nidus of thrombus formation. Posterior fossa dissections can result in fatal subarachnoid hemorrhage, as well as cerebellar infarction.[48] The treatment paradigm for dissections generally includes anticoagulation therapy, antiplatelet therapy, angioplasty with or without stenting, or conservative obser-

TABLE 4: University Hospitals of Cleveland guidelines for newer anticoagulation therapy and reversal of anticoagulants for adults

Scenario	Guideline
converting from warfarin to dabigatran etexilate	discontinue warfarin & start dabigatran etexilate when the INR is below 2
converting from dabigatran etexilate to warfarin	starting time of warfarin is based on creatinine clearance (CrCL) as follows: CrCL >50 ml/min: start warfarin 3 days before discontinuing dabigatran etexilate; CrCL 31–50 ml/min: start warfarin 2 days before discontinuing dabigatran etexilate; CrCL 15–30 ml/min: start warfarin 1 day before discontinuing dabigatran etexilate
converting from intravenous heparin to dabigatran etexilate	start dabigatran etexilate at the time of intravenous heparin discontinuation

TABLE 5: Periprocedural risk stratification for surgical or invasive procedures in patients needing anticoagulation: CHADS2 score*

Risk Stratum	Indication for Anticoagulation			
	Mechanical Heart Valve	Embolic Stroke	AF	VTE
high	recent (w/in 6 mos) stroke or TIA; older (caged-ball or tilting disc) aortic valve prosthesis; any mitral valve prosthesis	recent stroke (w/ in 3 mos)	CHADS2 score of 5 or 6; recent (w/in 3 mos) stroke or TIA; rheumatic valvular heart disease	recent (w/in 3 mos) VTE; severe thrombophilia (e.g., deficiency of protein C)
moderate	bileaflet aortic valve prosthesis & 1 of the following: congestive heart failure, hypertension, age >75 yrs, diabetes, AF, or prior stroke or TIA	Hx of stroke (>3 but <6 mos prior)	CHADS2 score of 3 or 4	VTE w/in past 3–12 mos; nonsevere thrombophilic conditions; recurrent VTE; active cancer (treated w/in 6 mos or palliative)
low	bileaflet aortic valve prosthesis w/o AF & no other risk factors for stroke	Hx of stroke (≥6 mos prior)	CHADS2 score of 0–2 (& no prior stroke or TIA)	single VTE occurred >12 mos ago & no other risk factors

* Data were obtained from the study by DeLoughery. The CHADS2 score is calculated as follows: congestive heart failure (1 point), hypertension (1 point), age older than 75 years (1 point), diabetes (1 point), and stroke (2 points). Abbreviation: VTE = venous thromboembolism.

vation without specific medical therapy. As established, risk of stroke is greatest within the first few days after initial vascular injury, and early anticoagulation with heparin or low-molecular-weight heparin has been recommended as the mainstay of treatment.[59]

A Cochrane systematic review of 327 patients with carotid artery dissection in 26 case series reported no statistically significant difference in death or disability between antiplatelet and anticoagulant therapy (23.7% with antiplatelet vs 14.3% with anticoagulant; OR 1.94; 95% CI 0.76–4.91).[31,45] Recurrent stroke was seen in 1.7% of patients receiving anticoagulation, 3.8% receiving antiplatelet therapy, and 3.3% receiving no therapy. Another systematic review that included 762 patients with carotid or vertebral artery dissection from 34 case series showed no significant difference in risk of death (antiplatelet: 5 [1.8%] of 268 patients; anticoagulation: 9 [1.8%] of 494 patients; $p = 0.88$), stroke (antiplatelet: 5 [1.9%] of 268 patients; anticoagulation, 10 [2.0%] of 494 patients; $p = 0.66$), or stroke and death.[47] Of 2 larger studies, including a retrospective cohort of 432 patients with carotid or vertebral artery dissection[61] and a prospective cohort of 298 individuals with only carotid artery dissection,[33] one reported a much lower risk of subsequent stroke: 0.3% over the 3- to 12-month period after dissection. The latter study also included a nonrandomized comparison of anticoagulation versus antiplatelet therapy and found no difference in risk of recurrent stroke (0.5% vs 0%, $p = 1.0$), and major bleeding events occurred more often than recurrent stroke with both interventions (2% vs 1%). These observational data reveal that antiplatelet therapy and anticoagulation are associated with a similar risk of subsequent stroke, the latter being less safe. Dissections that persist pose a low risk for subsequent stroke and rupture, which do not warrant aggressive treatment.[31,37] Many physicians recommend limited physical activity for those with a cervical arterial dissection but no real data exist to define the limits of activity for these patients.

Dissections usually heal over time, and patients are commonly maintained on antithrombotic therapy for at least 3–6 months, which is determined by image verification of recanalization of the dissected artery.[15,25,26] The relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection. For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite optimal medical therapy, endovascular therapy (stenting) may be considered. Patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who are not candidates for endovascular therapy or in whom it has failed may be considered for surgical treatment.[31]

Patent Foramen Ovale. A PFO is an embryonic defect in the interatrial septum that allows right to left passage of emboli. Although thrombus is rarely detected within the heart, it is a presumed cause, supported mostly by its higher frequency in patients with cryptogenic stroke, particularly those younger than 55 years, compared with the 15%–25% prevalence in the adult population.[19] Although endovascular device closure of the PFO has gained considerable interest, the recently completed CLOSURE study did not support superiority of the Starflex endovascular PFO closure device compared with medical therapy alone for stroke prevention.[32]Antiplatelet therapy remains the treatment of choice for patients with ischemic stroke (along with optional anticoagulation therapy), and other trials of PFO closure devices are ongoing. The presence of a PFO can pose a unique challenge for neurosurgical patients during operations performed in the sitting position. The risk of venous air embolism is reported to be 23%–45% and can be associated with paradoxical cerebral embolism in up to 14% of patients.[29,58]

Current Treatment for Stroke From Noncardioembolic, Atherosclerotic Source or Unidentified Cause

For patients who suffered a noncardioembolic stroke or a TIA, the strongest evidence supports antiplatelet therapy as a first of line of treatment to prevent future strokes. Initial antiplatelet therapy can be in the form of aspirin (50–

325 mg), clopidogrel 75 mg monotherapy, or a combination or aspirin 25 mg with extended-release dipyridamole 200 mg twice daily depending on each patient's underlying conditions, limiting allergies, and tolerance.[12,20,21,31] There are no good data on patients in whom aspirin therapy has failed, and although many physicians use this opportunity to increase the dosage of aspirin, switch to an alternative antiplatelet therapy, or switch to anticoagulation, there are no data to support these practices. Alternative antiplatelet therapies are available for CHD, such as prasugrel, a third generation of thienopyridine. However, it is not indicated in patients with a history of TIAs or strokes because of the increased risk of intracranial bleeding. Studies evaluating lower doses are ongoing.

Risk Factor Identification and Management for Primary and Secondary Stroke Prevention

Hypertension

Hypertension is the single most important risk factor for stroke due to its impact on ischemic and hemorrhagic stroke and its prevalence in the population; therefore, blood pressure measurement should be a routine part of any patient interaction. Around 72 million Americans suffer from hypertension, defined as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg[35,43] with normal blood pressure lower than 120/80 mm Hg. There is a clear and graded association between elevated blood pressure and stroke risk starting at a systolic blood pressure of 115 mm Hg. Meta-analysis of randomized controlled trials has shown that lowering of blood pressure is associated with a 30%–40% reduction in stroke risk.[20] The risk continues to decrease with further reduction of blood pressure and can be achieved with a variety of medications, with available data prioritizing the use of angiotensin-converting enzyme inhibitors and diuretics, and lifestyle interventions such as weight loss, consuming a diet rich in fruits, vegetables, and low-fat dairy products, regular aerobic exercise, and limiting daily alcohol intake to ≤ 2 servings for men and ≤ 1 servings for nonpregnant women.

Dyslipidemia

Epidemiological studies have long established a strong correlation between abnormal cholesterol levels in blood and CHD, which is also present for atherosclerotic stroke subtypes. Meta-analysis of more than 90,000 patients included in statin trials showed that the larger the reduction in low-density lipoprotein cholesterol (LDL-C), the greater the reduction in all stroke subtypes (both ischemic and hemorrhagic). The Stroke Prevention by Aggressive Reduction Levels (SPARCL) study of 4731 TIA or stroke patients without a history of CHD supports the use of intensive statin therapy for secondary stroke prevention. High-dose atorvastatin (80 mg daily) significantly reduced the risk of stroke from 13.1% to 11.2%; the 18% relative risk reduction means that 258 patients must be treated to prevent 1 recurrent stroke over the course of 1 year.[6] Guidelines recommend statin therapy with intensive lipid-lowering effects for patients with ischemic stroke or TIA who have an LDL (low-density lipoprotein) cholesterol ≥ 100 mg/dl and, if accompanied by known CHD, the target in these patients should be either a 50% reduction in LDL or an LDL lower than 70 mg/dl. If these patients suffer from low HDL (high-density lipoprotein) cholesterol (≤ 40 mg/dl), they may be considered for treatment with niacin or gemfibrozil.[31]

Diabetes

The prevalence of diabetes is estimated at about 8% in the US.[7] Among patients who suffered an ischemic stroke, the prevalence of diabetes increases to as high as 33%.[41,46] Diabetic patients who suffer a stroke are also at an increased risk of morbidity and mortality in comparison with nondiabetic stroke patients. In addition, diabetes is an independent risk factor for recurrent strokes; it has been estimated to be the culprit in 9.1% of recurrent strokes.[39] Criteria that support the diagnosis of diabetes mellitus are a fasting glucose ≥ 126 mg/dl, hemoglobin A1C ≥ 6.5%, or a random fasting glucose higher than 200 mg/dl.[7] In addition, an A1C higher than 7% is indicative of poor control of hyperglycemia. Several randomized clinical trials of intensive glucose management in persons with diabetes who had a history of cardiovascular disease, stroke, or other risk factors could not demonstrate a reduction in cardiovascular events and deaths in the tight glycemic control group. However, tight control of hypertension and dyslipidemia is associated with a significant reduction in all vascular events. An ongoing trial at the National Institutes of Health, the Insulin Resistance Intervention after Stroke (IRIS) trial is currently evaluating whether treatment with the insulin sensitizer pioglitazone will reduce secondary stroke or MI.

Unhealthy Lifestyles: Tobacco Abuse, Excessive Alcohol Intake, and Physical Inactivity

In addition, promoting smoking cessation, encouraging regular physical activity, and limiting alcohol intake are proven to be indispensable in secondary stroke prevention. Counseling stroke patients on the importance of smoking cessation and prescribing oral cessation medications are all effective measures for helping smokers quit. It is recommended that patients who have had ischemic stroke or TIA who are able to engage in physical activity do so regularly. Beneficial physical activity is defined as at least 30 minutes of moderate intensity physical exercise that is vigorous enough to cause sweating or an increase in heart rate as often as 1–3 times a week.

Joint Commission and Primary Stroke Center Certification

Many US hospitals lack the necessary infrastructure and organization required to triage and treat patients with stroke quickly and efficiently, and do not deliver adequate stroke care. Even though a 2003 statewide assessment of hospital-based stroke care and prevention in North Carolina demonstrated that many hospitals had improved in key elements necessary to provide care over the 5-year study, the data indicate that the hospitals were still lack-

ing in a number of areas, including the use of a tissue plasminogen activator protocol (54%), the availability of a neurologist (30%) or interventional radiologist (9%) at all times, use of stroke care maps (30%), presence of a stroke unit (19%) and a stroke team (16%), and a sufficient community awareness program (27%). While this evidence supports a growth in infrastructure, there is room for improvement.[4,63]

In 2005, the Brain Attack Coalition published recommendations for the establishment of comprehensive stroke centers. A PSC stabilizes and treats acute stroke patients, providing initial acute care.[62] Primary Stroke Centers are able to appropriately use tissue plasminogen activator and other acute therapies such as stabilization of vital functions, provision of neuroimaging procedures, and management of intracranial pressure and blood pressure. Comprehensive stroke centers treat patients at all needed levels of care, even in cases of the most complex strokes. They offer specialized diagnostics and other interventions, including tertiary care centers, and have the infrastructure and personnel necessary for highly technical procedures. Based on patient needs and the hospital's capabilities, they either admit patients or transfer them to a comprehensive stroke center. As of January 2006, there were 174 PSCs certified by the Joint Commission on Accreditation of Healthcare Organizations in the US.[3]

According to the Joint Commission and recommendations from Brain Attack Coalition's task force, specific standards for PSC certification include the following elements: standardize methods of delivering the recommendations established by the Brain Attack Coalition's task force, support a patient's self-management activities, tailor treatment and intervention to individual needs, standardize performance measures data to improve treatment plans, demonstrate compliance with clinical practice guidelines, and promote the flow of patient information across settings and providers while protecting patient rights, security, and privacy.[5] Effective January 1, 2010, PSCs must collect and report data on National Inpatient Hospital Quality measures for stroke, which include venous thromboembolism prophylaxis, discharge of patients on a regimen of antithrombotic therapy, anticoagulation therapy for atrial fibrillation/flutter, thrombolytic therapy, and antithrombotic therapy by end of hospital Day 2.[5]

Through standardizing care and strict compliance with a universal set of measures nationwide, hospitals and providers are able to provide improved quality of stroke management, increased efficiency of patient care, reduced mortality and morbidity, reduced costs to the health care system, and improved patient satisfaction.

Physician Quality Reporting System in Stroke Management

To participate in the 2011 PQRS, eligible professionals may choose to report information on individual quality measures or on a group of measures. Professionals who meet the criteria for satisfactory submission of quality measures and submit data via one of the reporting mechanisms during a 2011 reporting period will qualify to earn a PQRS payment equal to 1.0% of their total estimated Medicare Part B Physician Fee Schedule allowed charges for covered professional services furnished during that same reporting period.

To qualify to earn a PQRS incentive payment, eligible professionals must meet specified criteria for satisfactory reporting during the applicable reporting period. Given the broad array of specialties and settings in which eligible professionals practice, Centers for Medicare and Medicaid Services has designed the PQRS program in a manner that gives eligible professionals flexibility in determining how best to integrate PQRS quality measures reporting into their practice work flows. Practitioners participating in stroke management already engage in the following measures: deep venous thrombosis prophylaxis for stroke or intracranial hemorrhage, discharging patients on antiplatelet therapy, screening for dysphagia in the acute setting, prescribing anticoagulation for atrial fibrillation, and providing rehabilitation services (Table 6). Also, management options such as CEA, the use of an arterial patch graft during conventional CEA, and thrombolytic therapy are easily reportable measures included in the PQRS program.[14] Providers have already incorporated the above as standards of best practice within stroke care. The PQRS incentive program simply offers providers a financial incentive to aid in standardizing patient care and therefore improve the quality of practice across various institutions.

Conclusions

We have provided a comprehensive update on the evi-

TABLE 6: Highlighted 2011 PQRS Measure Specifications for Reporting of Individual Measures: role of stroke prevention*

Measure No.	Measure Title
31	Stroke and Stroke Rehabilitation: Deep Vein Prophylaxis (DVP) for Ischemic Stroke or Intracranial Hemorrhage
32	Stroke and Stroke Rehabilitation: Discharged on Antiplatelet Therapy
33	Stroke and Stroke Rehabilitation: Anticoagulant Therapy Prescribed for Atrial Fibrillation at Discharge
35	Stroke and Stroke Rehabilitation: Screening for Dysphagia
36	Stroke and Stroke Rehabilitation: Consideration of Rehabilitation Services
158	Carotid Endarterectomy: Use of Patch During Conventional Carotid Endarterectomy
187	Stroke and Stroke Rehabilitation: Thrombolytic Therapy

* Measures were obtained from https://www.cms.gov/apps/ama/license.asp?file=/pqrs/downloads/2011_PhysQualRptg_MeasureSpecificationsManual_033111.pdf.

dence-based guidelines for primary and secondary stroke prevention including risk factor management. Common neurosurgical issues such as perioperative adjustment of anticoagulation, management of atrial fibrillation, and incorporating the CHADS scoring method are discussed along with new pharmacological options for prevention of cardioembolic strokes. The new reporting incentives in the changing medical reimbursement scene and hence the mandatory guidelines for PSC certification may have a much greater impact on the contemporary vascular neurosurgical practice.

Disclosure

Dr. Sila is a consultant for Abbott Vascular and Hoffman-La Roche.

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Evidence-based treatment of carotid artery stenosis

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Carotid atheromatous disease is an important cause of stroke. Carotid endarterectomy (CEA) is a well-established option for reducing the risk of subsequent stroke due to symptomatic stenosis (> 50%). With adequately low perioperative risk (< 3%) and sufficient life expectancy, CEA may be used for asymptomatic stenosis (> 60%). Recently, carotid angioplasty and stent placement (CAS) has emerged as an alternative revascularization technique. Trial design considerations are discussed in relation to trial results to provide an understanding of why some trials were considered positive whereas others were not. This review then addresses both the original randomized studies showing that CEA is superior to best medical management and the newer studies comparing the procedure to stent insertion in both symptomatic and asymptomatic populations. Additionally, recent population-based studies show that improvements in best medical management may be lowering the stroke risk for asymptomatic stenosis. Finally, the choice of revascularization technique is discussed with respect to symptom status. Based on current evidence, CAS should remain limited to specific indications. *(DOI: 10.3171/2011.3.FOCUS1143)*

Key Words • carotid endarterectomy • carotid angioplasty and stent placement • evidence-based medicine

Stroke accounts for 1 in every 18 deaths in the US, and leaves nearly 30% of those afflicted permanently disabled.[3,49] Worldwide, stroke is a leading cause of disability and the third leading cause of death, with 5 million deaths reported annually.[7] In the US alone, each year nearly 800,000 individuals suffer a stroke, with one-quarter of those cases being recurrent strokes.[49] Despite advances in stroke prevention, imaging, treatment, and rehabilitation, the costs of care continue to increase. In 2008, the costs of stroke care were $65 billion/year.[16] The estimated cost of care for patients with stroke in 2010 is $73.7 billion, with overall costs expected to exceed $2 trillion by 2050.[49]

One of the most important causes of ischemic stroke is carotid atheromatous disease, representing approximately 20% of the total incidence of this type of stroke.[31] Severe carotid stenosis is the most important risk factor for recurrent stroke in symptomatic patients with carotid atheromatous disease. Several large randomized trials have shown marked early benefit from CEA. Timely CEA (within 2 weeks from onset of symptoms) results in an absolute risk reduction of 15.6% and a relative risk reduction of 52% over best medical management.[4,18,35,37,41] Results of these large-scale trials and their pooled patient-level meta-analyses have made CEA the standard of care in patients with severe (> 70%) symptomatic carotid stenosis, and have provided Level I/A evidence for decisions regarding symptomatic patients with lesser degrees of stenosis by demonstrating modest benefits of CEA for symptomatic 50%–69% stenosis, and no benefit for stenosis < 50%.[10,41] In contrast, patients with asymptomatic carotid stenosis have a vastly different natural history, with much lower upfront risks of stroke. Two large-scale randomized controlled trials have demonstrated modest benefits achieved over several years from treatment.[18,28] Indeed, significant improvements in stroke prophylaxis achieved by BMT have led to a reappraisal of CEA for asymptomatic stenosis, with current and upcoming trials of carotid revascularization now including an arm for BMT.[1,39]

Abbreviations used in this paper: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; BMT = best medical treatment; CAS = carotid angioplasty and stent placement; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy versus Stenting Trial; DWI = diffusion-weighted imaging; ECST = European Carotid Surgery Trial; EVA-3S = Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS = International Carotid Stenting Study; MI = myocardial infarction; NASCET = North American Symptomatic Carotid Endarterectomy Trial; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE = Stent-Protected Percutaneous Angioplasty of the Carotid artery versus Endarterectomy.

Over the past decade, CAS has emerged as a potential alternative to CEA. The appeal of CAS has been driven in part by patient, physician, and hospital preferences for less invasive procedures, with underlying assumptions that this would lead to a reduction in complications, length of stay, and cost, although the latter 2 appear to not be borne out in practice.[25,28,38,51] The choice between CEA and CAS has therefore been primarily centered around which technique provides better clinical outcomes. Multiple CAS case series and registries have emerged, of mixed quality and with conflicting data, which will not be reviewed here. Unfortunately, large-scale randomized controlled trials comparing the 2 revascularization techniques have proven controversial, and have not convincingly identified a superior technique.[11,17,22,26,33,34,40,50] The most recent trial, CREST, was designed to avoid prior pitfalls and to reach definitive conclusions regarding choice of revascularization technique for carotid stenosis, although interpretation of its results has not been free of controversy either.[2,5]

Health care is undergoing a radical transformation. The economic environment has challenged health care organizations to deliver optimal services in the face of compromised cash flows, reduced resources, and declining margins. There is an overwhelming need for health care policy makers to audit current practices to ensure incorporation of cost-effective guidelines without compromising quality and outcomes of care. Our objective in this review of trials comparing CEA, CAS, and BMT in patients with carotid artery stenosis was to analyze existing evidence and cite comparative measures to consider while making such treatment decisions.

Trial Design

The trials of CEA compared with BMT were designed as superiority trials, whereas some of the recent trials comparing CAS to CEA were designed as noninferiority trials. As an example, NASCET, ACST, and ACAS tested the proportion of stroke following CEA (P_{CEA}) and BMT (P_{BMT}) to show that one treatment is superior to the other. In this case, the null hypothesis was defined as H_0: $P_{CEA} = P_{BMT}$. The 2-sided alternate hypothesis was defined as H_A: $P_{CEA} \neq P_{BMT}$. The data analysis would either 1) reject the null hypothesis (the proportions are different), or 2) fail to reject the null hypothesis. Although there is an equal sign in the null hypothesis, equivalence cannot be proven when the null hypothesis is not rejected. It can only be said that there is not enough evidence to show a difference.

Instead of testing for superiority, several trials of CEA and CAS have used a noninferiority design. The SAPPHIRE, EVA-3S, and SPACE trials tested whether the upper limit of the CI for the difference between P_{CEA} and the proportion of stroke following CAS (P_{CAS}) is within a prespecified margin (δ).[33,40,50] The null hypothesis is H_0: upper limit of the CI ($P_{CEA} - P_{CAS}$) ≥ δ, whereas the alternate hypothesis is H_A: upper limit of the CI ($P_{CEA} - P_{CAS}$) < δ.[6,48]

Examples using superiority and noninferiority are illustrated in Fig. 1. The prespecified δ margin for noninferiority for each trial is indicated *(dashed line)*. In EVA-3S, the 95% CI exceeds 2%; thus, it cannot reject the null hypothesis for noninferiority. The 95% CI does not include zero, therefore demonstrating superiority of CEA over CAS. The SPACE trial failed to show noninferiority and it failed to show superiority; the CI crosses the 2.5% δ margin (fails to show noninferiority) and contains zero (failing to show superiority). The SAPPHIRE (noninferiority design), CREST (superiority design), and ICSS (superiority design) trials are presented for comparison.

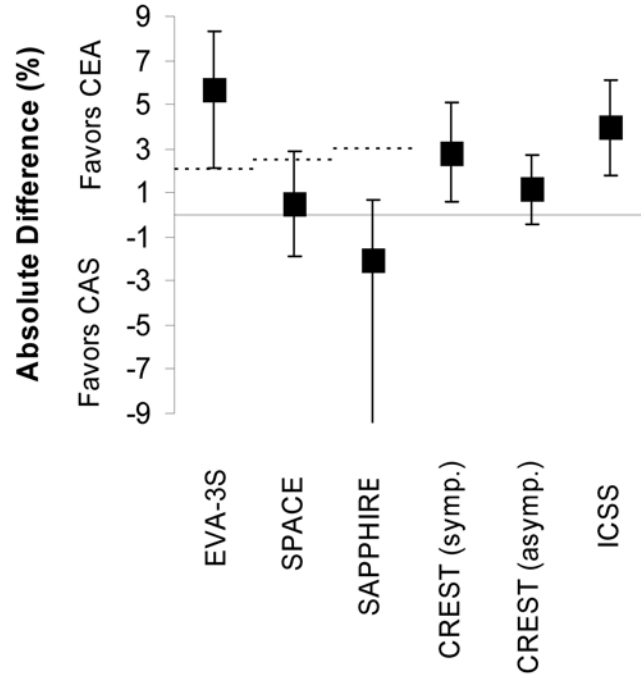

Fig. 1. All numbers are 30-day stroke/death rates (except SAPPHIRE; only stroke/death/MI rates are available), are analyzed by intention-to-treat (except ICSS; only per-protocol data are available), and are for symptomatic patients (except where indicated for CREST).

Symptomatic Carotid Stenosis: CEA Versus BMT

Three key trials have compared the effectiveness of CEA (combined with BMT) versus BMT alone for symptomatic carotid stenosis: NASCET, Veteran's Affairs, and ECST.[4,18,35,37] The first pivotal results of NASCET, examining 659 patients with > 70% stenosis, found an absolute risk reduction of 16.5% and a relative risk reduction of 51% in any stroke or perioperative death after CEA at 2 years.[37] Similar results were observed in the other 2 trials, despite differences between them regarding aspirin dosage, time from symptoms to CEA, sex, degree of stenosis, and its measurement. Because of the overall similarity between the 3 trials and the availability of individualized patient-level data, a meta-analysis incorporating uniform (NASCET) criteria for stenosis measurement and outcomes was performed (6092 total patients).[41] This meta-analysis validated NASCET's results for CEA based on degree of stenosis (Table 1), with no benefit in stenosis < 50%, modest benefit in stenosis 50%–69%, high benefit for stenosis 70%–99%, and a trend toward benefit for near-occlusion at the 2-year but not at the 5-year follow-up.[4,18,35,37,40]

TABLE 1: Benefit of CEA for symptomatic carotid artery stenosis*

Degree of Stenosis	% ARR	p Value	FU (yrs)
near occlusion	5.6/−1.7†	0.19/0.9†	2/5
70%–99%	16.0	<0.001	5
50%–69%	4.6	0.04	5
30%–49%	3.2	0.6	5
<30%	−2.2	0.05	5

* Pooled results of ECST, NASCET, and Veteran's Affairs trials (Rothwell et al., 2003; trial #8008), demonstrating reduction in ipsilateral carotid stroke or any perioperative stroke/death after CEA for each stenosis category. Abbreviations: ARR = absolute risk reduction; FU = follow-up.

† Data are given as the 2-year/5-year results.

The added power of pooled CEA data has permitted subgroup analyses to demonstrate a significant differential benefit in certain groups of patients: men, patients ≥ 75 years of age, and those presenting with stroke rather than transient ischemic attack derive greater benefit from CEA for symptomatic stenosis > 50%.[42] Women derive less benefit from CEA, particularly in the 50%–69% stenosis category. A key finding of both NASCET and subsequent pooled meta-analyses was that the risk of recurrent stroke was primarily within the first few weeks following the initial presenting event (especially in women).[4,37,42,43] This led to recommendations that CEA be performed within 2 weeks of symptom onset.[10,15,42] Similar to that in patients treated with BMT, the risk of stroke after CEA is mostly up front (within the 30-day periprocedural period), with otherwise durable benefits beyond 30 days when performed successfully.[18,42] As a result, the overall benefit from CEA is very dependent on a low perioperative 30-day complication (stroke/death) rate, with a cutoff threshold set at 6%.[10]

Symptomatic Carotid Stenosis: CEA Versus CAS

In 2004, SAPPHIRE was the first multicenter randomized trial of CAS versus CEA.[50] The SAPPHIRE study was a noninferiority trial that enrolled patients with both symptomatic and asymptomatic stenosis who were at "high surgical risk" associated with CEA. This trial did not present the 30-day risk of stroke or death as a means of benchmarking against American Heart Association performance guidelines. Instead, the primary end point included stroke, death, or MI (Table 2[11,17,22,26,33,34,40,50]). Although the incidence of the composite primary end point appeared to be lower in CAS (2.1%) compared with CEA (9.3%), this difference did not reach statistical significance. Numerous criticisms have been leveled against this trial, including the following: 1) the inclusion of MI in a composite end point (traditionally only including stroke/death); 2) mixing symptomatic and asymptomatic "high surgical risk" patients, the majority (> 70%) of whom were asymptomatic and who might have been most effectively treated with BMT rather than CAS or CEA; 3) use of dual antiplatelet agents in CAS versus a single antiplatelet agent in CEA; 4) the fact that > 22% of each group had restenosis after prior CEA (a much higher risk for repeat CEA); and 5) high prevalence of contralateral occlusion (> 25% of patients treated with CEA and > 23% of patients treated with CAS), which doubled the risk related to CEA in NASCET.[11,12,20,36]

Two other large-scale noninferiority trials of CAS compared with CEA have taken place since SAPPHIRE, attempting to answer these criticisms by more specific selection criteria, in particular restricting entry to symptomatic patients (Table 2). First, EVA-3S showed that CEA was superior to CAS in the 30-day periprocedural period (see Fig. 1).[33] The SPACE trial failed to show noninferiority during the periprocedural period at their prespecified δ margin of 2.5%.[40] Subsequent criticisms of these trials include the following: 1) premature stoppage at 1200 patients (SPACE trial) due to futility; 2) relative operator inexperience (particularly in the CAS group); and 3) nonuniform use of embolic protection devices.

The CREST and ICSS are the 2 most recent large-scale trials comparing CEA with CAS for carotid stenosis. They were in part designed to answer criticisms of prior CEA versus CAS trials.[11,26] Both trials reported data separately for asymptomatic versus symptomatic patients (CREST) or only included symptomatic patients (ICSS); both had rigorous selection of proceduralists based on operator experience (verified during a lead-in phase in CREST); both mandated (CREST) or recommended (ICSS) use of embolic protection devices; and both presented traditional (stroke/death) as well as composite (stroke/death/MI) end points (Table 2).

The primary end point of CREST, in a population of asymptomatic and symptomatic patients, was stroke, MI, or death during the periprocedural period, or any ipsilateral stroke within 4 years after randomization. There was no difference in the composite primary end point for CAS (7.2%) versus CEA (6.8%, HR 1.11 for stenting, 95% CI 0.81–1.51). However, the difference in the 4-year stroke or death rate did reach statistical significance for CAS (6.4%) versus CEA (4.7%, HR 1.5, 95% CI 1.05–2.15). Patients who underwent CEA were less likely to have a stroke (4.1% for CAS vs 2.3% for CEA, $p = 0.01$) or die (0.7% vs 0.3%, respectively; $p = 0.18$), but more likely to have an MI (1.1% vs 2.3%, respectively; $p = 0.03$). The SAPPHIRE study also reported excess MI after CEA, although more recent results from ICSS contradict these findings.[23]

The long-term effects of MI and stroke were different in CREST. At 1 year postprocedure, quality of life was significantly impacted by stroke but not by MI. The increased rate of MI in patients treated with CEA has been ascribed to the following factors: 1) the more frequent use of general rather than local anesthesia in patients undergoing CEA (although choice of anesthesia failed to play a part in post-CEA MI in the General Anaesthesia Versus Local Anaesthesia for carotid surgery [GALA] trial); and 2) use of dual (aspirin and clopidogrel) rather than single antiplatelet agents in patients undergoing CAS.[30]

The CREST investigation did not show a difference in composite primary end points for symptomatic revascularization compared with asymptomatic revascularization. However, the natural history and acceptable periop-

TABLE 2: Literature review of symptomatic carotid stenosis: CEA versus CAS*

Authors & Year	Trial	No. of Pts		% 30-Day Stroke/Death (guidelines: <6%)			% 30-Day Stroke/Death/MI (guidelines: none)			% LT Stroke/Death			% LT Stroke/Death/MI			
		CEA	CAS	CEA	CAS	p Value	CEA	CAS	p Value	CEA	CAS	p Value	CEA	CAS	p Value	LT FU Period
Yadav et al., 2004; Gurm et al., 2008	SAPPHIRE†	167	167				9.3	2.1	0.18	21.7	32.0	ND				3 yrs
Mas et al., 2006; Mas et al., 2008	EVA-3S	259	261	3.9	9.6	0.01				21.6	26.9	0.08				4 yrs
Ringleb et al., 2006; Eckstein, 2008	SPACE‡	599	584	6.16	7.51	NS				9.7	10.5	NS				2 yrs
Brott et al., 2010	CREST§	1262	1240	3.2	6.0	0.02	5.4	6.7	0.30	6.4	8.0	0.14	8.4	8.6	0.69	4 yrs
ICSS Investigators, 2010	ICSS¶	858	855	3.4	7.4	0.0004	4.0	7.4	0.003				5.2	8.5	0.006	120 days

* In most of the comparisons the p value is for the hazard ratio; for SAPPHIRE it is the p value of the log-rank test. Abbreviations: LT = long term; ND = not done; NS = not significant; pts = patients.

† In SAPPHIRE, long-term events were defined as death or ipsilateral stroke only.

‡ In the SPACE study, long-term follow-up events were defined as ipsilateral stroke or vascular death.

§ In CREST, long-term follow-up events were defined as periprocedural stroke or death, plus any ipsilateral stroke. Long-term stroke/death/MI is defined as any periprocedural stroke, MI, or death, or postprocedural ipsilateral stroke.

¶ In ICSS, 30-day data were per-protocol, not intention-to-treat results. The long-term events were defined as stroke, death, or periprocedural MI.

erative complication rates (6% vs 3%) are very different for symptomatic versus asymptomatic patients. Thus, these 2 groups will be presented separately, beginning with symptomatic patients (Table 2). The 30-day stroke or death rate for CAS was 6%, and for CEA it was 3.2% (HR 1.89, 95% CI 1.11–3.21; $p < 0.05$), implying that CEA has a far better short-term prognosis in patients with symptomatic stenosis. The long-term results were less clear, with 4-year rate of stroke or death for symptomatic patients being 8% for CAS and 6.4% for CEA (HR 1.37, 95% CI 0.9–2.09; $p = 0.14$). Although this suggests a longer-term benefit with CEA rather than CAS in symptomatic patients, these rates do not reach statistical significance due to a lack of power (the analysis was powered to look at symptomatic and asymptomatic groups combined).

A critique of CREST has been the use of biochemical markers for MI and electrocardiography studies in all patients, effectively screening for "silent MI."[2,5] This aspect of trial design may explain why quality of life in CREST patients was not significantly affected by MI at 1 year postprocedure. The authors have argued that inclusion of silent MI as a surrogate end point for future cardiovascular-related death was not necessary when the cause of death was directly examined within the trial, and that screening for silent MI should be counterbalanced within the trial by also screening for silent stroke, namely with postprocedural MR imaging studies. In ICSS, prospectively collected MR imaging studies demonstrated significantly fewer lesions on diffusion-weighted imaging after CEA versus CAS, which appears to be evident in a meta-analysis by Schnaudigel et al., as well as in case series published after that meta-analysis (Table 3[9,13,29,45–47,53]). Interestingly, new lesions appear more frequently on diffusion-weighted images obtained after CAS both inside (37% vs 10%, $p < 0.01$) and outside (14.5% vs 0.01%, $p < 0.01$) the carotid territory being revascularized, suggesting that aortic arch navigation/manipulation alone may be responsible for some of these embolic phenomena.[45] The latter mechanism would not be prevented by embolic protection devices, perhaps contributing to reports from EVA-3S, SPACE, and ICSS that fail to show a difference in patients undergoing CAS with or without embolic protection devices.

A meta-analysis of patient-level data from EVA-3S, SPACE, and ICSS data showed that overall CAS had a 30-day risk of stroke or death of 8.9%, whereas CEA had a 30-day risk of 5.8% ($p < 0.001$).[8] This meta-analysis did show that the 120-day risk following CAS for patients ≥ 70 years of age was 12%, whereas the 120-day risk for this population following CEA was 5.9%. This risk ratio of 2.04 (95% CI 1.48–2.82) was significant and consistent with the CREST data, showing that CAS, where possible, should be avoided in patients ≥ 70 years of age. A more recent meta-analysis, adding CREST to the prior 3 trials (excluding asymptomatic patients), found a relative risk of 1.77 (95% CI 1.38–2.26) for any stroke or death in patients undergoing CAS. Neither meta-analysis nor CREST showed a difference in outcomes based on sex. Such analyses cannot address whether revascularization or timing of the intervention is the appropriate choice for females; the analysis only suggests that sex may not be an important determinant of technique.

TABLE 3: Summary of trials comparing DWI incidence of new ischemic lesions after CEA or CAS*

Authors & Year	Stenosis Category	CEA		CAS		p Value
		%	No. of Patients	%	No. of Patients	
ICSS Investigators, 2010	symptomatic	17.0	107	50.0	124	<0.0001
Schofer et al., 2008	symptomatic	ND	ND	63.0	8	
	asymptomatic	ND	ND	27.5	51	
Capoccia et al., 2010	asymptomatic	0.0	20	22.0	23	0.035
Schnaudigel et al., 2008	mixed	10.0	754	37.0	1363	<0.01
Skjelland et al., 2009	mixed	6.7	30	21.4	28	0.103
Zhou et al., 2009	mixed	12.0	100	46.3	68	<0.05
Leal et al., 2010	mixed	ND	ND	12.5	31	

* All references are primary material, with the exception of Schnaudigel et al. (meta-analysis).

For the most part CAS demonstrates higher 30-day risks than CEA. One must place these results within the context of acceptable risks. As outlined above, the American Heart Association/American Academy of Neurology guideline for 30-day stroke or death following CEA for symptomatic stenosis is 6%.[10] With respect to the guidelines, the above-mentioned trials suggest that the risk in patients treated with CAS for revascularization of symptomatic stenosis may be too high (EVA-3S, SPACE, ICSS) or borderline (CREST).

The cost-effectiveness and economics of CAS and CEA have been reported. Although many studies have shown that the initial hospitalization costs for CAS exceed the cost of CEA, further evidence suggests that CEA has greater benefit per dollar spent than CAS over the long term.[25,27,28,38,51] The higher initial costs of CAS could be offset by a decrease in the length of hospital stay for the procedure.[21] However, considering total length of stay over a lifetime, the marginal savings for the initial hospital stay could be offset by avoiding hospitalization for future events. In fact, CEA appears to be the dominant (preferred) treatment option because it has lower lifetime costs while also having increased quality-adjusted life-years—CEA will continue to be preferred as long as it is less expensive and has comparable or slightly better outcomes than CAS.[51]

Asymptomatic Carotid Stenosis: CEA Versus BMT

Two key trials, ACAS and ACST (Table 4), randomized asymptomatic patients with angiographically confirmed stenosis > 60% (ACAS) or stenosis > 50% on ultrasonography studies (ACST) to an upfront CEA versus a BMT group (or BMT/deferred CEA in the case of ACST).[19,23,24] Despite slight differences in entry criteria and analysis, overall outcomes were fairly similar, with a slightly less than 5% decrease in stroke/death over 5 years. The larger number of patients enrolled into ACST and its longer follow-up period provide a much more specific understanding of the modest gains of CEA versus BMT, as follows: 1) of the 4.1% absolute reduction in stroke/death over 5 years, only half of this benefit came from preventing disabling strokes/death (a net gain < 0.5%/year); 2) after 5 years, no further benefit accrues, with a net gain of only 4.6% at 10 years (CEA vs BMT lines parallel each other after 5 years); 3) no benefit exists for patients older than 75 years; 4) women derive less benefit (reaching statistical significance only at 10 years); and 5) patients on a regimen of lipid-lowering agents have less benefit. Given the underwhelming gains achieved by CEA in asymptomatic patients relative to symptomatic patients, benefit was critically dependent on an extremely low perioperative complication rate, with 3% set as the threshold margin for periop-

TABLE 4: Literature review of asymptomatic carotid stenosis: CEA versus BMT*

Authors & Year	Study	No. of Pts		% 30-Day Stroke/Death		% LT Stroke/Death			LT FU Period
		CEA	BMT	CEA	BMT/Deferred	CEA	BMT/Deferred	p Value	
Ex Comm for ACAS, 1995	ACAS	825	834	2.3	0.4	12.4	17.5	0.09	5 yrs†
ACST Collaborative Group, 2004; Halliday et al., 2010	ACST	1560	1560	2.9	3.6‡	6.4/13.4§	11.8/17.9§		5/10 yrs
Marquardt et al., 2010	OXVASC		101				annual risks: 0.3% ipsilat stroke; 8.3% other territory stroke; 7.7% vascular death		301 pt yrs

* Ex Comm = Executive Committee; OXVASC = Oxford Vascular Study.

† ACAS calculated 5-year risks from a median follow-up of 2.7 years; 5-year risks are for any stroke or perioperative death.

‡ ACST 30-day stroke or death rates are given with respect to the 30 days after CEA, even when the CEA was deferred. Long-term stroke/death is defined as any stroke or perioperative death.

§ Data are given as the 5-year/10-year results.

erative stroke/death.[10,15] However, significant improvements in BMT have occurred over time, especially in the use of lipid-lowering drugs such as statins, which were used in only 10% of patients in the ACST at trial initiation and in 80% at 10-year follow-up. More recent data from the Oxford Vascular Study (OXVASC) demonstrates a stroke risk of only 0.3%/year attributable to ipsilateral asymptomatic carotid stenosis treated with BMT alone.[32] Therefore, the most recent guideline for carotid revascularization states:

> It is important to emphasize that selection of asymptomatic patients for carotid revascularization should include careful consideration of life expectancy, age, sex, and comorbidities. The benefit of surgery may now be less than anticipated on the basis of earlier randomized trials, and the cited 3% complication rate should be interpreted in the context of interim advances in medical therapy.[10]

Asymptomatic Carotid Stenosis: CEA Versus CAS

The CREST and SAPPHIRE studies are 2 randomized trials comparing CEA and CAS in patients with asymptomatic carotid artery stenosis (Table 5).[11,22,50] In the SAPPHIRE study, the 30-day risk of MI, stroke, or death was 5.4% for CAS, and 10.2% for CEA (not significantly different). Of note, these complication rates are higher for asymptomatic individuals compared with symptomatic participants within the same trial, and probably exceed the threshold of 3%.[10,15] For this reason, a persistent criticism of this trial remains that the enrolled patients should not have undergone revascularization at all, given the trial's perioperative complication rates.[36]

In CREST, the 4-year rate of stroke or death in asymptomatic patients was 4.5% for CAS and 2.7% for CEA (HR 1.86, 95% CI 0.95–3.6; p = 0.07). Although the null hypothesis cannot be rejected at the 5% level, it is appropriate to conclude that, with a 7% chance of being incorrect, CEA was superior to CAS. The periprocedural risk of stroke or death was 2.5% in the CAS group and 1.4% in the CEA group (HR 1.88, 95% CI 0.79–4.49; p = 0.15). It is reassuring that the 30-day complication rates from CREST for asymptomatic revascularization are within the recommended 3% benchmarks. However, neither the SAPPHIRE nor the CREST investigations address the question now posed by improvements in BMT, namely whether patients with asymptomatic carotid stenosis should undergo any revascularization procedure. Future trials of CEA versus CAS in asymptomatic stenosis may include a third arm for BMT (Table 6).[39]

Current practice of CAS and CEA in the US for asymptomatic stenosis was recently examined, and in-hospital complication rates were presented, and CAS was associated with increased odds of stroke or death (OR 1.28, 95% CI 1.03–1.58).[52] However, CAS was not associated with increased odds of stroke, death, or cardiac complications (OR 1.12, 95% CI 0.99–1.27; p < 0.14). The in-hospital complication rates for stroke or death for age ≥ 80 years were 1.5% following CEA and 2.7% following CAS, although this did not reach statistical significance at the 5% level (p < 0.07). Nonetheless, the 30-day complication rates would be equal to or greater than the in-hospital rates. Because the complication rate following

TABLE 5: Literature review of asymptomatic carotid stenosis: CEA versus CAS*

Authors & Year	Trial	No. of Pts		% 30-Day Stroke/Death (guidelines: <3%)			% 30-Day Stroke/Death/MI (guidelines: none)			% LT Stroke/Death			% LT Stroke/Death/MI			LT FU Period
		CEA	CAS	CEA	CAS	p Value	CEA	CAS	p Value	CEA	CAS	p Value	CEA	CAS	p Value	
Yadav et al., 2004; Gurm et al., 2008	SAPPHIRE†	NA	NA	NA	NA	NA	10.2	5.4	0.2	29.2	21.4	ND	NA	NA	NA	3 yrs
Brott et al., 2010	CREST‡	1262	1240	1.4	2.5	0.15	3.6	3.5	0.96	2.7	4.5	0.07	4.9	5.6	0.56	4 yrs

* In most of the comparisons the p value is for the hazard ratio; for SAPPHIRE it is the p value for the absolute difference in the event rate. Abbreviation: NA = not available.

† In SAPPHIRE long-term events were defined as death or ipsilateral stroke only.

‡ In CREST, long-term follow-up events were defined as periprocedural stroke or death plus any ipsilateral stroke. Long-term stroke/death/MI is defined as any periprocedural stroke, MI, or death, or postprocedural ipsilateral stroke.

TABLE 6: Current and ongoing trials*

Trial	Groups	Trial Arms	Hypothesis
SPACE-2	asymptomatic	BMT, CEA, CAS	1) either CEA or CAS is superior to BMT; 2) CAS is noninferior to CEA
ACT-1	asymptomatic	CEA, CAS	noninferiority of CAS vs CEA
ACST-2	asymptomatic	CEA, CAS	CEA vs CAS (design not published)

* ACT-1 = Carotid Stenting vs Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients.

CAS was rapidly approaching the 3% 30-day benchmark, CAS should be considered with extreme caution in this age group.

Current/Ongoing Trials

There are several ongoing or planned trials examining the best treatment for carotid stenosis; these are summarized in Table 6.[14,39,44] Most current work is examining CEA versus CAS in asymptomatic patients. Fortunately, at least one trial (SPACE-2) also includes a third arm for BMT.

Summary

Patients with symptomatic stenosis > 70% should undergo carotid revascularization. There is clear evidence that CEA is superior to BMT for such a group, with an absolute risk reduction of 15.6%. The benefits of CEA for 50%–69% stenosis, although significant, were modest compared with those in patients with 70% stenosis. Therefore, revascularization is recommended for 50%–69% symptomatic stenosis, with the understanding that aggressive lipid management and other antiplatelet agents have been added to the BMT regimen since NASCET and ECST were conducted, and may be useful in this population. Based on meta-analysis and recent data, CEA remains the procedure of choice for revascularization of symptomatic stenosis ≥ 50%; however, CAS is a potential alternative for patients with specific high-risk factors for CEA (for example, contralateral occlusion, radiation therapy, restenosis). Also, CAS has other, less well-defined indications, such as severe chronic obstructive pulmonary disease or the somewhat ambiguous "high risk" criteria.

We found that CEA has a modest benefit for asymptomatic stenosis, given at least a 3–5 year life expectancy after surgery. In contrast, CAS has a dubious benefit for asymptomatic stenosis; procedural morbidity and mortality rates approach or exceed 3%, whereas the procedural risks with CEA remain much lower. With the declining incidence of stroke due to asymptomatic lesions and the current natural history, SPACE-2 and other trials are well justified to compare BMT against CAS or CEA. The CAS procedure for asymptomatic stenosis should remain relegated to clinical trials, which should also include an arm for BMT.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Jahromi, Young. Analysis and interpretation of data: Jahromi, Young. Drafting the article: Jahromi, Young, A Jain, M Jain. Critically revising the article: Jahromi, Young, Replogle, Benesch.

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See the corresponding article in this issue (E2).

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Editorial

Evidence-based treatment of carotid stenosis: is the evidence strong enough?

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Young et al.[12] present a timely review of evidence-based treatment of carotid artery disease. With the publication of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[2] and the release of preliminary International Carotid Stenting Study (ICSS)[7] data, the management of carotid stenosis has gained a substantial amount of recent attention. Since the advent of the carotid angioplasty and stenting (CAS) procedure, there has been significant debate as to what is, or what will ultimately be, the most effective and safe treatment modality for atherosclerotic carotid artery disease.

As Davis and Donnan[3] noted in a recent editorial in the *New England Journal of Medicine*, trends in the evolution of stroke treatment have consistently followed those developed for the management of myocardial infarction. Effective preventive strategies such as blood pressure modification and antiplatelet regimens were successfully translated from cardiac disease to stroke. The application of thrombolytic therapy for acute cerebral revascularization was adopted from the cardiac catheterization labs. Many of the translational neuroprotective strategies proposed today were first presented in the cardiac and vascular biology literature. The medical community and the general public continuously seek to embrace less invasive therapies. It is not unreasonable to surmise, then, that carotid endarterectomy (CEA) surgeries may one day be displaced by CAS techniques (or the indications may be significantly narrowed), much like coronary artery bypass graft procedures. The question is whether we have yet reached that point. Young et al. argue that we have not.

The treatment of carotid artery stenosis has historically been guided by evidence-based practice and large clinical studies.[1,4–6] Relatively few neurosurgical procedures have been assessed with such rigor, or with a comparable breadth of trials. Years ago, indications appeared to be fairly clear; a safe and effective surgical procedure (CEA) was performed to treat a potentially devastating disease. Over time, however, endovascular techniques and best medical therapies have improved significantly. Symptomatic and asymptomatic lesions clearly have dissimilar natural history patterns. The current data on the treatment of carotid artery disease is inconsistent and appears to be inconclusive. Meta-analyses and pooled studies are difficult to interpret due to variations in techniques, device utilization, and operator experience. Proponents of each treatment modality interpret results of carotid revascularization studies in very different ways. This lack of consensus highlights the uncertainty with respect to an optimal treatment algorithm.

Rather than simply reviewing the existing literature, the authors present a manuscript that focuses on trial design and statistical interpretation with respect to the relevant randomized and population-based studies. Their review not only evaluates the current data, but the models used for its generation and interpretation.

The section of this paper addressing methods of statistical analysis illustrates an important concept. Whereas the initial CEA studies were designed to assess for superiority, many of the recent trials comparing CEA and CAS use a noninferiority design.[8,9,11] The CREST study assessed for superiority, but did not demonstrate a statistically significant difference in the primary outcome end point. These data are summarized in Fig. 1 of Young et al.'s manuscript. Pertinent results must be interpreted within the scope of the study design.

Based on the CREST data,[2] the US FDA's Circulatory System Devices Advisory Panel has recommended expanding the availability of the CAS procedure to patients at standard risk for adverse events while undergoing surgery.[10] A critical issue is whether the Centers for Medicare and Medicaid Services (CMS) will approve reimbursement for CAS in standard-risk patients. It is important to realize that the qualifications of "safe and effective" used by the FDA are quite different from the standards of "reasonable and necessary" used by the CMS.

Do the existing study designs (and resultant data) address the necessity of the procedure(s)? As the authors remark, several of the investigations (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [SAPPHIRE], Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis [EVA-3S], and Stent-Protected Percutaneous Angioplasty of the Carotid artery versus Endarterectomy [SPACE]) were initiated to demonstrate noninferiority rather than superiority.[8,9,11,12] As opposed to an equivalence trial, a noninferiority design retains the capacity to claim superiority. Results from these investigations, however, were somewhat inconsistent (SAPPHIRE[11] favored stent treatment, whereas EVA-3S[8] favored endarterectomy) due to varying inclusion criteria and diverse patient populations. Two investigations were terminated early.[8,9]

Positive primary outcome results from a large, randomized superiority trial would be compelling. The CREST study, however, does not demonstrate superiority with regard to the primary end point for either CEA or CAS. Each procedure exhibited benefit with respect to alternate end points (decreased number of myocardial infarctions in the stent-treated group, decreased number of strokes in the endarterectomy group) and according to patient age (stent placement procedures for younger patients, endarterectomy for older patients).

In the setting of perceived clinical equipoise, factors such as cost effectiveness, complications, and ease of administration were evaluated. It remains unclear whether either procedure provides clear secondary advantages. An argument can be made that, as technology evolves, the efficacy of CAS procedures may continue to improve. Supporters assert that this trajectory warrants consideration when evaluating clinical practice patterns.

In an age of radical health care transformation designed to promote cost-effective medicine, it will be interesting to see whether the CMS approves CAS coverage for symptomatic patients, asymptomatic patients, both, or neither. Proponents and detractors can probably find arguments and evidence to support or dispute any decision.

The approval of the CAS procedure in standard-risk patients would be likely to have broad implications for the quantity of procedures undertaken and the allocation of the 2 treatment modalities. The number of specialties that train members to perform angioplasty and stenting procedures (radiology, neurology, neurosurgery, cardiology, vascular surgery) is far greater and the operator volume is larger than in those that train physicians to perform CEA. Practice standards appear to shift with the publication of each new clinical trial. Decisions by the FDA and CMS can be assumed to have a more far-reaching impact.

The authors' conclusions are logical based on the evidence to date. There do not appear to be enough existing data to favor CEA or CAS procedures uniformly. The paper serves as a comprehensive review of the existing literature. Furthermore, it reminds us of the impact of trial design and statistical analysis on the results of an investigation. Utilization trends will reflect individual physicians' interpretation of the studies within the scope of guidelines determined by the FDA and CMS. Until clear and convincing data demonstrate the superiority of one procedure or the other, appropriate patient selection should remain the guiding principle in treatment allocation. (*DOI: 10.3171/2011.3.FOCUS1186)*

Disclosure

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Utility of CT perfusion scanning in patient selection for acute stroke intervention: experience at University at Buffalo Neurosurgery–Millard Fillmore Gates Circle Hospital

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Computed tomography perfusion scanning generates physiological flow parameters of the brain parenchyma, allowing differentiation of ischemic penumbra and core infarct. Perfusion maps, along with the National Institutes of Health Stroke Scale score, are used as the bases for endovascular stroke intervention at the authors' institute, regardless of the time interval from stroke onset. With case examples, the authors illustrate their perfusion-based imaging guidelines in patient selection for endovascular treatment in the setting of acute stroke. *(DOI: 10.3171/2011.2.FOCUS1130)*

Key Words • **computed tomography perfusion** • **acute stroke** • **stroke intervention**

Despite advances in pharmacological and mechanical thrombolytic therapy, acute ischemic stroke treatment remains challenging because of the limited time window during which therapy must be administered.[3,4,17] Intravenous tPA, for example, is only given to between 3% and 5% of patients admitted with ischemic stroke, largely due to a delay in presentation outside the treatment window[2] and patient ineligibility. Recent studies suggest that clinical improvement is noted even in the setting of late reperfusion if patients are selected carefully using advanced imaging techniques. With the application of CT perfusion–based selection for endovascular therapy, 20% of patients presenting to our institution 8 or more hours postictus improved to a modified Rankin Scale score of 2 or less at 3 months.[16] As a result, there has been growing interest in developing CT and MR imaging techniques to identify patients in whom a large area of ischemic penumbra is present even if the patients present beyond the traditional treatment window. The rationale is that by limiting recanalization to patients with large areas of ischemic penumbra, neuronal function may be restored without increasing the risk of hemorrhage.[1,7] Compared with MR perfusion imaging, CT perfusion scanning has the advantages of practicality, speed, lower cost, availability, quantitative parameters, and ease of patient monitoring.[18] We review the clinical application of CT perfusion imaging in the setting of acute stroke and present our CT perfusion–based institutional protocol for patient selection in acute stroke intervention, along with illustrative cases.

Abbreviations used in this paper: CBF = cerebral blood flow; CBV = cerebral blood volume; MCA = middle cerebral artery; MTT = mean transit time; NIHSS = National Institutes of Health Stroke Scale; rCBF = relative CBF; rCBV = relative CBV; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue plasminogen activator; TTP = time to peak.

Techniques and Parameters

Computed tomography perfusion imaging involves the injection of a single bolus of iodinated contrast material and subsequent spiral CT scanning when the contrast bolus is passing through the cerebral vasculature.[8] The commonly available parameters include CBF, CBV, TTP, and MTT. Cerebral blood flow is measured in milliliters of blood per 100 g of brain tissue per minute (normal is approximately 50 ml/100 g/min), and CBV is measured in milliliters of blood per 100 g of brain (normal is approximately 5 ml/100 g).[14,19] The MTT, the average time for blood to travel through a given volume of brain, is measured in seconds and reflects the time required for

the contrast bolus to travel from the arterial to the venous circulation. The TTP is the delay between the first arrival of contrast intracranially and the time when the contrast medium reaches its peak concentration, which is measured in seconds. Both CBF and CBV are derived from the time-density curve generated from the preprocessing source data using the deconvolution technique;[10] the MTT is then calculated through the central volume principle: MTT = CBV/CBF.[12]

Both CBF and CBV maps created using the deconvolution technique are sensitive to contrast bolus delay and can overestimate the core infarct in patients with severe extracranial hemodynamic compromise caused by chronic disease states, such as extracranial internal carotid artery stenosis, atrial fibrillation, and congestive heart failure. On such occasions, algorithms that correct for the delay by shifting the tissue time-density baseline curve to generate a delay map can reduce the occurrence of overestimation.[20] The core infarct that can be corrected by the delay-correction algorithm is referred to as pseudoreversible. By correcting the underestimation of cerebral perfusion and the overestimation of core infarct, delay maps can improve our ability to differentiate irreversible core infarct from salvageable penumbra in patients with low-flow states.

The appropriate selection of arterial input function and venous output function from CT perfusion source images is important to generate representative arterial input and venous outflow time-attenuation curves from which CT perfusion parameters are calculated. The arterial input function is usually obtained from the A_2 segment of the anterior cerebral artery because it is orthogonal to the axial plane and can be found easily on multiple images. Venous outflow is typically obtained from one of the dural venous sinuses. Inaccurate arterial input function and venous output function placements can affect both qualitative and quantitative assessment of CT perfusion scans.[20]

Normal Perfusion, Core Infarct, Ischemic Penumbra, Penumbra Mimics, and Clinical Implications

With normal brain perfusion, there is symmetric perfusion with higher CBF and CBV in gray matter than in white matter, reflecting the metabolic differences between these 2 regions (Fig. 1). Regions of irreversible core infarct exhibit matched areas of significant decrease in CBF and CBV due to the loss of cerebral autoregulation, with increased TTP and MTT demonstrated on perfusion maps (Fig. 2). Specifically, rCBV of < 30%–40% (compared with the normal contralateral side) and rCBF of < 30% (again, compared with the normal contralateral side) are indicative of core infarct.[9,13,21] A significant reduction in CBV is particularly sensitive and specific for core infarct.[24,25] It is widely believed that reperfusion of such necrotic core is ineffective and would likely increase the risk of hemorrhage.[6]

By contrast, ischemic penumbra shows normal or mildly decreased CBF, increased TTP and MTT, and a relatively spared CBV (with early ischemia, vasodilation, and recruitment occurring as a result of autoregulation) (Fig. 3A). In areas of oligemia, rCBF and rCBV are > 60% and 80%, respectively, whereas in areas of ischemic penumbra (tissue at risk), rCBF and rCBV are > 30% and 60%, respectively.[9,13,21]

Several disease states mimic the perfusion patterns seen in acute ischemia. In extracranial carotid artery stenosis, proximal intracranial stenosis, atrial fibrillation, and congestive heart failure, MTT prolongation is frequently seen,[22,23] mimicking or overestimating the ischemic penumbra. This highlights the importance of obtaining a concurrent CT angiogram to assess the extra- and intracranial vasculature in conjunction with the interpretation of the delay maps to help distinguish these chronic disease states from acute ischemia.

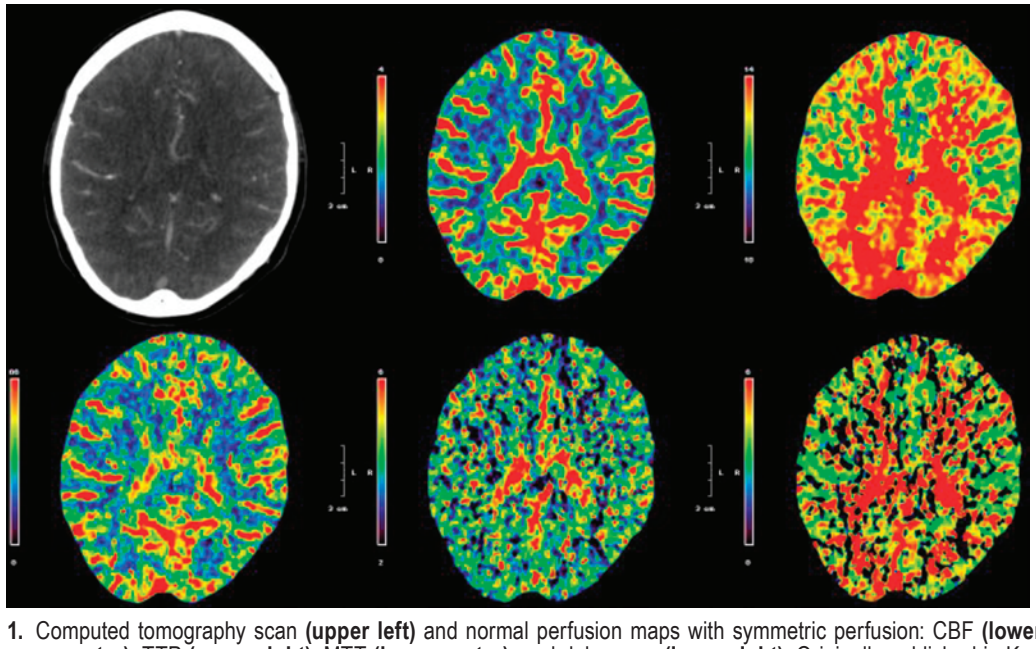

Fig. 1. Computed tomography scan **(upper left)** and normal perfusion maps with symmetric perfusion: CBF **(lower left)**, CBV **(upper center)**, TTP **(upper right)**, MTT **(lower center)**, and delay map **(lower right)**. Originally published in Kan et al: Computed tomography (CT) perfusion in the treatment of acute stroke. **World Neurosurg 74:**550–551, 2010.

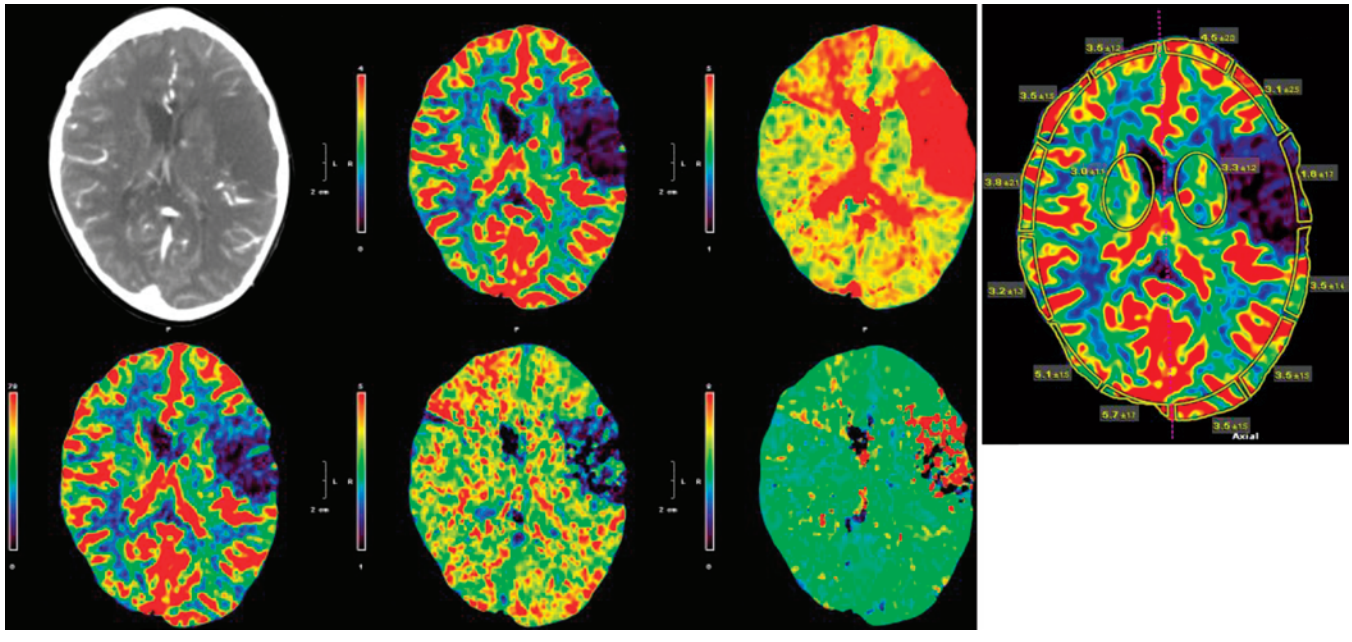

Fig. 2. **Left:** Matched reduction in CBF and CBV and increase in TTP/MTT indicating an area of core infarct. Originally published in Kan et al: Computed tomography (CT) perfusion in the treatment of acute stroke. **World Neurosurg 74:**550–551, 2010. **Right:** Quantitative CBV map (same patient) showing the area of core infarct with a relative CBV of < 30%.

Thresholds for Penumbra and Infarcts

Currently, no consensus exists on the thresholds of CBF, CBV, and TTP used to define core infarcts and ischemic penumbra. According to Konstas et al.,[11] a < 50% reduction of CBF on CT perfusion imaging suggests salvageable penumbra, whereas tissue with a > 66% reduction of CBF would likely progress to infarction. Wintermark et al.[24,25] selected a threshold CBV of 2.0 ml/100 g to define core infarcts. These investigators believe that the relative increase in MTT (145% over baseline) or a product of CBF and CBV most accurately defines the ischemic penumbra.[15,24]

Given the lack of consensus on operational thresholds and potential variations in absolute values of CT perfusion parameters from different scanners, our group and others favor the use of relative CT perfusion values (with the contralateral unaffected hemisphere serving as the control) in clinical decision making.

Acute Stroke Protocol and Patient Selection

At our institution, patients with suspected stroke undergo immediate noncontrast cranial CT, cranial and cervical CT angiography, and brain CT perfusion scanning. The scans are acquired using the Aquilion 320-slice CT scanner (Toshiba America Medical Systems, Inc.). Perfusion maps of the whole brain are derived using the appropriate software (Vital Images) and generate the standard perfusion parameters of TTP, MTT, CBF, CBV, and a delay map. If hemorrhage is identified on the noncontrast cranial CT scan, the protocol is aborted. The CT angiogram helps to identify structural lesions that can be targets for endovascular therapy as well as extracranial stenoses. The CT perfusion scan is used to identify core infarcts and ischemic penumbra. Ischemic penumbra is defined as the area of mismatch between increased TTP/MTT and the loss of CBV on perfusion maps; core infarct is defined by a significant loss in CBV (rCBV < 30%).[6,9,13,21,24,25]

Time of onset, NIHSS score, and CT perfusion patterns are used to select patients for therapy. Eligible patients presenting within the intravenous tPA window (3–4.5 hours from symptom onset) are treated with intravenous tPA. Patients with proximal vessel occlusion (M_2 or more proximal) in whom intravenous tPA failed to effect an improvement are eligible for mechanical intervention after CT exclusion of a hemorrhage. Eligible patients treated between 4.5 and 6 hours usually receive a combination of intraarterial thrombolytics and mechanical thrombolysis. Beyond 6 hours, only patients with a significant deficit (NIHSS score > 8 or severe aphasia), a large penumbra (> 50% of the occluded vessel territory) with limited core infarct on CT perfusion imaging, and a proximal lesion (M_2 or more proximal) on CT angiography would be selected for mechanical revascularization. Pharmacological thrombolysis is minimized in this late-treatment group because of an increased risk of hemorrhage.[5,7,17] Patients with a large core infarct or a core infarct within the basal ganglia are excluded because of the increased risk of hemorrhage.

Our patient selection protocol for endovascular therapy is summarized in Fig. 4.

Clinical Outcomes

On the basis of our perfusion-based protocol for patient selection, we reviewed the outcomes of patients at our institution who underwent endovascular stroke intervention.[16] Thirty patients were identified, and outcomes were measured according to recanalization rates, NIHSS score, and modified Rankin Scale score. Among the 30 patients, the

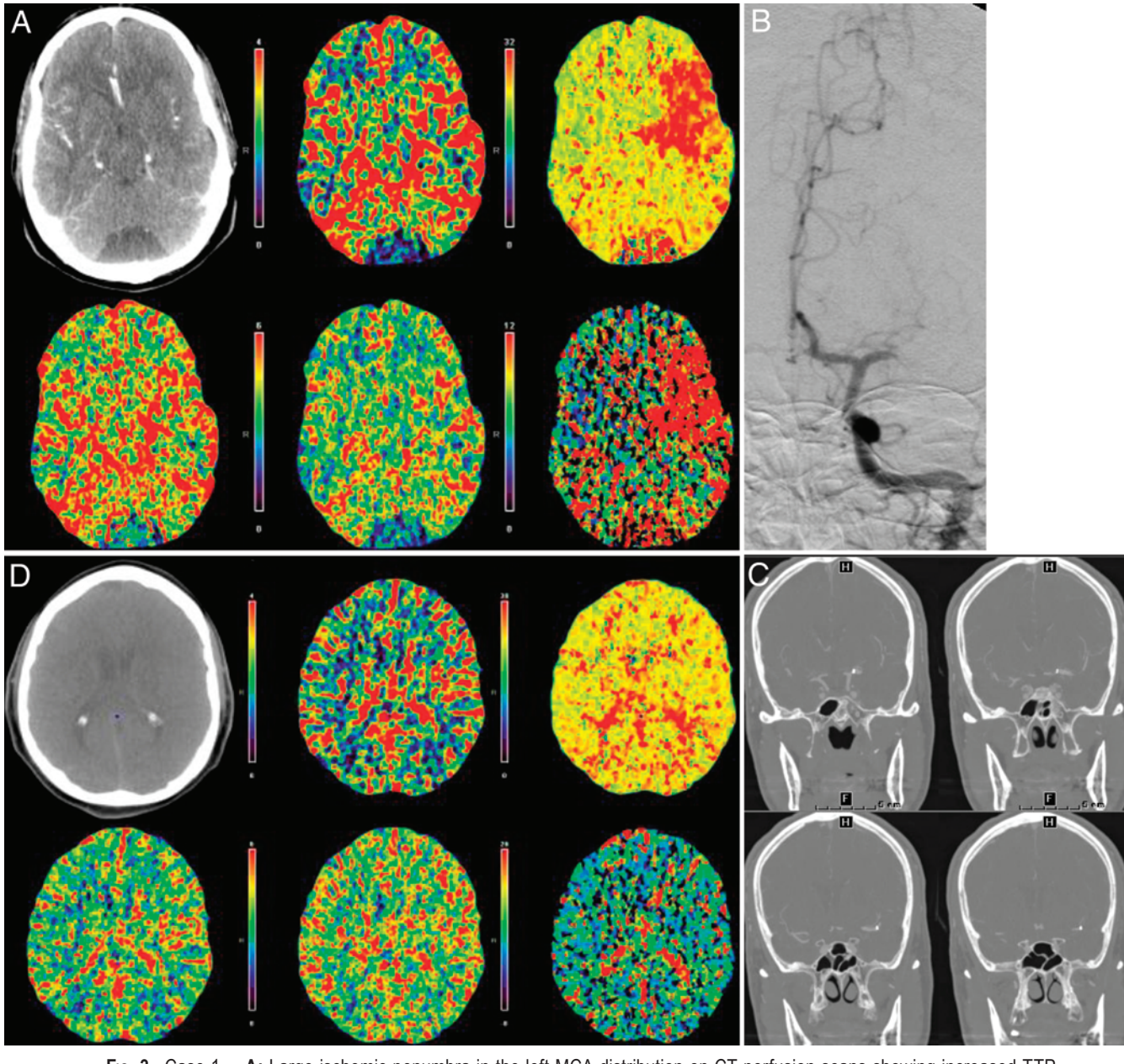

Fig. 3. Case 1. **A:** Large ischemic penumbra in the left MCA distribution on CT perfusion scans showing increased TTP **(upper right)** and preserved CBF **(lower left)** and CBV **(upper center)**. Originally published in Kan et al: Computed tomography (CT) perfusion in the treatment of acute stroke. **World Neurosurg 74:**550–551, 2010. **B:** Catheter-based angiogram (antero-posterior projection, cranial view) revealing migration of thrombus into the left M_1 segment. **C:** Postoperative CT angiograms (coronal view) demonstrating complete vessel recanalization and stent patency. **D:** Follow-up CT perfusion scan showing normal symmetric perfusion.

mean NIHSS score at presentation was 13, and the mean interval between symptom onset and angiography was 12.75 hours. Twenty-six patients (86.7%) presented with complete or near-complete vessel occlusion (TIMI Grade 0 or 1), and successful recanalization (TIMI Grade 2 or 3) was achieved in two-thirds of all patients. Symptomatic intracerebral hemorrhage occurred in 10% of the patients. The mean discharge NIHSS score was 9.5. At 3 months posttreatment, 20% of patients had good outcomes (modified Rankin Scale score ≤ 2) and 33% of patients had acceptable outcomes (modified Rankin Scale score ≤ 3).

Illustrative Cases

Case 1

This 60-year-old man presented with right-sided weakness and aphasia and an NIHSS score of 2. He had a history of atrial fibrillation, but warfarin therapy had been discontinued because of recent falls. His initial CT angiogram showed a left internal carotid artery terminus occlusion, and he was started on aspirin, clopidogrel, and a heparin drip. Seven hours later, his status declined acutely (NIHSS score of 10). Repeated CT perfusion scanning continued to

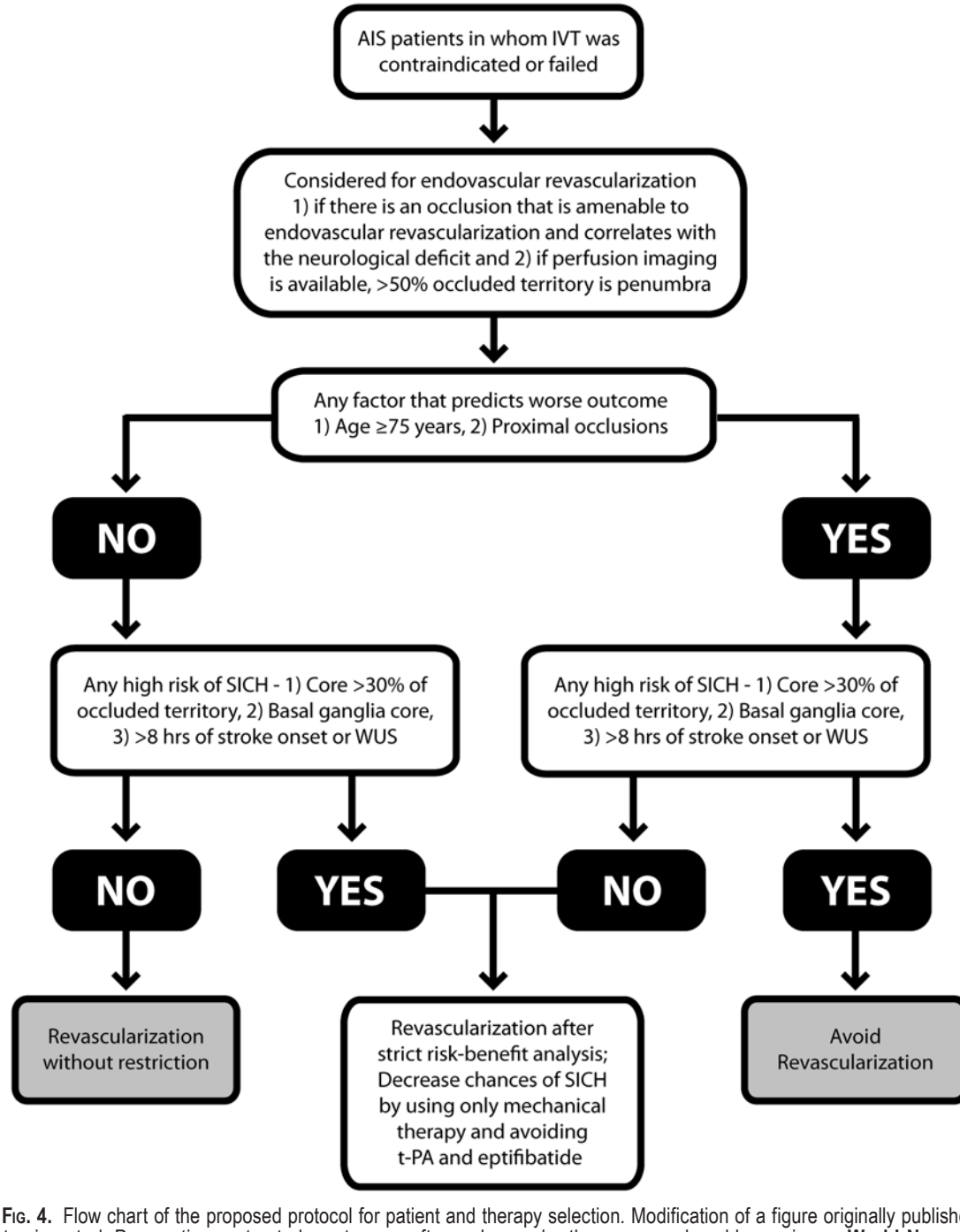

Fig. 4. Flow chart of the proposed protocol for patient and therapy selection. Modification of a figure originally published in Natarajan et al: Prospective acute stroke outcomes after endovascular therapy: a real-world experience. **World Neurosurg 74:**455–464, 2010. AIS = acute ischemic stroke; IVT = intravenous thrombolysis; SICH = symptomatic intracranial hemorrhage; WUS = wake-up stroke.

show a large penumbra in the left MCA distribution (Fig. 3A). Follow-up catheter-based angiography showed migration of thrombus into the left M_1 segment (Fig. 3B), compared with the findings on the original CT angiogram (not shown). Emergency Wingspan stent (Boston Scientific) revascularization of the left M_1 segment was performed. Postoperatively, the patient's NIHSS score improved to 1, and he was subsequently discharged to home. His postprocedural CT angiogram revealed stent patency and TIMI Grade 3 flow (complete recanalization) in the left MCA (Fig. 3C). Follow-up CT perfusion imaging showed normal symmetric perfusion (Fig. 3D).

Case 2

This previously healthy 53-year-old man presented within 1 hour postictus with left-sided hemiplegia, right gaze deviation, and left hemineglect with an NIHSS score of 16. Computed tomography angiography showed an oc-

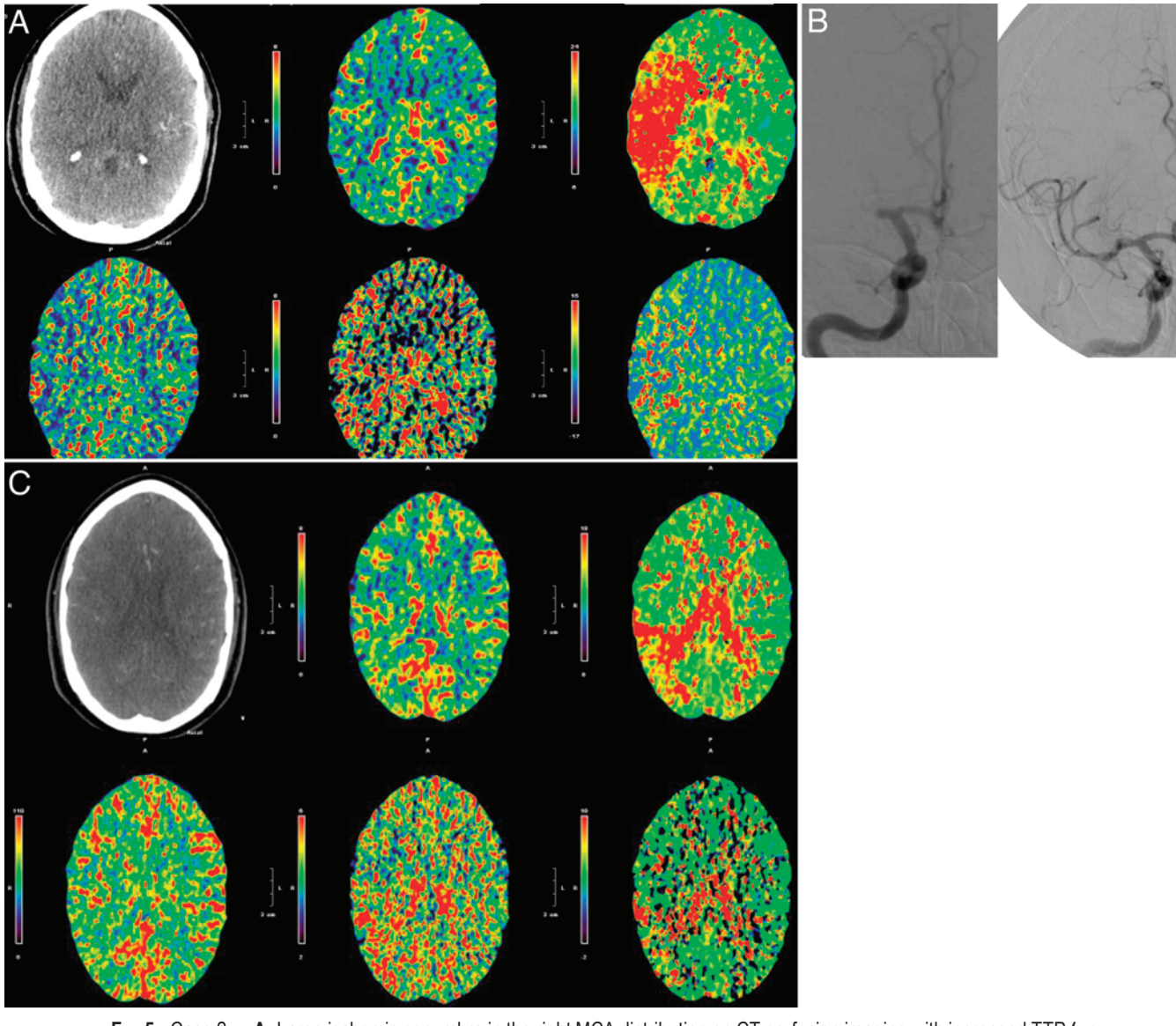

Fig. 5. Case 2. **A:** Large ischemic penumbra in the right MCA distribution on CT perfusion imaging with increased TTP **(upper right)** and MTT **(lower center)** and a mild reduction in CBF **(lower left)** and preserved CBV **(upper center)**. **B:** Preprocedural angiogram (*left*; anteroposterior projection, cranial view) showing acute M_1 occlusion. Postprocedural angiogram (*right*; aningteroposterior projection, cranial view) revealing complete vessel recanalization. **C:** Follow-up CT perfusion imaging showing marked improvement in the perfusion mismatch with only a mildly elevated TTP in the posterior MCA distribution **(upper right)**.

clusion of the right M_1 segment, and CT perfusion imaging revealed a large penumbra in his entire right MCA distribution (Fig. 5A). The patient received intravenous tPA. No clinical improvement was observed after 40 minutes had elapsed. After an intracranial hemorrhage was excluded on repeated CT scanning, emergency mechanical revascularization was performed using the Merci retrieval device (Concentric Medical). Postoperatively, the patient's NIHSS score improved to 0, and he was discharged to home. His postoperative angiogram revealed TIMI Grade 3 flow in the right MCA (Fig. 5B). His follow-up CT perfusion imaging study demonstrated a marked reduction in perfusion mismatch (Fig. 5C).

Case 3

This 63-year-old man, who underwent transurethral prostate resection 24 hours previously at an outside hospital, presented to our institution with right-sided hemiplegia and severe aphasia (NIHSS score of 23) 6 hours after symptom onset; he was intubated at the time of presentation. His initial CT perfusion imaging study was suggestive of a basal ganglia infarct with a large left hemispheric penumbra (Fig. 6A). A CT angiogram showed a patent left M_1 (spontaneous recanalization likely had occurred) and an inferior M_2 trunk occlusion. He underwent emergency revascularization with the Solitaire stent retriever (ev3/Covidien Vascular Therapies) in an attempt to salvage the large hemispheric penumbra. Final angiographic runs showed recanalization of the inferior M_2 trunk. During the procedure, the patient underwent heparinization to a therapeutic activated coagulation time, with no antiplatelet or thrombolytic agents given. His immediate postop-

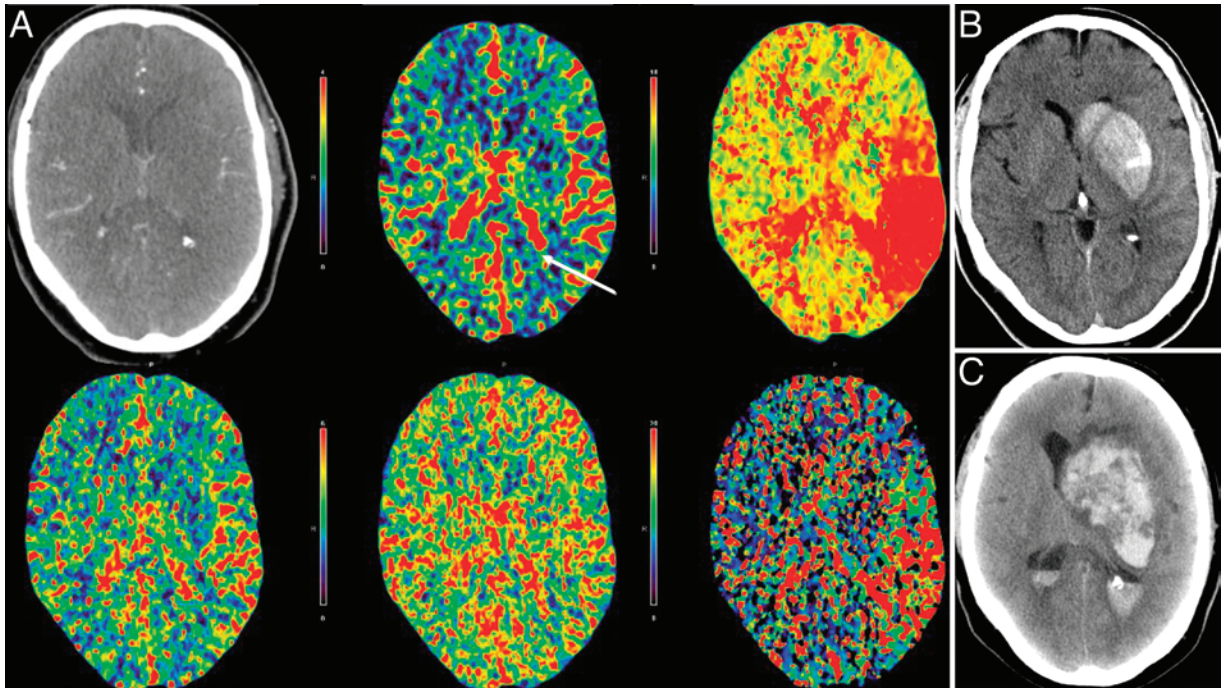

Fig. 6. Case 3. **A:** Large ischemic penumbra in the left MCA distribution on CT perfusion images with increased TTP **(upper right)** and relatively preserved CBF **(lower left)** and CBV **(upper center)**. Notice the loss of CBV in the left basal ganglia *(arrow)*. **B:** Postprocedural CT scan revealing basal ganglia staining and hemorrhage. **C:** Follow-up CT scan demonstrating a large basal ganglia hemorrhage with intraventricular extension.

erative CT scan revealed basal ganglia staining and hemorrhage (Fig. 6B). Three hours after intervention, he was noted to have a fixed and dilated left pupil. Repeated CT scanning (Fig. 6C) revealed a large basal ganglia hemorrhage with intraventricular extension. The patient was extubated and placed on comfort care. This case illustrates the markedly increased risk of hemorrhage if a basal ganglia infarct is noted on the initial study.

Conclusions

Computed tomography perfusion scanning can accurately identify areas of ischemic penumbra and core infarct, guiding treatment based on physiological parameters rather than an arbitrary time frame. This functional approach is gaining importance in the evaluation and treatment of acute stroke. In our experience, revascularization can be achieved safely in patients who present beyond the traditional 6-hour treatment window even in the presence of a significant penumbra.

Disclosure

Dr. Hopkins receives research support from Toshiba; serves as a consultant to Abbott, Boston Scientific,* Cordis, Micrus, and W. L. Gore; holds a financial interest in AccessClosure, Boston Scientific,* Claret Medical, Inc., Micrus, and Valor Medical; has a board/trustee/officer position with AccessClosure, Claret Medical, Inc., and Micrus (until September 2010); belongs to the Abbott Vascular speakers' bureau; and receives honoraria from Bard, Boston Scientific,* Cordis, Memorial Healthcare System, Complete Conference Management, SCAI, and Cleveland Clinic. (*Boston Scientific's neurovascular business has been acquired by Stryker.)

Dr. Levy receives research grant support (principal investigator: Stent-Assisted Recanalization in acute Ischemic Stroke [SARIS]), other research support (devices), and honoraria from Boston Scientific, and research support from Codman & Shurtleff, Inc., and ev3/Covidien Vascular Therapies; has ownership interests in Intratech Medical Ltd. and Mynx/Access Closure; serves as a consultant on the board of Scientific Advisors to Codman & Shurtleff, Inc.; serves as a consultant per project and/or per hour for Codman & Shurtleff, Inc., ev3/Covidien Vascular Therapies, and TheraSyn Sensors, Inc.; and receives fees for carotid stent training from Abbott Vascular and ev3/Covidien Vascular Therapies. Dr. Levy receives no consulting salary arrangements. All consulting is per project and/or per hour.

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Drs. Kan, Snyder, and Yashar report no financial relationships.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Kan. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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Advanced neuroimaging in acute ischemic stroke: extending the time window for treatment

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Early treatment of ischemic stroke with thrombolytics is associated with improved outcomes, but few stroke patients receive thrombolytic treatment in part due to the 3-hour time window. Advances in neuroimaging may help to aid in the selection of patients who may still benefit from thrombolytic treatment beyond conventional time-based guidelines. In this article the authors review the available literature in support of using advanced neuroimaging to select patients for treatment beyond the 3-hour time window cutoff and explore potential applications and limitations of perfusion imaging in the treatment of acute ischemic stroke. *(DOI: 10.3171/2011.3.FOCUS1146)*

Key Words • **stroke** • **neuroimaging** • **thrombolysis** • **perfusion imaging**

Tissue plasminogen activator remains the only FDA-approved treatment for acute ischemic stroke, but only about 2% of patients suffering an ischemic stroke receive tPA, largely because of the rigorous inclusion and exclusion criteria for its use.[31] Among these is the requirement for a 3-hour interval, from onset of symptoms to initiation of therapy. Recent data, however, suggest that the benefits of tPA may extend beyond the 3-hour cutoff.[22] Advanced neuroimaging modalities may help in identifying patients who may still benefit from thrombolytic therapy 3 hours after symptom onset.[15,19,49] This review will focus on current imaging modalities used to assess acute ischemic stroke and explore their potential application in patient selection for treatment outside of conventional time-based guidelines.

Thrombolysis in Unselected Patients Using Extended Time Windows

Thrombolysis for acute ischemic stroke in a 0- to 6-hour window was first investigated in large multicenter trials using streptokinase.[13,39,40] These trials were halted prematurely when high rates of early fatality and hemorrhage were noted in streptokinase-treated patients.[39,40] Patients treated with streptokinase after 3 hours were noted to have higher mortality rates than those treated within 3 hours.[13] The use of streptokinase was thus abandoned in favor of rt-PA.

The National Institute of Neurological Disorders and Stroke rt-PA trial was the first trial to establish the efficacy of rt-PA in the treatment of acute ischemic stroke.[41] The trial randomized patients with ischemic stroke into 2 groups (those treated with rt-PA 0–3 hours after stroke onset and those treated with placebo 0–3 hours after stroke onset) and found that rt-PA–treated patients were at least 30% more likely to have mild or no disability on 4 different outcome scales compared with placebo-treated patients.[41] In contrast, the first ECASS failed to show any significant difference in mRS scores or Barthel Index at 90 days using a 0- to 6-hour window between rt-PA– and placebo-treated patients on an intention-to-treat basis.[23] The ECASS II and the subsequent ATLANTIS A and B trials also failed to show any benefit to tPA within 0–6 or 3–5 hours after stroke onset compared with placebo while demonstrating an increased risk of intracerebral hemorrhage.[10,11,24] Unlike the streptokinase trials, however, no increase in mortality rate was seen between the 2 groups.[11,24] A pooled analysis of these trials demonstrated benefit to rt-PA up to 4.5 hours after symptom onset at which point the number needed to treat exceeded the number needed to harm.[20,35] These findings were confirmed in the recently published ECASS III trial, which

Abbreviations used in this paper: CBF = cerebral blood flow; CBV = cerebral blood volume; ECASS = European Cooperative Acute Stroke Study; MCA = middle cerebral artery; mRS = modified Rankin Scale; MTT = mean transit time; rt-PA = recombinant tissue plasminogen activator; tPA = tissue PA.

showed a significant benefit to rt-PA treatment within 4.5 hours of ischemic stroke onset despite an increase in intracerebral hemorrhage.

Collectively, the aforementioned data suggest that there may indeed be a point in time at which rt-PA is not only of no clinical benefit but also may have the potential to cause harm. Of note, however, is that the aforementioned trials relied exclusively on clinical impression and noncontrast CT scanning criteria to establish eligibility for treatment. As such, the time windows established in these trials are not based on any physiological basis per se but rather arbitrary cutoff points based on clinical observation. Understanding the pathophysiological changes that occur during ischemic stroke and the ability to observe these changes in real time may be the keys to identifying patients who would derive the most benefit from treatment.

Cerebral Perfusion and the Ischemic Penumbra

Cerebral perfusion refers to tissue blood flow and can be expressed as CBF, CBV, and MTT. Cerebral blood volume is defined as the total volume of blood in a given volume of brain tissue and is described in ml/100 g of brain tissue. Cerebral blood volume is defined as the volume of blood passing through a volume of brain tissue per unit time, and MTT is defined as the average transit time of blood through a given brain region and is measured in seconds.[32] Neuronal dysfunction results after reduction in the CBF below 20 ml/100 g/min.[4,26] Further reductions in CBF result in failure of the sodium/potassium adenosine triphosphate pump and the ability to maintain the normal cellular osmotic gradient resulting in cellular death.[4,26,38] The concept of the ischemic penumbra relates to neuronal tissue that exhibits impaired function but has not progressed to cell death. The ischemic core relates to the latter tissue, which is irreversibly damaged. Without restoration in blood flow, the threshold for the core approaches that of the penumbra, resulting in expansion of the core size.[6] Because both the penumbra and core contribute to clinical symptoms, theoretically the restoration of blood flow to the ischemic penumbra would result in improved clinical function while little would be gained by improving blood flow to the core. In fact, some data suggest that patients with large infarct cores may be harmed by thrombolytic treatment.[2]

Data from PET scanning studies suggest that the size of the penumbra declines over time,[5] but even at 18 hours, a substantial amount of penumbral tissue may be demonstrated in up to 30% of patients.[36,37] Identifying patients in whom the penumbra is salvageable regardless of time of onset is paramount in selecting patients for intervention. Below we summarize the 2 most widely available and clinically relevant techniques to evaluate acute ischemic stroke and detect the presence of penumbra.

Magnetic Imaging Studies

Diffusion-weighted imaging is extremely sensitive in the diagnosis of acute ischemic stroke and can be abnormal even within minutes of onset.[9,28] A reduction in the apparent diffusion coefficient along with a high diffusion-weighted signal correlates to restricted diffusion of water molecules within areas of cellular edema.[46,52] Perfusion-weighted imaging parameters can be derived after an injection of Gd-based contrast. The difference between the diffusion-weighted MR imaging lesion and the perfusion-weighted imaging lesion is taken to represent tissue at risk for progressing to infarction, which can be saved by restoring blood flow.[29] Data in support of this approach comes from observational studies that have shown smaller final infarct volumes on MR images and improved clinical outcomes in patients treated with thrombolytics irrespective of time (Figs. 1 and 2).[29,42,45]

The DIAS (Desmoteplase In Acute Ischemic Stroke) trial was the first randomized study to evaluate the feasibility of using multiparametric MR imaging to extend the time window for treating ischemic stroke.[19] The trial randomized patients with mismatch between diffusion-weighted and perfusion-weighted imaging within 0–9 hours of stroke onset to thrombolytic desmoteplase or placebo treatment. The first part of the study was halted prematurely due to high rates of intracerebral hemorrhage. In the second part, patients were randomized to weight-adjusted doses (60, 90, and 125 μg/kg) of desmoteplase or placebo. Reperfusion rates were significantly higher in the desmoteplase group: 71.4% for the 125-μg/kg group and 19.2% for placebo. In addition, favorable outcome was more common in the desmoteplase group than the placebo group (60% for the 125-μg/kg group vs 22.2% for the placebo).[19] The subsequent DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) study randomized an additional 37 patients with mismatch between diffusion-weighted and perfusion-weighted imaging within 9 hours and found similar results.[15]

Thomalla and coworkers[49] compared MR imaging–selected patients treated with tPA within 0–6 hours and placebo-treated patients in ECASS, ATLANTIS (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke), and NINDS (National Institute of Neurological Disorders and Stroke) trials. Patients selected for treatment based on MR imaging criteria were more likely to achieve good functional outcome, defined as a mRS score of 1 or less, than patients selected us-

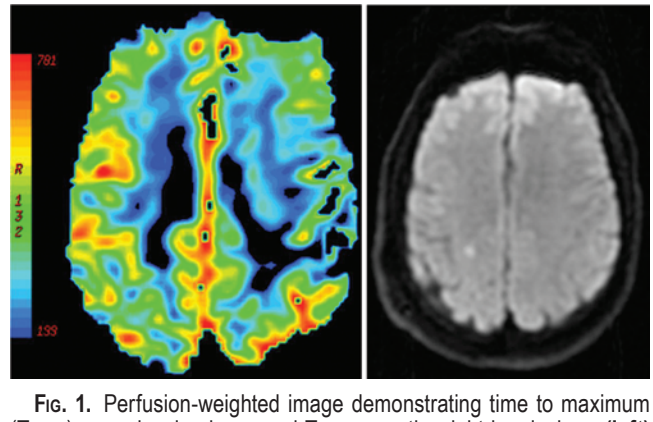

Fig. 1. Perfusion-weighted image demonstrating time to maximum (Tmax) map showing increased Tmax over the right hemisphere **(left)** without corresponding increase in signal on diffusion-weighted image **(right)** suggesting the presence of ischemic penumbra.

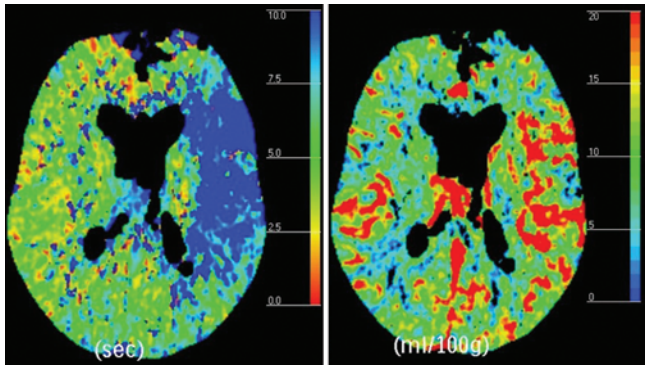

Fig. 2. Perfusion-weighted CT scans demonstrating an increase in MTT **(left)** and increase in CBV **(right)** suggesting the presence of a salvageable penumbra.

ing CT scanning and clinical criteria alone. Furthermore, the rate of symptomatic hemorrhage (3%) was similar to the rates noted in placebo-treated patients (2%) and lower than those in the pooled tPA-treated patients (8%).[49]

The recent EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) randomized patients to rt-PA or placebo 3–6 hours after stroke onset and obtained diffusion- and perfusion-weighted images in all patients.[12] Although the study's primary end point—a decrease in mean geometrical growth of the infarct—was not significantly different between the rt-PA and placebo groups, the investigators did find higher rates of reperfusion with rt-PA compared with placebo in patients with diffusion/perfusion-weighted mismatch. Reperfusion was significantly associated with better neurological outcome.[12] The trial, however, did not use baseline diffusion- and perfusion-weighted imaging profiles to select patients for treatment and, as such, provides only preliminary data.

In addition to selecting patients who may benefit from thrombolysis, MR imaging may be a powerful tool in identifying those patients in whom thrombolysis may cause harm. The DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) study evaluated the MR imaging profiles of patients treated with rt-PA 3–6 hours after symptom onset.[2] Patients without a diffusion/perfusion-weighted imaging mismatch did not benefit from early reperfusion and individuals with large diffusion- and/or perfusion-weighted MR imaging–documented lesions had more frequent symptomatic intracerebral hemorrhage upon reperfusion. Similarly, the authors of a retrospective study of 650 patients found an almost 6-fold increase in symptomatic intracerebral hemorrhage for patients with large (> 100-ml) diffusion-weighted imaging–documented lesions compared with patients with moderate or small infarct volumes.[47]

To date, few studies have evaluated the utility of perfusion-weighted MR imaging in selecting patients for endovascular treatment.[1,25] Preliminary data suggest that a combined intravenous and intraarterial tPA approach may be beneficial beyond conventional time windows when patients are selected by the presence of perfusion-weighted MR imaging mismatch.[25] The ongoing MR imaging–based RESCUE (Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations) trial, which aims to identify patients who may benefit from mechanical thrombectomy based on baseline MR imaging profiles, may provide additional information.

Computed Tomography Scanning Studies

Noncontrast CT has been the primary modality of choice in the evaluation of acute ischemic stroke since the early 1970s.[44,53] It is primarily used in the identification of intracerebral hemorrhage, parenchymal ischemic changes, and stroke mimics. Ischemic changes include sulcal effacement, loss of gray/white matter differentiation or hypoattenuation, and hypodensity.

Early ischemic changes on noncontrast CT hold some clinical predictive abilities. Studies have shown that the risk of hemorrhagic transformation of ischemic stroke is higher and no clinical benefit is derived from treatment if there is documentation of hypodensity involving more than one-third of the MCA territory.[51] The ASPECT (Alberta Stroke Program Early CT) scale is an instrument that is useful in assessing the extent of ischemic findings in the MCA territory on CT scans.[44,53] The scale classified a normal brain as represented by a score of 10, and for certain ischemic findings involving different parts of the MCA territory, a point is subtracted for each change. An ASPECT score of more than 7 predicts a better outcome after thrombolysis, whereas an ASPECT score of 7 or less reflects a higher risk of hemorrhagic transformation following thrombolysis.[44] Both PET and MR imaging studies suggest that areas of hypoattenuation on CT scans represent decreased CBV that could be a indicator of the infarct core, whereas areas of sulcal effacement have been shown to represent areas of increased CBV that may correlate with the penumbra that could be saved with thrombolytic therapy.[8,17,44]

Computed tomography perfusion scanning is more sensitive than noncontrast CT in identifying ischemic stroke in patients presenting less than 12 hours after ischemic stroke symptom onset and in detecting the extension of the infarction.[54] A large rapid bolus of iodine-based contrast material is injected during continuous rapid scanning of one or multiple slices at fixed time interval and the wash-in and wash-out of the bolus can be analyzed by a computer. Maps of regional CBF, CBV, MTT, and time to peak can be generated from the tissue-time density curve. Cerebral blood flow is proportional to the top of the curve and CBV to the area under the curve.[44] As in perfusion-weighted MR imaging, the optimal definitions of ischemic core and penumbra have not been established. The difference between CBF and CBV or MTT and CBV is commonly used as a marker for the presence of mismatch with the CBV lesion volume representing the core and the CBF or MTT lesion volume hypoperfused tissue.[32]

Clinically, CT perfusion offers several advantages over MR perfusion including faster acquisition times and wider availability. Disadvantages include longer postprocessing times, inability to image the whole brain, and potential for anaphylactic or nephrotoxic reactions to iodine-based contrast agents. The main advantages and disadvantages of the 2 perfusion modalities are summarized in Table 1.

TABLE 1: Primary advantages and disadvantages of CT and MR perfusion imaging

Perfusion Imaging Modality	Advantages	Disadvantages
CT	shorter image acquisition times, widespread availability	potential contrast reactions including anaphylaxis & renal impairment; scanning area limited to a few slices
MRI	whole-brain perfusion imaging, no radiation involved	contraindicated in patients w/ metal implants, longer acquisition times, rare instances of nephrogenic systemic fibrosis

Despite its wide availability, CT scanning has been explored in few studies for patient selection for treatment. Recently, Abou-Chebl[1] studied the efficacy and safety of intraarterial therapy including intraarterial tPA, mechanical embolectomy, or angioplasty with or without stenting in patients presenting with acute ischemic stroke less than 6 hours (early) and greater than or equal to 6 hours (late) based on CT perfusion scanning for anterior circulation mismatch or clinical–MR imaging mismatch for posterior circulation, rather than time. The mean time to treatment was 3.4 ± 1.6 hours for the early-onset group and 18.6 ± 16 hours for the late-onset group. Successful recanalization (Thrombolysis in Myocardial Ischemia score of 2 or 3) was achieved in 84.0% of all patients (early vs late onset, 82.8% vs 85.7%, respectively, p = 1.0). Intracerebral hemorrhage, 30-days mortality rate, and mRS scores of 2 or less at 3 months were similar in both groups (early vs late onset): 8.8% versus 9.5% (p = 1.0), 29.4% versus 23.8% (p = 0.650), and 41.2% and 42.9% (p = 0.902), respectively. The author of the study concluded that intraarterial therapy could be safely used in patients with acute ischemic stroke based on mismatch, rather than time, with no increase in intracerebral hemorrhage or death.[1]

Additional Applications of Advanced Imaging in Extending Time Windows

Patients with ischemic stroke may present without a known onset time, and this would disqualify them from thrombolytic treatment. One category of unknown stroke onset is patients who awaken with symptoms, often referred to as "wake-up strokes." Wake-up strokes are not uncommon, accounting for up to 25% of all cases of ischemic stroke.[14,34] Despite being excluded from treatment by current guidelines, patients' wake-up strokes have imaging findings that are often similar to those of patients in whom the time of onset is known.[14,50] Fink et al.[14] reported the clinical and imaging findings of wake-up stroke patients including perfusion imaging findings. Diffusion/perfusion-weighted imaging mismatch was present in 79% of patients with wake-up stroke who were imaged within 3 hours of stroke detection similar to 82% of those with known onset time.[14] These findings confirm that a significant proportion of patients with wake-up strokes may benefit from treatment, and in fact preliminary evidence suggests that these patients may undergo intravenous thrombolytic or endovascular therapy with similar results to patients treated under current guidelines.[7,33]

Patients who have suffered a transient ischemic attack or minor stroke who are at risk of developing worsening symptoms may also be potential candidates for treatment and can be identified through perfusion imaging.[3,43] In a recent study of patients with anterior circulation transient ischemic attack who underwent CT perfusion scanning, approximately one-third had perfusion deficits.[43] Subsequent in-hospital events were significantly more common in patients with defects documented on perfusion imaging than in those without such defects (22.7% vs 0%, respectively). Furthermore, patients with perfusion defects were more likely to have ipsilateral arterial stenosis, which may represent a target for surgical or endovascular early intervention.[43]

Limitations of Perfusion Imaging

Despite optimism surrounding the use of advanced neuroimaging to select patients for ischemic stroke treatment, this strategy remains far from being widespread. To date, perfusion/diffusion imaging is typically limited to academic or specialized medical centers with expertise in acute stroke management and neuroradiology. Furthermore, some authors have questioned the reliability of MR perfusion imaging in predicting final infarct volumes. Perfusion-weighted PET studies suggest that acute diffusion-weighted lesions may contain areas of penumbra as well as infarct, thus overestimating the size of infracted tissue,[18] while some authors have shown that the mismatch may overestimate the penumbral size.[48] Optimal definitions of penumbra/mismatch and standardized perfusion parameters across studies are lacking, and individual parameters may vary in their predictive abilities.[16,27,30]

The results of the recent DIAS-2 trial have also reinvigorated the debate over perfusion imaging and patient selection.[21] Similar to the previous DIAS and DEDAS, the DIAS-2 trial randomized patients 3–9 hours after symptom onset and selected individuals based on the presence of a mismatch for treatment with desmoteplase or placebo. The primary outcome measure of a composite improvement in NIHSS, Barthel Index, and mRS score was similar in the placebo and desmoteplase groups, whereas rates of symptomatic intracerebral hemorrhage were higher in the treatment group.[21] These findings may be unsurprising given the low number of patients in the trial with significant penumbra or visible vessel occlusion suggesting thrombus (30%), which is the ultimate target of thrombolytic treatment. Additional trials to clarify the optimal "penumbral size" and in patients with visible occlusions on vascular imaging are needed.

Conclusions

Currently, few patients with ischemic stroke receive

thrombolytic therapy in part because of the 3-hour-window requirement established by guidelines. Advanced MR perfusion and CT perfusion imaging may play an important role in identifying both patients who may still benefit from or be harmed by thrombolytic therapy outside of conventional time windows.[1,12,19] Perfusion imaging may also help to identify patients who are at risk of further neurological deterioration and should be considered candidates for early intervention.[43] Additional studies to validate and standardize perfusion parameters are needed before this approach can be recommended for widespread use.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Duffis, Gandhi. Drafting the article: Duffis, Al-Qudah. Critically revising the article: Prestigiacomo, Gandhi.

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Computed tomography perfusion–based selection of patients for endovascular recanalization

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Intravenous and intraarterial recombinant tissue plasminogen activator remains underutilized in the treatment of acute ischemic stroke, largely due to strict adherence to the concept of the therapeutic time window for administration. Recent efforts to expand the number of patients eligible for thrombolysis have been mirrored by an evolution in endovascular recanalization technology and techniques. As a result, there is a growing need to establish efficient and reliable means by which to select candidates for endovascular intervention beyond the traditional criteria of time from symptom onset. Perfusion imaging techniques, particularly CT perfusion used in combination with CT angiography, represent an increasingly recognized means by which to identify those patients who stand to benefit most from endovascular recanalization. Additionally, CT perfusion and CT angiography appear to provide sufficient data by which to exclude patients in whom there is little chance of neurological recovery or a substantial risk of postprocedure symptomatic intracranial hemorrhage. The authors review the current literature as it pertains to the limitations of time-based selection of patients for intervention, the increasing utilization of endovascular therapy, and the development of a CT perfusion-based selection of acute stroke patients for endovascular recanalization. Future endeavors must prospectively evaluate the utility and safety of CT perfusion-based selection of candidates for endovascular intervention. *(DOI: 10.3171/2011.4.FOCUS10296)*

Key Words • **acute ischemic infarct** • **computed tomography perfusion** • **endovascular recanalization** • **recombinant tissue plasminogen activator**

Despite the recent advances in imaging techniques and the evolution of endovascular intervention, stroke has remained the third leading cause of death within the US.[7,45] Ischemic stroke also represents the leading cause of disability, as one-third of the 730,000–760,000 individuals who are afflicted each year will be left permanently disabled.[7,45] In the 14 years following the approval of rt-PA for use in the treatment of acute stroke by the US FDA, approval has been granted in nearly every country.[65] Unfortunately, underutilization of the drug has remained a persistent problem, with only 3%–8.5% of stroke victims receiving intravenous rt-PA.[51] In a vast majority of patients, the primary barrier preventing the use of rt-PA is the narrow therapeutic time window within which the drug must be administered.[2] Strict adherence to time limitations bars most patients from thrombolysis, as there is rarely sufficient time for symptom recognition, transport to a medical facility, diagnosis, evaluation of exclusion criteria, and intervention. Additionally, 16%–28% of patients with ischemic stroke awaken with their deficits, thereby preventing identification of the time of symptom onset.[15,53] Unfortunately, in these patients, the time of symptom onset is equated with the time the patient went to sleep, the "time last seen well," thereby excluding them from thrombolytic therapy.[15,44,53]

An exhaustive search of the existing literature suggests that successful vascular recanalization maximizes the opportunity to reduce mortality and improve functional outcome.[52] Unfortunately, additional shortcomings of intravenous rt-PA include low rates of recanalization and high rates of vessel reocclusion. Angiographic evaluation of patients with an NIHSS score ≥ 10 revealed that more than 80% of patients have a persistent arterial occlusion after the administration of intravenous rt-PA, with only 10% of internal carotid artery and 25% of proximal middle cerebral artery occlusions partially or complete-

Abbreviations used in this paper: CBF = cerebral blood flow; CBV = cerebral blood volume; mRS = modified Rankin Scale; MTT = mean transit time; NIHSS = National Institutes of Health Stroke Scale; rt-PA = recombinant tissue plasminogen activator.

ly recanalizing.[64] Furthermore, reocclusion occurs in as many as 34% of cases.[3,13] In light of these persistent limitations of intravenous rt-PA therapy, research has focused on developing additional interventions to improve the outcome in acute ischemic stroke.

Perhaps no advancement in any area has been as significant as the development of endovascular intervention and intraarterial thrombolysis. Using cerebral angiography, neurosurgeons and interventionalists have developed both pharmacological and mechanical interventions for the treatment of major vessel occlusion. Endovascular intervention offers clear advantages in the management of stroke, including direct assessment of the occluded vessel, focused delivery of thrombolytics to the point of occlusion, and the ability to directly evaluate the result of treatment.[8,48] In addition to balloon angioplasty and stent placement, advances in technology have led to the development of multiple mechanical devices that use agitation, aspiration, and snaring of the thrombus to recanalize large caliber vessels.[9,57] Most importantly, the evolution of endovascular surgery has extended the therapeutic window for intervention (http://clinicaltrials.gov/ct2/show/NCT00359424?term=IMS+III&rank=1).[27,28]

Current Guidelines for Intravenous and Intraarterial Thrombolysis

Current guidelines for intravenous and intraarterial thrombolysis are centered around the concepts of the therapeutic window of intervention and the risk of hemorrhagic complications after thrombolysis. The National Institute of Neurological Disorders and Stroke study strictly established a 3-hour period from the time of symptom onset as the therapeutic window within which intravenous rt-PA could be administered.[45] Due to the limited practicality associated with such a narrow window for drug administration, significant research efforts explored the possibility of extending the time interval.[22,23]

The results of a pooled analysis of 6 individual studies, published in 2004,[20] suggested that the beneficial effect of rt-PA could be observed beyond 3 hours. In 2008, The Safe Implementation of Thrombolysis in Stroke Treatment Registry (SITS-ISTR) retrospectively compared outcomes between patients treated with rt-PA under 3 hours with those treated in the 3–4.5-hour window.[59] The analysis showed the groups to display no significant differences in symptomatic intracranial hemorrhage, mortality rate, or independence at 3 months, thus suggesting intravenous thrombolysis could be used safely beyond the 3-hour window. Although earlier randomized prospective trials evaluating the effectiveness of intravenous thrombolysis beyond the 3-hour window failed to show benefit, the results of the European Cooperative Acute Stroke Study (ECASS) III demonstrated a significant improvement in outcome when rt-PA was administered in the 3–4.5-hour window.[21–23] These findings prompted the American Heart Association and American Stroke Association to revise the guidelines in 2009, thereby extending the treatment window from 3 hours to 4.5 hours from the onset of symptoms.[14]

The concept of a therapeutic window is not limited to intravenous administration of rt-PA, and the time window limiting endovascular intervention continues to be a source of debate. One of the greatest limitations to endovascular intervention resides in its relatively low availability within the community, as the vast majority of providers are most commonly found in large tertiary academic centers. In addition to the initial evaluation and diagnosis, a significant amount of time may also be lost in transport to a facility with endovascular capabilities, thereby limiting the utility of intraarterial interventions. Currently, the American Heart Association guidelines have established a 6-hour therapeutic window for intraarterial thrombolysis. This time limit was derived from data emanating from the prospective, randomized, placebo-controlled Prolyse in Acute Cerebral Thromboembolism (PROACT II) study in which patients treated with intraarterial prourokinase within 6 hours of symptom onset experienced improved outcomes (40% vs 25%, respectively) and higher rates of vessel recanalization (66% vs 18%, respectively) when compared with the control population.[16]

The therapeutic window for endovascular mechanical recanalization is less defined and embolectomy via clot retrieval device has only been studied in 2 prospective nonrandomized trials.[30] The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial enrolled patients ineligible for intravenous rt-PA who presented within 8 hours of symptom onset and with large-vessel occlusions.[58] The multicenter MERCI trial examined a similar patient population treated with various clot retrieval systems, while also including patients who had not improved with the administration of intravenous rt-PA.[55] When compared with the rates of recanalization in the PROACT II study, mechanical thrombolysis resulted in higher rates of recanalization within 8 hours of symptom onset. Based on this finding, the FDA approved the use of the Merci Retriever in cases of acute stroke, but the effect of the device on clinical outcome remains unknown.[18,30] Thus, the advent of mechanical recanalization has potentially extended the therapeutic time window in which revascularization can be safely performed.

These temporal guidelines are based on clinical criteria, neurological examination, and the potential for symptomatic intracranial hemorrhage following the administration of thrombolytics. Unfortunately, the underlying pathophysiology of stroke and an evaluation of tissue salvageability are not included in these treatment protocols.[11,49] As the pharmacological and technological evolution of endovascular neurosurgery continues to expand the therapeutic window, reliable identification of appropriate candidates for intervention has become increasingly important. With the widening time window, the risk of symptomatic intracranial hemorrhage also has the potential to increase. Furthermore, in the absence of vascular imaging, patients that have no possibility of benefiting from thrombolysis, such as those with "stroke mimics" and completed infarcts with no salvageable tissue, receive intravenous rt-PA or undergo an endovascular procedure.[49] Concurrently, those with salvageable tissue and the potential of receiving the greatest benefit from thrombolysis go untreated due to their presentation outside of the window. This time window varies with each patient and depends mainly on the presence

and quality of the collateral vessels, which will determine the size of the penumbra compared with the core infarct. As a result, rapid evaluation of the acute stroke patient has evolved to include noninvasive imaging techniques to assist in the prediction of clinical outcome, the determination of tissue viability upon presentation, and the estimation of ultimate infarct size.[19] Central to this effort has been the increasing sophistication of CT scanning, particularly in the field of CT angiography and CT perfusion.

Radiological Evaluation of the Acute Stroke Patient

The relatively wide availability of modern CT scanners within the community and the relatively short acquisition time needed to generate meaningful data renders CT the ideal modality for imaging the acute stroke patient. The use of CT perfusion in the management of acute stroke was first described in 1980 by Axel,[5] yet its practical application to patient care was not possible due to the limited technology of those early imaging systems. The technological evolution that has occurred now makes it possible to identify the location of a thrombus within the vasculature while also evaluating the viability of the brain tissue. These advances have led to the development of imaging protocols by which acute stroke patients are emergently evaluated upon admission. Briefly, we discuss a commonly described protocol for the incorporation of CT angiography and CT perfusion data into the diagnosis and management of the acute stroke patient.[39]

Prior to any intervention, a noncontrast CT scan is routinely obtained to identify hemorrhage, chronic ischemic disease, and intracranial mass lesions that may have induced a seizure, thereby representing a "stroke mimic."[49] At present, a noncontrast CT scan remains the only imaging study required for the selection of candidates for thrombolysis.[33] The noncontrast CT scan should be performed within 1 hour of thrombolytic therapy to avoid the development of hemorrhage and infarction that may occur between the time of imaging and intervention.[25] The identification of any intracerebral hemorrhage on the noncontrast CT scan immediately excludes the patient as a candidate for thrombolysis.

The fact that the patient is already in the CT scanner allows for rapid acquisition of CT angiography and CT perfusion images.[32,43,61] A CT angiogram should include the vasculature from the aortic arch through the intracranial circulation to identify the site of vessel occlusion and sources of thromboembolism, while also evaluating for the potential presence of collateral circulation.[56] Finally, CT perfusion is used to assess the volumes of the infarct core and penumbra.[26,31,54,60] The data from these 3 studies is interpreted and, along with the neurological examination results, used to determine candidacy for intraarterial thrombolysis.

Within the community there is undoubtedly resistance to the use of iodinated contrast for the acquisition of CT angiography and CT perfusion images. It should be noted that the newer generations of CT scanners are capable of generating high quality images with lower doses of contrast.[33] Additionally, the incidence of contrast-induced nephropathy has been shown to be extremely low, with a recent study of 481 patients undergoing CT angiography, cerebral angiography, or both, identifying only 7 (3.3%) of 244 eligible patients with evidence of mild nephropathy.[35]

Computed Tomography Perfusion: Technical Considerations

The term cerebral perfusion refers to the blood flow within the capillary networks of the brain.[34] Computed tomography perfusion, a dynamic imaging modality, captures quantitative data pertaining to the measurement of CBF and CBV.[34,37] This advantage is derived from the linear relationship between contrast concentration and attenuation in CT imaging.[34] As a result, the volume of contrast agent within a vascular distribution may be calculated by imaging the related transient increase in attenuation as it passes through the tissue.[63] Modern imaging systems interpret this data, create time- versus contrast-concentration curves based on the selection of an "input artery" and "vein," and quantify cerebral perfusion in terms of 3 parameters: CBF, MTT, and CBV. Cerebral blood flow represents the volume of blood that passes through a volume of brain tissue within a given unit of time (ml of blood per 100 g of brain tissue per min). Mean transit time measures the average amount of time that it takes blood to flow through a region of brain (seconds), while CBV is defined as the total volume of blood in a region of brain (ml of blood per 100 g of brain tissue).[34]

In the setting of acute stroke, this model, in conjunction with an understanding of the concept of cerebral autoregulation, can be used to differentiate between the irreversible core of infarction and the ischemic penumbra.[62,63] Infarcted tissue, which lacks autoregulation, demonstrates decreased MTT and CBV, while vessels within the salvageable penumbra maintain autoregulation of blood flow. In these areas, MTT is increased, while CBV is also preserved.[6,34,62] Clinically, this distinction is of the utmost importance, as emerging evidence suggests that the mismatch between core and penumbra may exist as long as 12–24 hours from the onset of symptoms, thus extending the therapeutic window far beyond the current limitations.[10,46]

Computed Tomography Perfusion: Identification of the Candidate for Thrombolysis

The predominant flaw in treating acute stroke patients based on the concept of a strict therapeutic window is the inability to evaluate for the presence of a salvageable ischemic penumbra. There is great variability in the volume of penumbra among individual stroke patients due to the percentage of vessel lumen occlusion, the caliber of the obstructed vessel, and the presence or absence of collateral circulation. Thus, patients presenting within 1 hour of symptom onset may have no penumbra, while others presenting at much later time points may have a large volume of viable tissue.[10,49,50] Accurate identification of each population is paramount to successful treatment

of acute stroke, to both maximize the number of salvageable patients receiving intervention and to exclude those who would only inherit the risk of intracranial hemorrhage without the prospect of improvement.

In light of recent efforts to extend the length of the therapeutic window, it has become even more critical to determine the effectiveness of CT perfusion in identifying those who remain thrombolysis candidates beyond the current time limitations. Of the 3 variables described above, the size of the infarct core on CT perfusion appears to be the strongest predictor of clinical outcome in patients receiving intraarterial thrombolysis. Gasparotti et al.,[17] in their retrospective review of 42 patients receiving endovascular recanalization within 3–6 hours of symptom onset, found infarct core size to be a more relevant determinant of clinical outcome than penumbra and total perfusion deficit volume.

In a study of 22 consecutive patients treated with intraarterial thrombolysis for a middle cerebral artery stem occlusion within 6 hours of symptom onset, Lev et al.[39] showed that the volume of the infarct core on CT perfusion significantly correlated with the final infarct volume. This correlation was strongest in those patients in whom complete recanalization was achieved. Furthermore, infarct volume on admission CT perfusion was found to correlate with clinical outcome as measured by the mRS score, but not with the initial NIHSS score. For those patients presenting with a CT perfusion infarct core > 100 ml, the predictive value for a poor clinical outcome was 100%, while those with an infarct core < 100 ml had a 77% positive predictive value for a good clinical outcome. Although further analyses are needed, these results suggest that the volume of infarct core on CT perfusion is a more accurate predictor of clinical outcome than the NIHSS score.

Wintermark et al.[62] investigated the prognostic accuracy of CT perfusion in a study of 22 acute stroke patients (8 of whom were status post thrombolytic therapy) by examining the correlation between admission CT perfusion data and diffusion-weighted MR imaging performed at an average of 3 days postinfarct. Where postinfarct MR angiography demonstrated persistent arterial occlusion, the total volume of ischemia on admission CT perfusion (infarct and penumbra) correlated with the average volume of diffusion restriction on diffusion-weighted MR imaging. In cases of recanalization, infarct volume on admission CT perfusion was greater than or equal to the infarct volume on diffusion-weighted MR imaging, while the volume of diffusion restriction was significantly smaller the total area of ischemia on CT perfusion. Importantly, the admission NIHSS score correlated with the size of the ischemic lesion on CT perfusion, thus providing insight into the clinical prognosis. These studies suggest that CT perfusion reliably assesses the volume of irreversible infarction and accurately predicts the clinical outcome in potential candidates for endovascular recanalization. (Figs. 1 and 2)

Perfusion-Based Identification of Endovascular Candidates: Long-Term Outcomes

There are multiple measures of outcome following endovascular thrombolysis of the acute stroke patient. Recanalization rate, the development of intracranial hemorrhage, improvement in the NIHSS or mRS score, and mortality rates are among the most commonly evaluated variables within the literature. In light of efforts to extend the therapeutic window for endovascular therapy, it has become necessary to compare results between studies utilizing strict time window criteria and those relying on perfusion imaging.

The PROACT I and II studies represent two of the first randomized, prospective trials evaluating intraarterial recombinant prourokinase (r-proUK) treatment within a 6-hour therapeutic window.[12,16] Patient selection for intervention was dependent upon presentation within the therapeutic window and perfusion imaging data were not included in the decision-making process. The PROACT I data shows a 57.7% recanalization rate and 30.8% of patients to have an mRS score < 2. Symptomatic intracerebral hemorrhage was found in 15.4% of patients and 26.9% of patients had died at 3 months. The PROACT II study found a slightly higher rate of recanalization (66%) resulting in a greater percentage (40%) of patients exhibiting an mRS score < 2 at 3 months. The patients in the PROACT II study also experienced a lower rate of symptomatic intracerebral hemorrhage (10%) and virtually identical mortality rate at 3 months (26%).[16]

Natarajan et al.,[44] using CT perfusion data as the primary inclusion criteria for endovascular intervention, published their retrospective analysis of 30 patients who underwent endovascular intervention ≥ 8 hours after the onset of stroke symptoms. All patients selected for intervention were chosen based on CT perfusion findings of > 30% relative CBV within the affected hemisphere compared with the unaffected hemisphere. The authors reported a recanalization rate of 66.7%, a value consistent with the results published in the PROACT I and II studies. The fact that only 20% of patients possessed an mRS score < 2 at 3 months, a value considerably lower than those published in the aforementioned studies, may be explained by the expected loss of viable tissue that occurs as time from stroke onset elapses. Furthermore, it is important to note that patients in this study also experienced a 3.5-point decrease in their NIHSS score, a value not measured in the other studies. Finally, the rates of symptomatic postintervention intracerebral hemorrhage (10%) and mortality at 3 months (33.3%) were comparable to the rates observed in patients presenting at least 2 hours earlier, but treated strictly based on time of presentation. Supporting these findings is the retrospective analysis of Abou-Chebl[1] in which the safety and efficacy of intraarterial thrombolysis was compared between patients presenting < 6 hours (early group) and > 6 hours (late group) from symptom onset. All patients were selected for endovascular intervention based on the presence of perfusion mismatch on CT perfusion or MR imaging. Similar rates of symptomatic intracerebral hemorrhage were found between the groups (8.8% early vs 9.5% late), while 30-day mortality was not statistically significant between the groups (29.4% early vs 23.8% late). Perhaps most importantly were the relatively similar functional outcomes between the groups at 3 months as measured by the mRS score (41.2% mRS score ≤ 2 early vs 42.9% mRS

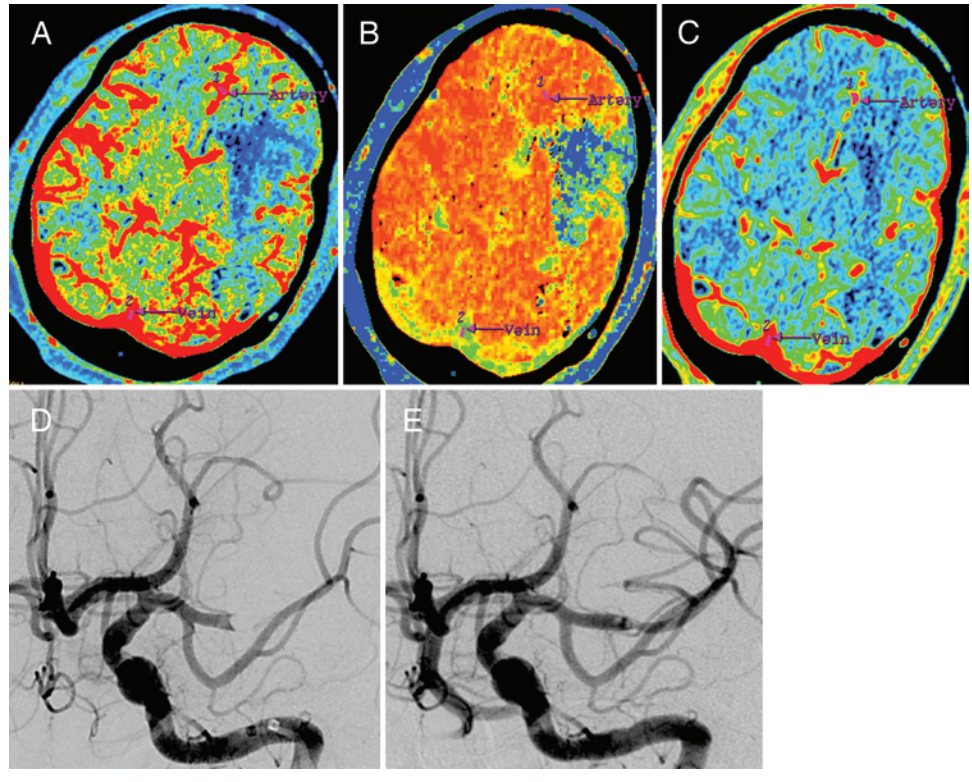

Fig. 1. Computed tomography perfusion-based selection of an appropriate candidate for endovascular thrombolysis. A 36-year-old woman presented to the emergency room 5 hours after the acute onset of right-sided hemiplegia. Her NIHSS score on admission was 22. The patient received intravenous rt-PA and was transferred to our institution without resolution of symptoms. Computed tomography perfusion on arrival exhibited decreased CBF **(A)** and increased MTT **(B)** with minimal decreased CBV **(C)** in the left basal ganglia. A cerebral angiogram **(D)** showed proximal left-sided M_1 occlusion. Two attempts to retrieve the thrombus were made with the Merci retriever, at which point angiography revealed recanalization of the middle cerebral artery **(E)**. The patient was found to have 4/5 motor strength in the right upper and lower extremities after the procedure (NIHSS score = 3).

score ≤ 2 late). These findings demonstrate the utility of perfusion imaging in determining the true salvageability of tissue, regardless of timing of symptom onset.

Utilizing diffusion-weighted MR imaging, and not CT perfusion, to identify potential candidates for endovascular intervention, Janjua et al.[29] were still able to show benefit from intervention in patients presenting more than 8 hours after the onset of stroke symptoms. The authors reported a decrease in the NIHSS score of more than 4 points in 72% of the patients selected for intervention. Once again, none of the patients undergoing endovascular recanalization suffered a postprocedure intracranial hemorrhage.

Recently, Hassan et al.[24] performed a retrospective evaluation of the efficacy of CT perfusion-guided selection of candidates for endovascular thrombolysis. The multicenter analysis compared outcomes and complications between patients selected for endovascular therapy by CT perfusion criteria versus patients selected based on time elapsed from symptom onset. The CT perfusion-guided selection of endovascular candidates failed to significantly improve clinical outcome or reduce complication rates. The retrospective nature of this study, in addition to the relatively small sample size, obviates the need for prospective randomized evaluation of CT perfusion-guided selection of endovascular candidates.

The DAWN trial (DWI/PWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention) is an ongoing multicenter study evaluating the safety and efficacy of perfusion-based endovascular therapy in patients presenting more than 8 hours after symptom onset or in cases of "wake-up" strokes.[47] Although not completed, preliminary data emanating from the study has produced results similar to those observed in endovascular intervention occurring within 8 hours of symptom onset. In a stroke population with a mean time of 16.3 hours from last-seen-well to treatment, successful recanalization was achieved in 73% of cases and 161 (83%) of 193 patients had an mRS score < 3 at 3 months. Again, the rates of symptomatic intracerebral hemorrhage (10.4%) and mortality (22%) were comparable to those in patients treated within the 6-hour time window based on timing of symptom onset alone.

Although the existing literature appears to support the utility of perfusion imaging in the selection of candidates for endovascular therapy, the data has been largely generated from retrospective analyses. Future research endeavors must include prospective randomized trials to better evaluate the true effectiveness of therapy, incidence of complications, and long-term outcome of endovascular revascularization in the ischemic stroke population presenting outside of the traditional therapeutic window.

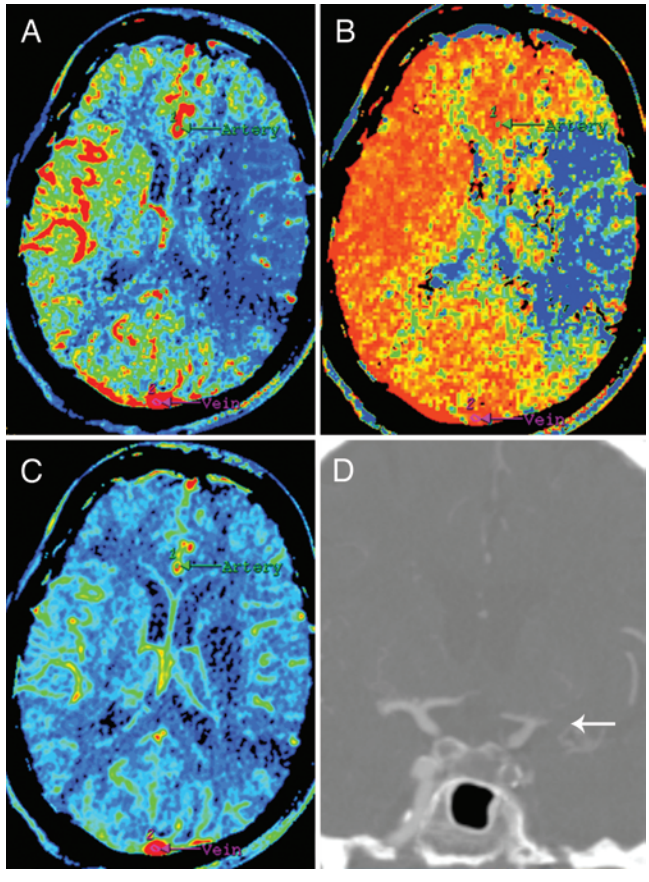

Fig. 2. Exclusion of a patient for endovascular intervention based on an unfavorable CT perfusion. A 79-year-old man presented to the emergency room 6 hours after the acute onset of right-sided hemiplegia. An emergency CT perfusion exhibited decreased CBF **(A)** and increased MTT **(B)**, as well as loss of CBV **(C)** in the distribution of the left middle cerebral artery. Coronal CT angiography **(D)** revealed a thrombus in the proximal left middle cerebral artery *(arrow)*. The patient was considered an unsuitable candidate for endovascular intervention due to the lack of a significant ischemic penumbra and a large area of completed infarct.

Institutional Protocol for CT Perfusion–Based Management of Acute Stroke

The effective utilization of CT perfusion requires, in part, implementation of an established protocol to ensure prompt evaluation, diagnosis, and intervention. At Thomas Jefferson University–Jefferson Hospital for Neuroscience, the acute stroke protocol is initiated immediately upon notification from the outside institution. If the patient is a candidate for intravenous thrombolysis, the treating physicians are encouraged to initiate therapy. Patients are transferred via helicopter or ambulance directly to the endovascular suite where the initial neurological examination is performed and noncontrast CT, CT angiography, and CT perfusion can be acquired. The decision to initiate endovascular intervention is made based on the neurological examination and the results of the imaging studies. If CT perfusion data reveals a "mismatch" between infarct core and salvageable penumbra, the patient immediately undergoes intervention, regardless of the time from symptom onset. In cases of completed infarction, the patient is transferred to the intensive care unit for supportive care.

Limitations of CT Perfusion

There is little doubt that in the vast majority of cases, CT perfusion confirms the clinical diagnosis of acute stroke and reliably assesses the volume of infarcted tissue and salvageable penumbra. However, in its current state, CT perfusion technology is limited by interobserver variability, inconsistencies between different software programs, and a lack of standardization in diagnostic criteria. Multiple investigations have attempted to define the values of CBF and CBV most sensitive for penumbra and infarct.[41,42] Murphy et al.,[41] in a prospective analysis of acute stroke patients, demonstrated that CBF and CBV measurements derived from CT perfusion were sensitive and specific in identifying infarction and penumbra. However, when logistic regression with an interaction term (CBF × CBV) was used, the data demonstrated greater sensitivity and specificity than CBF or CBV alone. Thus, these data suggest that the CBV at which infarction occurs is variable, at least in part, dependent on CBF, and incompletely defined. Further prospective analyses will be needed to better define these parameters.

The risk of hemorrhagic transformation following an acute infarct must always be contemplated when considering endovascular intervention. Multiple clinical criteria are associated with an increased risk of hemorrhagic transformation, including clinically severe strokes, the use of anticoagulants or antiplatelets, and violations of thrombolytic protocols.[22,23,36,40] At present, CT perfusion is not routinely used to determine which patients will hemorrhage following intraarterial thrombolysis. Aviv et al.[4] prospectively analyzed CT perfusion data from 41 patients presenting with acute stroke. Using CT perfusion, the authors determined the permeability–surface area product, a measure of the rate of contrast extravasation from the intravascular to the extravascular space through a disrupted blood-brain barrier.[38] In the hemorrhagic transformation group, the mean permeability–surface area product (0.49 ml × min^{-1} × $[100\ g]^{-1}$) was significantly higher than the permeability–surface area product for the group that did not hemorrhage (0.09 mL × min^{-1} × $[100\ g]^{-1}$). These findings translated into a 77% sensitivity and 94% specificity for the prediction of hemorrhagic transformation when the PS threshold was set at 0.23 ml × min^{-1} × $(100\ g)^{-1}$. Clearly, further investigation may reveal CT perfusion to be a useful tool in better defining the risk of hemorrhage.

There are a number of scenarios in which the utility of CT perfusion and its contribution to patient care have become the subject of debate. In many instances, CT perfusion reveals information pertaining to infarct and penumbra volume that clearly assists in the decision to intervene.[50] In patients presenting with a small area of completed infarct and a large penumbra, the decision to proceed with thrombolysis is considered to have a favorable risk-benefit ratio. Likewise, patients with large infarcts and relatively little or no penumbra would be considered poor candidates for intervention.[49] The controversy arises in scenarios in which the difference in infarct and penumbra volumes is less dramatic. For example, there are currently no guidelines for patients presenting with a small infarct core and

small penumbra, nor is there data to define the appropriate treatment for patients with large infarcts and penumbra. As there is currently no classification scheme for CT perfusion volumetric data, decisions in these circumstances must be made based on neurological examination and clinical acumen. Furthermore, the ability of CT angiography to identify the site of vessel occlusion in these circumstances is a key component of the decision-making process. Thrombus in a large-caliber proximal vessel on CT angiography may be amenable to endovascular therapy, whereas distal vessel disease is unlikely to improve with endovascular intervention.

There is no doubt that CT angiography plays an essential role in the diagnosis of posterior circulation ischemic stroke through its rapid identification of thrombus within the vertebral or basilar arteries.[26] Unfortunately, the utility of CT perfusion in the evaluation of brainstem and cerebellar ischemia is extremely limited and data generated from these studies are less reliable predictors of outcome.

Conclusions

The obvious limitations of intravenous thrombolysis have driven the need to develop effective endovascular techniques to better treat acute ischemic stroke. The evolution of endovascular therapy has been mirrored by the need to lengthen the therapeutic window for potential pharmacological and mechanical revascularization. Evidence is now emerging that supports the need for treatment protocols based on the pathophysiology of each individual stroke patient. Computed tomography perfusion, used in conjunction with noncontrast head CT and CT angiography, appears to reliably distinguish between infarcted and salvageable tissue, thus providing important data when deciding upon intervention. Due to the relatively recent introduction of this technology into clinical practice, lack of widespread use, and longstanding reliance on the concept of the therapeutic time window, prospective randomized trials assessing the utility of CT perfusion will be needed. At present, the existing data appears to support the safe and effective implementation of endovascular intervention beyond the traditional therapeutic time windows and future advances in imaging offer the potential of expanding the possibility of intervention to an even larger number of patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Improving patient selection for endovascular treatment of acute cerebral ischemia: a review of the literature and an external validation of the Houston IAT and THRIVE predictive scoring systems

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Outcome after intraarterial therapy (IAT) for acute ischemic stroke remains variable, suggesting that improved patient selection is needed to better identify patients likely to benefit from treatment. The authors evaluate the predictive accuracies of the Houston IAT (HIAT) and the Totaled Health Risks in Vascular Events (THRIVE) scores in an independent cohort and review the existing literature detailing additional predictive factors to be used in patient selection for IAT. They reviewed their center's endovascular records from January 2004 to July 2010 and identified patients who had acute ischemic stroke and underwent IAT. They calculated individual HIAT and THRIVE scores using patient age, admission National Institutes of Health Stroke Scale (NIHSS) score, admission glucose level, and medical history. The scores' predictive accuracies for good outcome (discharge modified Rankin Scale score ≤ 3) were analyzed using receiver operating characteristics analysis. The THRIVE score predicts poor outcome after IAT with reasonable accuracy and may perform better than the HIAT score. Nevertheless, both measures may have significant clinical utility; further validation in larger cohorts that accounts for differences in patient demographic characteristics, variation in time-to-treatment, and center preferences with respect to IAT modalities is needed. Additional patient predictive factors have been reported but not yet incorporated into predictive scales; the authors suggest the need for additional data analysis to determine the independent predictive value of patient admission NIHSS score, age, admission hyperglycemia, patient comorbidities, thrombus burden, collateral flow, time to treatment, and baseline neuroimaging findings. *(DOI: 10.3171/2011.3.FOCUS1144)*

Key Words • **intraarterial therapy** • **acute cerebral ischemia** • **futile recanalization** • **patient selection** • **predictive scale validation** • **vascular disorders**

Stroke is the third leading cause of mortality and is a similarly significant cause of disability in the US; of the 795,000 annual cases of stroke per year, 87% are considered to be ischemic or resulting from a clot in the cerebral vasculature that obstructs the flow of oxygen and nutrients to the brain.[40] Rates of morbidity and mortality due to cerebral ischemia are expected to increase as a large portion of our population grows closer to the age of greatest cerebrovascular risk. The standard of care for acute stroke patients presenting to emergency service within 3 hours of symptom onset is IVtPA, or aspirin if presenting outside of the 3-hour time window. There is an increased risk of hemorrhagic transformation when IVtPA is administered after 3 hours from onset, and aspirin is not thought to provide sufficient therapeutic benefit to acute stroke patients; thus, practitioners have turned to IAT as a treatment option for acute ischemic stroke. The problem with IAT, however, is that only 40%–50% of patients with successful recanalization of blood vessels demonstrate positive, long-term functional outcomes.[26]

Abbreviations used in this paper: ASPECTS = Alberta Stroke Program Early CT Score; DM = diabetes mellitus; DW = diffusion-weighted; HIAT = Houston IAT; IAT = intraarterial therapy; IVtPA = intravenous tissue plasminogen activator; MCA = middle cerebral artery; MRA-DWI = MR angiography–DW imaging; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; PW = perfusion-weighted; ROC = receiver operating characteristics; THRIVE = Totaled Health Risks in Vascular Events; TIMI = Thrombolysis in Myocardial Ischemia; UCLA = University of California Los Angeles.

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In the scope of acute ischemic stroke, endovascular intervention is not synonymous with therapeutic benefit, and it is important that medical practitioners acknowledge this fact and begin to treat patients accordingly. Stroke victims presenting to the hospital after hours or days of ischemia—far outside the therapeutic window for salvage of viable tissue—have irreversible damage that IAT will not clinically change. Further, futile intervention is not a simply benign procedure in these situations—patients with little chance of clinical benefit may be more likely to experience complications with intraarterial procedures involving tPA and mechanical devices, indicating that the risks outweigh the benefits in many cases. Beyond clinical considerations, one must consider that IAT is invasive, expensive, and requires a specially trained team. In light of clinical and practical considerations, selection of patients likely to benefit from IAT, as opposed to performing this risky procedure on all acute ischemic stroke patients not eligible for IVtPA therapy, is imperative. Specialists posit that a number of baseline factors could be useful in predicting functional outcomes in patients being considered for IAT, better enabling neurospecialists to select the best candidates for treatment.

Recently, the Agency for Healthcare Research and Quality of the US Department of Health and Human Services produced a draft technical brief on mechanical thrombectomy for acute ischemic stroke, providing scientific advice to the Centers for Medicare and Medicaid Services, a document that ultimately attests to the quantity of scientific evidence that IAT is a clinically efficacious procedure for acute ischemic stroke and the rationale for medical insurance coverage of the procedure.[30] One of the document's most salient points is that there is a lack of clinical equipoise in the current culture of IAT use for acute ischemic stroke and that more standards are needed for selection of candidates likely to benefit from intervention.

We sought to compare the application of two predictive scoring systems that have been shown to be able to select ideal candidates for IAT—the Houston IAT (HIAT) and THRIVE—to the Columbia University Endovascular Neurosurgery Patient Database. These scores were developed based on patient characteristics found to be predictors of outcome after IAT regardless of recanalization status. We also review the existing literature and provide an analysis of predictors of futile recanalization after IAT.

Methods

All patients who underwent neuroendovascular intervention at Columbia Presbyterian Hospital from 2004 through 2010 were enrolled in the Endovascular Neurosurgery Patient Database. Patients with the diagnosis of acute ischemic stroke who underwent either intraarterial thrombolysis or mechanical thrombectomy were included in the study. Demographic and admission clinical and radiographic characteristics were retrospectively acquired (Table 1). Outcome was assessed at discharge using the mRS. The HIAT and THRIVE scores were calculated for each patient based on the following variables: age, admission NIHSS score, admission blood glucose concentration, and medical history of atrial fibrillation, DM, and hypertension (see *Existing Predictive Scoring Systems*). The scores' performance and predictive accuracies for good outcome (discharge mRS score ≤ 3) were analyzed using the Fisher exact test and ROC analysis, respectively. We also performed a number of univariate analyses of factors—some included in the HIAT and THRIVE scores and some that were not—that we thought could also be independent significant predictors of patient outcome following IAT.

TABLE 1: Columbia University Endovascular Neurosurgery Patient Database—HIAT/THRIVE validation cohort demographics*

Characteristic	Value
male sex (%)	37 (49)
age in yrs	
average	63
range	21–89
admission NIHSS score	
average	17
range	2–35
history of hypertension	50
history of atrial fibrillation	21
history of DM	23

* Values represent numbers of patients unless otherwise indicated.

Results

One hundred fifty-one patients treated at Columbia Presbyterian Hospital during the study period met the initial inclusion criteria; 74 had sufficiently complete outcome data for analysis. Patients' HIAT scores were calculated on a scale of 0–3, as detailed in Table 2. Patients with a HIAT score of 0 or 1 were considered "low-risk," whereas those

TABLE 2: Calculation of predictive scores

HIAT*	THRIVE†
age	age
>75 yrs, 1 point	≤59 yrs, 0 points
baseline NIHSS score	60–79 yrs, 1 point
>18, 1 point	≥80 yrs, 2 points
baseline glucose level	baseline NIHSS score
≥150 mg/dl, 1 point	≤10, 0 points
	11–20, 2 points
	≥21, 4 points
	medical history
	DM, 1 point
	atrial fibrillation, 1 point
	hypertension, 1 point
range of possible scores: 0–3	range of possible scores: 0–9

* Based on Hallevi et al., 2009.
† Based on Flint et al., 2010.

with a HIAT score of 2 or 3 were considered "high-risk"; 68.5% of low-risk patients and 90% of high-risk patients had poor outcome (p = 0.07). THRIVE scores were calculated on a scale of 0–9 points, as detailed in Table 2. Patients with THRIVE scores of 0–2 were considered "low-risk," those with scores of 3–5 as "medium-risk," and those with scores of 6–9 as "high risk"; 46.15% of low-risk, 76.32% of medium-risk, and 86.96% of high-risk patients experienced poor outcome (p = 0.03). The HIAT and THRIVE scores demonstrated an area under the ROC curve of 0.616 (95% CI 0.481–0.752, p = 0.133) and 0.733 (95% CI 0.594–0.871, p = 0.003), respectively (Fig. 1). The THRIVE score was found to be a significant predictor of patient outcome following IAT for acute cerebral ischemia. The HIAT score trended toward predicting outcome, but was not found to achieve statistical significance. Univariate analyses of additional factors found that the following are significantly independent predictors of outcome following IAT: age (p = 0.013), history of hypertension (p = 0.006), history of tobacco use (p = 0.031), and admission NIHSS score (p = 0.047). Patient sex, history of atrial fibrillation, history of DM, history of hyperlipidemia, history of congestive heart failure, admission prothrombin time, admission international normalized ratio, admission partial thromboplastin time, admission values for serum sodium level, serum creatinine, and serum troponin were not found to be significant predictors in univariate analyses in our patient cohort (Table 3).

TABLE 3: Univariate association of admission characteristics with outcome*

Factor	mRS Score ≤3 (19 pts)	mRS Score >3 (55 pts)	p Value
mean age	55.58 ± 15.59	65.95 ± 15.23	0.013†
male sex	12 (63.1)	25 (45.4)	0.183
history of hypertension	8 (42.1)	42 (84.0)	0.006†
history of tobacco use	4 (21.1)	29 (52.7)	0.031†
history of atrial fibrillation	3 (15.8)	18 (32.7)	0.239
history of DM	6 (31.6)	17 (30.9)	1.000
history of hyperlipidemia	5 (26.3)	24 (82.8)	0.182
history of congestive heart failure	2 (10.5)	15 (27.2)	0.207
median NIHSS score (IQR)	15 (8–21)	18 (14–23)	0.047†
mean PT	14.74 ± 2.82	16.04 ± 2.87	0.093
mean INR	1.11 ± 0.28	1.23 ± 0.29	0.115
mean PTT	28.73 ± 7.09	38.66 ± 26.62	0.114
mean sodium level	136.37 ± 5.79	139.38 ± 7.62	0.120
mean creatinine level	1.05 ± 0.34	1.05 ± 0.53	0.990
mean troponin level	0.25 ± 0.86	0.32 ± 0.66	0.698

* Values represent numbers of patients (%) unless otherwise indicated; means are expressed ± SD, medians with IQR in parentheses. Abbreviations: INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time.

† Statistically significant difference.

Review

Forms of IAT and Existing Study Findings

Intraarterial therapy has become widely used to treat ischemic strokes and comprises a number of pharmaceutical or mechanical techniques used to enter the intracranial arteries and eradicate a blood clot to restore blood flow to the brain. Patients in whom recanalization is achieved do appear to have better outcomes and lower mortality than those patients without recanalization. A recent study analyzing the effects of recanalization found that there is a 4- to 5-fold increase in the odds of a positive functional outcome and a 4- to 5-fold decrease in the odds of death in patients whose vessels do regain patency.[49] While various forms of IAT have FDA approval for their technical efficacies, there remains to be any conclusive study or guidelines as to the exact populations and situations in which IAT has been shown to be clinically efficacious.

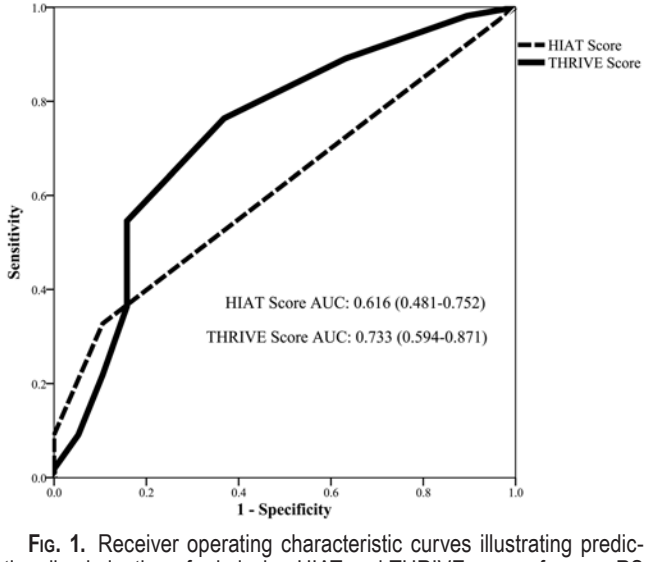

Fig. 1. Receiver operating characteristic curves illustrating predictive discrimination of admission HIAT and THRIVE scores for an mRS score of 3 or less at discharge. Data are expressed as area under the curve (95% CI). AUC = area under the curve.

Intraarterial administration of pharmaceutical agents can typically be undertaken up to 6 hours after symptom onset—delivering a larger dose of thrombolytic agent than is used intravenously—directly through a catheter to the ischemic core.[53] A major risk of this intervention is the occurrence of symptomatic intracranial hemorrhage following thrombolytic administration, necessitating that its use should be carefully considered in conjunction with other patient factors.[10,32,55,59] Many studies have demonstrated higher recanalization rates and reduced systemic exposure to the drug after IAT than experienced in patients given the drug intravenously.[53] One clinical series reports higher early recanalization rates (50%–80% of cases) compared with intravenous treatment (30%–50% of cases).[52,53]

Large intracranial thrombi often resist intravenous or intraarterial administration of thrombolytic agents, and in these cases many physicians turn to intraarterial mechanical thrombectomy to achieve recanalization. These mechanical devices have gained FDA approval for tech-

nical efficacy based on the results of many studies, including the PROACT II, MERCI, and Multi-MERCI trials. The PROACT II study authors reported that vessel patency was achieved in 48% of patients treated with the Merci retriever (Concentric Medical, Inc.) and 81% of patients treated with the Penumbra system (Penumbra, Inc.), compared with 18% patients who experienced spontaneous recanalization.[45]

Physicians have demonstrated that combined use of mechanical and pharmaceutical intervention can also result in recanalization. A study that looked at the utility of the Penumbra system alone or in conjunction with intraarterial administration of pharmaceutical thrombolytic agents reported a 93% revascularization rate; 52% of patients had complete revascularization and were more likely to experience positive clinical outcomes.[8] Another recent study found a combined use of aggressive mechanical clot disruption with a low-dose of intraarterial urokinase to be safe and effective in achieving recanalization in IVtPA failures; complete recanalization was achieved with aggressive microcatheter-microwire clot disruption in 83% of patients, and 67% of patients had an excellent outcome (mRS score 0 or 1) at 3 months.[59]

Existing Predictive Scoring Systems

Intraarterial therapy is an invasive and complex procedure that should require a careful patient selection process. As physicians ponder why some patients experience a better outcome than others regardless of recanalization status, it is important to look at all the predictors of outcome that have been assessed. Recently, research groups have begun to develop scales utilizing significant predictors to help physicians select patients for IAT; two of the most recently validated are the HIAT score and the THRIVE score.

The HIAT Score. Researchers from Houston and UCLA developed the HIAT score, which is composed of 3 factors found to be significant and independent predictors of patient outcome subsequent to IAT regardless of patient recanalization status: age, NIHSS score, and admission glucose level.[26] Patients treated with IAT at the University of Texas Houston Stroke Center were retrospectively assigned 1 point for each of the following factors: age > 75 years, NIHSS score > 18, and glucose level > 150 mg/dl. The median NIHSS score for good outcome was 16, while the median NIHSS score for poor outcome was 20. Poor outcome in patients treated with IAT was defined as an mRS score of 4–6 at hospital discharge. The researchers report that with increasing HIAT scores (maximum score, 3), there was an increase in poor outcome and mortality. The data were validated using a separate set of patients from UCLA. The HIAT enables interventional neuroradiologists to estimate the chance of poor outcome after IAT—regardless of recanalization status—and therefore aids in selecting patients who will benefit more from IAT treatment.

The THRIVE Score. Patient data from the MERCI and Multi-MERCI trials were analyzed to determine whether specific chronic diseases can be used—along with NIHSS score and age—to create a predictive scale that would indicate likely patient outcome following endovascular stroke treatment with the Merci retriever.[20] The investigators who created the THRIVE score report that recanalization status did not significantly differ between the poor and good outcome groups. NIHSS score and age were trichotomized, and specific chronic diseases were assigned point values to make up the THRIVE scoring system (see Table 2).

Two points were given for each level of the trichotomized NIHSS, 1 point for each level of trichotomized age, and 1 point for the presence of each chronic disease (hypertension, DM, and/or atrial fibrillation). Patients with a low THRIVE score (0–2) had good outcomes in 64.7% of cases and a mortality rate of 5.9% at 90 days after onset. Patients with a moderate THRIVE score (3–5) had good outcomes in 43.5% of cases and a mortality rate of 30.1% at 90 days, and patients with a high THRIVE score (6–9) had good outcomes in 10.6% of cases and a mortality rate of 56.4% at 90 days.

Among the patients with successful vessel recanalization, those with a low THRIVE score had good outcomes in 82.6% of cases and a mortality rate of 0% at 90 days; those with a moderate THRIVE score had good outcomes in 60% of cases and a mortality rate of 19.4% at 90 days; those with a high THRIVE score had good outcomes in 18.5% of cases and a mortality rate of 48.5% at 90 days. Among patients without successful vessel recanalization, those with a low THRIVE score had good outcomes in 27.3% of cases and a mortality rate of 18.2% at 90 days; those with a moderate THRIVE score had good outcomes in 6.9% of cases and a mortality rate of 53.3% at 90 days; and those with a high THRIVE score had good outcomes in 0% of cases and a mortality rate of 67.4% at 90 days (Mantel-Haenszel chi-square test).

This analysis shows that among the patients who underwent endovascular stroke treatment in the MERCI and Multi-MERCI trials, the THRIVE score effectively predicts 90-day clinical outcomes. Further validation of this score would make it a very effective tool in the selection of patients for IAT.

Individual Predictors of Futile Recanalization

There exist many suggested factors that might be used to predict which patients are most likely to benefit from IAT; risk factors that have been shown to independently predict negative functional outcomes—some regardless of recanalization status—may be used in weighing whether to treat patients with acute ischemic stroke who are not eligible for IVtPA. Patients whose profiles include a number of these predictive risk factors may need extra consideration before intervention, and some may be better suited for alternative therapy.

The NIHSS Score. The NIHSS score is a marker of stroke severity that is widely used at admission as a surrogate outcome marker in many ischemic stroke studies. As previously mentioned, the authors of the HIAT study found that the median baseline NIHSS score for patients with good outcomes after IAT was 16, while the median baseline NIHSS score for poor outcomes was 20; the rate of recanalization did not differ significantly between the

good and poor outcome groups (p = 0.4).[26] The THRIVE score author group trichotomized NIHSS scores (≤ 10, 11–20, and ≥ 21) and concluded that the breakdown of the scale could effectively predict those very likely, moderately likely, and least likely to experience good outcome subsequent to endovascular stroke treatment, respectively.[20] Yet another analysis reports that patients who experienced futile recanalization, defined as successful removal of the thrombus without corresponding clinical improvement, had higher median baseline NIHSS scores (19) compared with those with nonfutile recanalization pursuant to IAT (14).[29] Multiple groups report that an NIHSS score of < 10 is a predictor of a good clinical outcome for patients treated with IAT.[3,29]

Further, investigators also report that NIHSS scores can significantly predict reocclusion after tPA-induced recanalization, indicating that patients who experienced reocclusion presented with higher baseline stroke scale scores.[50] Reocclusion is associated with a worse clinical course and poor long-term outcome compared with patients with sustained recanalization. Thus, a patient's NIHSS score must be factored into the decision of whether to pursue IAT or not to, both to minimize likelihood of futile recanalization and the risk of deleterious reocclusion and maximize chances of actual therapeutic benefit.

Age. There are limited data available regarding the safety and efficacy of IAT specifically in elderly patients, despite the fact that this is the population most likely to experience cerebral ischemia and therefore be considered for this therapy.[11,17,23,42,58] Stroke is an age-related disease: per capita, people aged 85–94 years experience a 2-fold higher incidence of stroke compared with people aged 65–74 and a 26-fold higher incidence compared with people aged 45–54. As the elderly population in the US rapidly grows, advances in acute therapies for stroke shown to be effective in the elderly are urgently needed.

A study to identify age-specific aspects of response to IAT analyzed a large group of ischemic stroke patients and compared the outcomes between those patients older than 80 years and those younger than 80 years.[47] The 90-day outcomes among the elderly showed lower rates of excellent functional outcome (mRS score < 1, 26% of elderly patients vs 40% of younger patients) and survival (57% vs 80%, respectively), regardless of recanalization status. The authors ultimately report that patients 80 years and older had a higher risk for poor outcome at 1–3 months following IAT, even after adjusting for recanalization status. These results could be related to a higher frequency of prior stroke or TIA, higher frequency of prestroke comorbid conditions and poststroke medical complications, impaired collateral circulation, reduced neuronal reserve, and fewer social supports in the elderly population.

Age brings in to consideration a number of factors. It is posited that diminished neural plasticity in the elderly may lower the chances of recovery following cerebral injury.[12,47,56] Patients 80 years of age or older were reported to have more frequent comorbidities, more extensive coronary disease, and a 2- to 4-fold increase in risk for complications following IAT, including death, Q wave myocardial infarction, renal failure, stroke and vascular complications.[7,47] Studies also show that elderly patients have a reduced capacity for developing collateral blood flow and that increased age predicts the absence of collateral circulation to the ischemic region.[35,47] The presence of collateral flow is correlated with better outcomes, most likely due to its ability to provide at-risk areas of brain tissue with some blood flow; the independent predictive values of the presence of comorbidities and the presence of collateral flow are discussed later in this paper.

A second group studying IAT in acute cerebral ischemia reported that patients experiencing futile recanalization were older (73 ± 11) as compared with the nonfutile recanalization group (58 ± 15 years); further, age > 70 years was independently and positively associated with futile recanalization.[29] Yet another study found that between 2 groups of patients, one composed of patients 80 years of age and older and the other only patients younger than 80 years, outcomes at 90 days post-IAT showed lower rates of excellent functional outcome (mRS score ≤ 1, 26% vs 40%, p = 0.02) and survival (57% vs 80%, p = 0.01) in the older patient group; there were no detectable differences in recanalization (TIMI score 2–3) between the 2 groups.[33]

Intraarterial thrombolysis can be accomplished in the elderly with recanalization rates and hemorrhage rates equal to those obtained in younger patients. Even with higher mortality rates and lower rates of good functional outcomes than in younger patients, nondisabling outcomes may be achieved in a quarter of the elderly population treated with IAT. These findings suggest that the use of IAT in very elderly patients should not be avoided, but pursued with caution in an effort to treat those patients likely to benefit from it.[33]

Hyperglycemia. It is widely accepted that high serum glucose concentration at presentation in patients with acute cerebral ischemia often indicates a more serious stroke and, all else being equal, foreshadows a worse outcome. Hyperglycemia occurs in diabetic and nondiabetic acute ischemic stroke patients and it is present in up to 49% of stroke patients without a preexisting diagnosis of DM.[34] Although few studies have looked solely at the association between hyperglycemia and futile recanalization, a number of groups have established that a high admission glucose level is associated with worse outcome. The investigators who devised the HIAT and THRIVE scores took these studies into consideration and found admission hyperglycemia or a preexisting diagnosis of DM to be independent predictors of outcome after endovascular treatment of acute ischemic stroke.[20,26]

One of the many studies that have looked at the correlation between admission hyperglycemia and ultimate outcome found that in acute stroke patients, hyperglycemia was a predictor of poor outcome following recanalization, independent of age, DM diagnosis, and stroke severity.[2] The exact cause of poststroke hyperglycemia in nondiabetic patients is not definitively known, but some posit that it may be due to stress caused by the release of cortisol and norepinephrine or impaired glucose metabolism.[2,18] Additionally, the cause of the difference in outcome between patients with hyperglycemia at presen-

tation without a history of diabetes versus those with a previous diagnosis is unclear.

A number of correlations exist between hyperglycemia and stroke, including a smaller volume of salvageable penumbra, increased infarct volumes, and reduced efficacy of thrombolytic agents.[2,22] High glucose levels at admission may counteract the beneficial effects of tPA, regardless of recanalization status. A baseline blood glucose level greater than 140 mg/dl is linked to greater infarct size, worse outcome, and lower degree of neurological improvement after reperfusion. Leigh et al.[38] report that hyperglycemia (> 150 mg/dl) at admission was greater in patients who had hyperacute worsening (NIHSS score change ≥ 4 points within the first 24 hours) even in the presence of recanalization after IAT ($p = 0.004$, OR = 6.47). The group also reports that high blood glucose concentration was an independent predictor of in-hospital mortality.

Because of the associated risk of hyperglycemia and poor outcome, glucose monitoring is imperative. Poor glycemic control was associated with unfavorable prognosis in patients with persistent hyperglycemia, patients without a known history of diabetes, and patients with cortical infarction.[34] Early identification of patients with abnormal glucose metabolism or DM is important when considering glycemic control strategies as well as when considering other acute stroke treatment.[22]

Comorbidities. A patient's general state of health prior to stroke onset is another factor that must be used in determining the probability that he or she will experience a positive functional outcome after IAT, as the body's ability to quickly recover from injury is often compromised in patients with other illness. A history of cardiovascular disease, cerebrovascular disease, or neurological deficits may compound the effects of stroke and increase the difficulty of endovascular reperfusion.

The THRIVE scale investigators report that a patient's history of hypertension, DM, or atrial fibrillation is independently predictive of poor outcome following IAT, regardless of reperfusion status.[20] A history of stroke, coronary artery disease, or congestive heart failure has also been associated with worse outcomes in patients given endovascular therapy for acute cerebral ischemia.[20,26,39]

Other authors have investigated the impact of admission cholesterol level on outcome after ischemic stroke thrombolysis in 104 patients who received IVtPA, intraarterial tPA, or mechanical thrombus retrieval. Lower levels of low-density lipoprotein cholesterol, with or without statin treatment, were independently and significantly correlated with a higher risk of symptomatic hemorrhagic transformation after revascularization therapy.[5] Patients who were current smokers and who presented with greater stroke severity also had a greater risk of symptomatic hemorrhagic transformation. Old age, hypertension, hyperlipidemia, and previous coronary heart disease were more prevalent in patients with prior statin use. Restrepo et al.[48] reported that even after controlling for recanalization status, an analysis of a prospectively maintained stroke registry showed that a patient history of hyperlipidemia was negatively associated with excellent functional outcome (mRS score ≤ 1) at 3 months after stroke; the group reports that for every 50 mg/dl increment in a patient's total cholesterol level, there was a 64% decrease in the odds of excellent functional outcome (OR = 0.36, $p = 0.0253$). The presence of hyperlipidemia also was associated with a higher NIHSS score at 7 days after stroke or on the day of discharge, and statin use was related to an average 6.5-unit NIHSS score decrease at discharge ($p = 0.016$). Statin use was not associated with increased frequency of recanalization or symptomatic intracranial hemorrhage.

Another study found a relationship between blood pressure, vessel recanalization, and patient outcome. In most stroke patients, blood pressure is typically elevated; ischemic stroke patients with high blood pressure are more likely to experience dependency, death, or risk of recurrent stroke.[43,57] Another study that analyzed data obtained in patients after intraarterial therapy noted that in those patients in whom recanalization was achieved, systolic blood pressure measured 12 hours after therapy had declined more than when recanalization failed and thus made better outcome more likely.[43]

Patients who are already vulnerable due to a preexisting health condition are less likely to recover from an injury related to an endovascular procedure, but exactly which conditions make patients especially susceptible to injury have not been extensively studied. Although some studies report contrasting conclusions regarding specific comorbidities and their links to patient outcome following IAT, the individual patient's medical history, especially regarding current cardiovascular or cerebrovascular issues, must be taken into consideration when determining whether he or she is a good candidate for IAT. Once further analyses are done to reliably relate the presence of a specific comorbidity with a likely outcome of futile recanalization, physicians should screen all patients presenting with ischemic stroke for any proven predictors and take their presence into careful consideration before undertaking IAT. The utmost consideration should be given to the likelihood that a patient will benefit from an endovascular reperfusion strategy before any IAT measures are initiated.

Thrombus Burden. Thrombus size has been shown to affect endovascular interventions and predict poor clinical outcomes and is thus an important factor when considering endovascular stroke intervention. Qureshi et al.[46] modified the TIMI scale to include a 5-point angiographic thrombus burden grading scale in patients with cerebral ischemia; the scores range from 0 (no angiographic characteristics suggesting a thrombus) to 4 (large thrombus present, greatest dimension equivalent to 2 or more vessel diameters).[6,46] Multiple groups report that large thrombi present in the proximal MCA and the terminal internal carotid artery have demonstrated resistance to mechanical therapy and thrombolysis, thereby complicating and delaying recanalization efforts.[6,21,51] As discussed later in this paper, increased length of time to recanalization is often associated with poor outcome, so further delay in time to recanalization must be considered in patients presenting more than 8 hours after onset with large thrombus burdens.

Gralla et al.[25] studied thrombus length and its effect on success of recanalization during mechanical thrombectomy. They report that longer thrombi (20–40 mm) result in a decreased recanalization rate and an increased complication rate in comparison with shorter thrombi (10 mm), a finding that they attributed to thrombus-device interaction. They report that distal dislocation of thrombotic material increased with thrombus length; thromboembolic events into other vessels increased from 0% in the 10-mm thrombus group to 7.4% in the 20-mm thrombus group to 14.8% in the 40-mm thrombus group. They note that these events are clinically significant due to the likelihood that they will worsen neurological status by occluding a previously unaffected vascular territory. Similarly, another group found that the length of basilar artery occlusions was a predictor of clinical outcome independent of recanalization status, likely related to the extent of irreversible brainstem damage, vegetative dysfunction, and/or death in patients with larger thrombi.[9]

Researchers hypothesize that larger thrombi are more clinically significant due to their resistance to thrombolysis. Grade 4 thrombi require longer times for intraarterial therapy and often necessitate larger doses of thrombolytic agents.[6] The rate of successful recanalization did not differ significantly between Grade 4 thrombi and Grades 0–3; however, for patients in whom recanalization was achieved, the time from the diagnostic angiogram to recanalization was significantly longer in those with Grade 4 thrombi (median 118 vs 72 minutes) than those with lower-grade thrombi. After controlling for age, baseline NIHSS score, and artery of involvement, patients with Grade 4 thrombi are 2.4 times more likely to experience a poor clinical outcome and 4 times more likely to die. Patients with Grade 4 thrombi were 2.7 times more likely to be discharged to a nursing home or hospice. These poor outcomes in patients with Grade 4 thrombi may be a result of greater stroke severity (based on the NIHSS score), delay in recanalization, or occlusion of collateral pathways that could create larger infarctions. Because Grade 4 thrombi show resistance to thrombolytic agents, many researchers suggest early aggressive IAT therapy. This clinical decision should be made after considering other cofactors related to the individual patient in question.

Collateral Circulation. When cerebral vessel occlusions occur, some areas of neural tissue originally perfused by the occluded artery can be fed by collateral blood flow originating in other parts of the brain, including from large vessels at the circle of Willis or small pial vessels near the surface of the brain.[13] When blood flow to a part of the brain is blocked, these existing arterial connections may be able to compensate for the lack of perfusion in that territory. Collateral flow reduces the expansion of the infarct core and thereby helps to sustain tissue viability until reperfusion is achieved.[13,44]

Brandt et al.[9] report that collateral blood supply in basilar artery occlusions is, like length of occlusion, an independent predictor of clinical outcome independent of recanalization status. The group posits that existence of collateral blood supply correlates with the number of obstructed perforating arteries and therefore the degree and volume of brainstem ischemia, which is intimately associated with clinical state. They conclude that good collateral flow may restrict the hypoperfused tissue volume in the brainstem and enable survival.

Many researchers have wondered to what extent the presence of collateral vessels can act as a predictor of clinical outcome in ischemic stroke patients treated with thrombolysis. In one study, clinical data for 53 qualified patients who underwent intraarterial thrombolysis for the treatment of acute ischemic stroke were reviewed for age, sex, time to treatment, NIHSS score, and mRS score; site of occlusion, recanalization, and pial collaterals were analyzed on angiograms, and infarct volume was assessed on CT scans.[13] The investigators report that independent of age, site of occlusion, time to treatment, and recanalization, an assessment of pial collateral formation before thrombolysis could predict clinical outcomes and infarct volume in ischemic stroke patients. Those patients with both good pial collaterals and nearly complete recanalization appeared to have the best mRS scores at discharge. Those with poor collateral scores tended to have worse mRS scores, despite recanalization.[23,54] Even without complete recanalization, if good collaterals were present, there was significantly less infarct growth and a chance for good outcome.[4,44]

The site of the occlusion may also affect the extent of collateral circulation. Proximal occlusions affect larger areas of brain tissue than distal occlusions do and are therefore associated with poorer outcomes.[3] One group points out an example of a stroke in a particular region that might not receive collateral flow and thus indicates an infarct for which the benefits of IAT must be heavily weighed—a proximal MCA clot that occludes the lenticulostriate arteries supplying the basal ganglia and internal capsule. The lenticulostriate arteries are not collateralized from the cortex, so while transcortical collateral vessels might allow cortex to be salvaged, permanent hemiplegia might still result from infarction of the internal capsule.[27] About one-fourth of patients with proximal MCA occlusions have poor collateral flow measured by sylvian fissure and leptomeningeal convexity vessels on CT angiography and, therefore, have increased risk of poor outcome. However, because most patients demonstrated sufficient collateral vasculature comparable to those without an occlusion, some researchers believe it may be beneficial for patients with diminished collateral circulation to be treated with IAT techniques.[41] In contrast, others believe if little or no collateral vasculature is present on the angiogram, the chance of recanalization may be reduced and risky endovascular procedures may not be warranted.[4] In the case of good collateral vessel formation, neurointerventionalists may feel the need to try more aggressive IAT because there may be salvageable tissue. There is currently no general consensus on what the presence or absence of collateral circulation means with respect to treatment choices for acute ischemic stroke patients.

Time To Treatment. Time to treatment plays an important role in neurological worsening; it is generally accepted that the longer the time between symptom onset

and treatment, the greater the risk of complications. Because IVtPA can only be used within the first few hours following acute stroke, many groups have looked at the effects of later methods of recanalization and the impact that time to treatment has had on outcome.

A recent study concluded that good clinical outcome following angiographically successful reperfusion is significantly time dependent.[31] Reperfusion at 310 minutes after symptom onset corresponded to a 10.6% decrease in the probability of a good outcome compared with a time lapse of 280 minutes from symptom onset, and the probability of good clinical outcome decreased as time to revascularization increased. These findings were consistent with the results of animal studies, suggesting an approximately 6-hour time window before irreversible neurological deficit.[31,60] As IAT is the only available therapy for a patient at 6 or more hours after stroke onset, the results of these findings must be used when making treatment decisions for patients presenting long after symptoms start. Another study discovered that early treatment proved to be the most important factor for successful endovascular therapy in acute intracranial vertebrobasilar occlusion and was a better predictor of patient outcome than was achievement of recanalization.[19] Early intraarterial fibrinolysis treatment (with early defined as ≤ 6 hours from stroke onset) led to a significantly better neurological outcome than delayed treatment (> 6 hours from stroke onset). Of the 33 patients who received early treatment, 36% survived with a favorable outcome, 12% survived with an unfavorable outcome, and 52% died. Of the 43 patients who received delayed treatment, only 7% survived with a favorable outcome, 23% survived with an unfavorable outcome, and 70% died. There were 16 patients who were treated more than 10 hours after stroke onset. Of these, 75% died and 25% survived with an unfavorable outcome. This study indicated that rapid initiation of endovascular therapy is an incredibly important factor in determining improved neurological outcome of patients with acute vertebrobasilar occlusion and that endovascular treatment might not be a reasonable choice in patients presenting long outside of the 6- to 8-hour window; the investigators state that the delay in initiation of treatment might be a reason for high mortality rates despite successful recanalization.

Multimodal Imaging. It is hypothesized that multimodal imaging results at presentation can be used to predict which patients are likely to benefit from reperfusion therapies. One study looked at the predictive value of the Alberta Stroke Program Early CT Score (ASPECTS) for patients who would likely benefit from intraarterial pro-urokinase thrombolysis after acute MCA occlusion within 3–6 hours of symptom onset.[28] Each patient underwent baseline and 24-hour follow-up noncontrast CT imaging; patients were stratified based on ASPECTS (> 7 or ≤ 7), then randomly assigned to a treatment (intraarterial pro-urokinase) or control group. ASPECTS is a 10-point score that quantifies the presence of ischemia in 10 different regions of the brain; previous validations have dichotomized patients with a score of 0–7 versus those with a score of 8–10 at presentation, with a lower score indicating more extensive ischemic damage and a worse prognosis. Ischemic stroke patients with an ASPECTS of more than 7 who received intraarterial pro-urokinase were 3 times more likely to have a good outcome (defined as mRS score ≤ 2 at 90 days after treatment) than those with a similar ASPECTS in the control group, indicating that patients with good ASPECTS stood to benefit from IAT. However, among patients with an ASPECTS ≤ 7, there was no significant difference between the treatment and control arms of the study, indicating that those patients with extensive ischemia do not show significant improvement with IAT.

Gasparotti et al.[24] report the utility of perfusion CT imaging in selecting patients who are likely to benefit from IAT following acute ischemic stroke. The group reports that a multiparametric assessment of perfusion deficits on cerebral blood flow, cerebral blood volume, and time-to-peak maps (particularly the infarct core size), is a reliable tool for predicting clinical outcome after IAT. They posit that the size of the infarct core based on perfusion CT is a more relevant determinant of the severity of clinical outcome than penumbra and total perfusion deficit. Gasparotti et al. conclude that their results prompt speculation that some patients with stroke experiencing little or no improvement despite achieving recanalization might have a larger core size, which is easily detected with perfusion CT.

Another group analyzed the utility of MRA-DWI mismatch at patient presentation in predicting those individuals who were likely to benefit from reperfusion.[37] The authors suggest that the presence of an occlusion or intracranial vessel stenosis on MR angiography and with a small DW imaging lesion (collectively known as the "MRA-DWI mismatch") would be better suited for IAT. The study showed that those 44% of patients who had an MRA-DWI mismatch at baseline had an overall increased rate of a favorable clinical response after reperfusion, while those patients without mismatch experienced less benefit from IAT. The authors conclude that baseline MR angiography and DW imaging may be used to predict whether a patient is a good candidate for IAT.

Using a combination of MR imaging sequences enables practitioners to rapidly assess the ischemic infarct core (via DW imaging), visualize the underlying arterial pathology (via MR angiography), and visualize the area of tissue at risk (PWI > DWI mismatch).[16] One paper reports the utility of pretreatment MR imaging in predicting those patients who would likely benefit from reperfusion therapies in extended time windows (between 3 and 6 hours after symptom onset).[1] It is proposed that a diffusion-perfusion mismatch be used as a surrogate for indicating the ischemic penumbra and that those patients with a mismatch are more likely to benefit from IAT. Presence of a volumetric difference between a larger PW imaging lesion and a smaller DW imaging lesion is thought to represent the hypoperfused but potentially salvageable ischemic penumbra. Davis et al.[16] further specify the concept of PWI-DWI mismatch—a pure subtraction of the two images is oversimplified. They state that some areas of apparent lesions on PW images often include benign oligaemia. Further, lesions shown on DW imaging—generally accepted to indi-

cate irreversibly damaged tissue—may sometimes include areas salvageable with rapid reperfusion.

Several studies have been initiated to test the theory of a time-sensitive salvageable penumbra visualized with neuroimaging techniques: Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET),[36] Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE),[36] Desmoteplase in Acute Ischemic Stroke (DIAS),[15] Mechanical Retrieval and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE), and ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation (ROSIE).[15] There currently is no accepted standard of imaging used to determine which patients might benefit most from IAT, but it is clear that most modalities have significant potential to help a physician decide whether the extent of a patient's injury would preclude benefit from IAT.

Discussion

Despite the improvements that IAT has demonstrated in better patient functional outcome, this therapeutic method does not come without costs. Intraarterial therapy carries a significant risk for complications during or after the procedure, including vessel spasm, vessel rupture, vessel perforation, or the formation of new distal emboli derived from particles of the original thrombus.[14] Before a patient is treated with IAT, it is imperative that clinicians thoroughly examine predictors for the individual patient's clinical outcomes to avoid unnecessarily aggressive therapy.

In addition to risks inherent to the therapeutic procedure and devices, there is also a clinical risk of futile recanalization, or the absence of clinical benefit from recanalization following endovascular treatment of acute ischemic stroke. In a recent multicenter study[28] of 270 patients undergoing intraarterial thrombolysis, complete recanalization was observed in 96 (38%) of 254 patients that were eligible.[3] The occurrence of unfavorable outcome was defined by an mRS score greater than 3 at 1–3 months after treatment despite a complete angiographic recanalization. Of all the patients in whom complete recanalization was achieved, favorable outcome was observed in 49 (51%), while 47 patients (49%) had futile recanalization and did not experience therapeutic benefit. Another study found similar results, indicating that even with successful recanalization of blood vessels, only 40%–50% of these patients have positive functional outcomes.[26]

It is also necessary to consider the demand for and availability of trained specialists when considering IAT for a patient. Intravenous tPA is the first line of treatment for acute stroke patients within 3 hours of occlusion and is preferred over IAT because it is effective, safe, relatively inexpensive, and does not require a highly specialized physician; for these reasons, IVtPA is sometimes the only therapy offered to acute stroke patients at smaller health centers and hospitals with limited staff and technology.[14] Intraarterial therapy, the second line of attack in patients with acute cerebral ischemia, may only be administered at comprehensive stroke centers appropriately staffed with interventional neuroradiologists and other trained stroke specialists. As a result, many smaller stroke centers must either offer only IVtPA to patients presenting within 3 hours of stroke onset or rush patients to specialized hospitals that are able to provide IAT.

Significant financial burden is another facet of IAT that makes it imperative for physicians to consider whether a patient is truly a good candidate for treatment. One study examined the cost-effectiveness of mechanical therapy compared with standard medical therapy by comparing health benefits and costs.[45] Health and quality-of-life factors were measured in quality-adjusted life years (QALYs) and cost of hospitalization, rehabilitation, and long-term care. The authors found an incremental cost-effectiveness ratio (ICER) of $12,120 per QALY gained, which is considered cost-effective (ICER < $50,000 per QALY gained). Intraarterial therapy was found to be only borderline cost-effective in patients older than 82 years. This evidence indicates that endovascular mechanical thrombectomy appears to be cost-effective, but it is still very expensive and controlled randomized trials are needed to validate this hypothesis.

Through our literature analysis we have found that the mentioned predictors may be markers of stroke severity and directly correlate with treatment. It is evident that the presence of these predictors in combination with aggressive treatment options, such as endovascular therapy, could lead to more serious complications, including reperfusion injury. Although there are many factors related to outcome after IAT, there is abundant evidence supporting the relationship between the mentioned predictors and futile recanalization.

Many patient factors are, understandably, indicators of likely poor outcome altogether and perhaps are arguably not linked specifically to outcome following IAT. In patients with comorbidities such as high blood pressure or vascular disease, increased risk of hemorrhage during IAT points to a greater likelihood of poor outcome of intravascular therapy. Patients who are older and therefore less likely to recover from negative effects of treatment may be better off without risky intervention. Patients with high NIHSS scores, remarkable neuroimaging results, or a long time to treatment may have little salvageable tissue left and may therefore not be able to benefit from IAT. Reperfusion injury following a longstanding occlusion can occur. Perhaps in some patients, necrotic tissue flow through the brain days after a clot has set in will be significantly more detrimental than the treatment is helpful. It is imperative that practitioners consider these factors before deciding to treat acute ischemic stroke patients.

Application of our center's data to the HIAT and THRIVE scores verifies that these groups who have put together predictive scoring systems for patient outcome subsequent to IAT are justified in doing so. The THRIVE score proves to break down predictive factors and assign correct weight to each, but both scales indicate that some stroke patients experience much more risk than benefit from IAT. Our univariate analysis of potential predictive factors of patient outcome indicates that the HIAT and THRIVE scoring systems' inclusion of age, history of hypertension, and admission NIHSS scores are applicable to our population as well. Additionally, our finding that patients with a history of tobacco use may have less to

gain from IAT indicates that future comprehensive predictive models should include this factor in their analyses.

In light of the risks, costs, and requirements of IAT, physicians must assess all factors to make the best decision for the patient. If the stroke victim is likely to experience futile recanalization, it may be unwise to subject him or her to the costs and risks inherent to IAT. Thus, it is imperative that clinicians understand and consider possible predictors of long-term patient outcome following recanalization to decide whether to administer IAT.

Conclusions

Intraarterial therapy has great potential benefit, but the unique health profile of the individual patient must be taken into account before deciding to undertake IAT. Recently developed scoring systems like the HIAT and THRIVE are necessary tools for clinicians to better select patients for IAT. An analysis of a set of patients from our center indicates that the THRIVE score may be the better of the existing scales for use in assisting in the decision of whether to treat an individual patient with IAT after acute stroke. Furthermore, it is imperative that physicians and policymakers also consider factors such as the high monetary cost and required specialized workforce needed to implement IAT.

As it is evident that practitioners need a way to consistently select patients for whom IAT is likely to benefit rather than treating anyone with acute ischemic stroke, further research and validation of existing studies must be done to develop a general score incorporating all significant predictors. While the HIAT and THRIVE scales prove to be useful, each is missing information that the other proclaims important. Furthermore, there are predictors of outcome that other studies have found that are not included in either of these predictive scales. Thus, any existing databases of IAT patients should be used to externally validate or refute both of these scores, in addition to being checked for additionally independent and significant predictors of outcome, such as multimodal imaging results, presence of collateral vessels, time to treatment, and thrombus burden.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Sources of variability in computed tomography perfusion: implications for acute stroke management

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Object. Although dynamic, first-pass cerebral CT perfusion is used in the evaluation of acute ischemic stroke, a lack of standardization restricts the value of this imaging modality in clinical decision-making. The purpose of this study was to comprehensively review the reported sources of variability and error in cerebral CT perfusion results.

Methods. A systematic literature review was conducted, 120 articles were reviewed, and 23 published original research articles were included. Sources of variability and error were thematically categorized and presented within the context of the 3 stages of a typical CT perfusion study: data acquisition, postprocessing, and results interpretation.

Results. Seven factors that caused variability were identified and described in detail: 1) contrast media, the iodinated compound injected intravascularly to permit imaging of the cerebral vessels; 2) data acquisition rate, the number of images obtained by CT scan per unit time; 3) user inputs, the subjective selections that operators make; 4) observer variation, the failure of operators to repeatedly measure a perfusion parameter with precision; 5) software operational mode, manual, semiautomatic, or automatic; 6) software design, the mathematical algorithms used to perform postprocessing; and 7) value type, absolute versus relative values.

Conclusions. Standardization at all 3 stages of the CT perfusion study cycle is warranted. At present, caution should be exercised when interpreting CT perfusion results as these values may vary considerably depending on a variety of factors. Future research is needed to define the role of CT perfusion in clinical decision-making for acute stroke patients and to determine the clinically acceptable limits of variability in CT perfusion results.
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Key Words • **computed tomography perfusion** • **brain imaging** • **stroke** • **standardization**

There are increasing therapeutic options for patients with acute ischemic stroke, including chemical and mechanical intraarterial thrombolysis.[1] Brain imaging is used to determine therapy eligibility by discriminating between patients who may benefit from therapy and patients who will not benefit or may even be further injured by therapy.

In the setting of acute stroke, the most practical initial imaging test is CT. Noncontrast CT rapidly and accurately identifies intracranial hemorrhage and helps discriminate nonvascular causes of neurological symptoms. Computed tomography angiography detects intra- and extracranial vessel abnormalities, and may guide treatment decisions for endovascular recanalization therapies. Dynamic CT perfusion generates quantitative measures of cerebral perfusion and therefore has the unique potential to differentiate thresholds of reversible and irreversible ischemia.[16]

In conjunction with CT and CT angiography, CT perfusion has been shown to improve the diagnosis of acute stroke,[7] but the usefulness of CT perfusion in making acute treatment decisions has not yet been established because CT perfusion imaging information about the degree of reversibility of ischemic injury has been limited by a lack of standardization.[6] Patient selection for reperfusion therapies is not without significant risk because these drugs can cause life-threatening intracranial hemorrhage, and for CT perfusion results to be applied clinically, it is necessary to know that the data are accurate and reproducible. The purpose of this study was to systematically review the reported sources of variability in cerebral CT perfusion results and discuss the clinical implications for acute stroke management.

Abbreviations used in this paper: ASIST = Acute Stoke Imaging Standardization; CBF = cerebral blood flow; MCA = middle cerebral artery; STIR = Stroke Imaging Repository.

Methods

Data Acquisition

A systematic literature search was conducted. The following search key words were used in a variety of permutations: "CT," "computed tomography," "perfusion," "blood flow," "cerebral," and "stroke." Search limits included human species, English language, and publication dates from 1970 to 2010. The PubMed database was searched, which returned several hundred articles.

The abstracts of all articles were reviewed to identify reports that focused on cerebral CT perfusion, in which cerebral CT perfusion was defined as CT perfusion used in the context of brain imaging. One hundred twenty reports met this criterion. These reports and any relevant references listed within them were closely reviewed to identify original research articles that reported sources of real or potential variability and error in quantitative cerebral CT perfusion values. Twenty-three published original research articles fit these criteria. These studies were reviewed, and reported sources of real or potential variability and error in quantitative cerebral CT perfusion results were recorded (Table 1). In addition, non–peer-reviewed publications produced by the ASIST-Japan group (http://asist.umin.jp/index-e.htm) and the STIR consortium (https://stir.ninds.nih.gov/html/index.html) were reviewed. Non–peer-reviewed data included in this report are identified as such.

Data Organization

Sources of variability and error were thematically categorized to facilitate conceptualization.

Results

Variability in Quantitative CT Perfusion Results

Contrast Media. Contrast media is the iodinated compound injected intravascularly to permit imaging of the cerebral vessels. Contrast media is injected intravenously during CT scanning. Kloska et al.[10] compared 2 different contrast media concentrations (300 vs 370 mg iodine/ml) and found that they yielded equivalent CT perfusion source-image tissue enhancement in the caudate nucleus, thalamus, and frontal white matter of the nonischemic hemisphere, but significantly different CT perfusion source-image enhancement in the region of the superior sagittal sinus. Konig et al.[12] compared 300 versus 400 mg iodine/ml concentrations and found no significant difference between mean CT perfusion results derived from nonischemic frontal white matter. They did not assess the ischemic hemisphere. At a national stroke imaging meeting in 2007, participants recommended using 350–370 mg/ml concentrations,[28] but many institutions, including the authors', do not (we use 320 mg/ml).

Data Acquisition Rate. The data acquisition rate is the number of images obtained by the CT scanner per unit time. It is proportional to image resolution and radiation dose and therefore must be optimized to balance adequate image quality with radiation safety. The data acquisition rate affects CT perfusion results, but the specific relationship is controversial. For example, Wintermark et al.[31] found that sampling intervals > 1 second do not cause significant variability in CT perfusion results, while Kloska et al.[11] found that they do (for example, CBF values were increased [$p = 0.044–0.001$] with > 1 second intervals). Different studies recommend different data acquisition rates, ranging from 1 image/0.5 sec[8] to 1 image/3 sec.[27]

User Inputs. User inputs are the subjective selections that operators make during CT perfusion acquisition and postprocessing. For example, CT operators select the 2–4 cerebral slices that are scanned. Operators also select important inputs that are used to process image data. For instance, radiologists draw regions of interest on top of raw CT images to label 2 functions that are used to generate perfusion maps. These functions are called the arterial input function and the venous output function. Two studies[3,30] found that varying placement of the arterial input function did not cause significant variability in CT perfusion results. Arterial input function placement distal to an arterial thrombus, however, undermines perfusion calculation assumptions, and causes significant variability in CT perfusion results.[4] Two additional studies[9,19] found that varying placement of the venous output function caused significant variability in CT perfusion results. Although the anterior cerebral artery is commonly selected for the arterial input function and the superior sagittal sinus is commonly selected for the venous output function, there is no standard recommendation for selecting these user inputs.

Observer Variation. Observer variation is the failure of operators to repeatedly measure CT perfusion values with precision. Observer variation may occur whenever user inputs are made. Two types of observer variation have been reported: interoperator (between operators), and intraoperator (reproducibility of 1 operator). Several authors have concluded that observer variation causes a minimal amount of variability in CT perfusion results.[3,20,21,29] For example, Sanelli et al.[21] found high inter- and intraoperator correlations ($r = 0.87–0.99$ and $r = 0.91–0.99$, respectively) and low inter- and intraoperator coefficients of variability (2.5%–9.5% and 1.4%–6.5%, respectively) in CT perfusion results. Other studies[5,23] report observer coefficients of variability > 30%, suggesting that observer variation causes a substantial amount of variability in CT perfusion results.

Software Operational Mode. The software operational mode refers to manual, semiautomatic, or automatic data processing. For example, many software applications allow manual, semiautomatic, or automatic selection of input functions (for example, arterial input function or venous output function). Two studies[21,24] found that automated data processing caused more variability in CT perfusion results than manual mode data processing. In contrast, Soares et al.[23] found more consistent results.

Software Design. Software design is a broad category that refers to the mathematical algorithms used to process the image data. For example, CT perfusion software applications incorporate image data and operator inputs,

TABLE 1: Categorized list of original research articles included in this study*

Error Source	Authors & Year	No. of Patients	Patient Type
contrast media	Kloska et al., 2007[10]	90	suspected AIS
	Konig et al., 2007	21	suspected AIS
data acquisition rate	Kloska et al., 2010[11]	32	suspected AIS
	Wiesmann et al., 2008	8	suspected AIS
	Kämena et al., 2007	30	suspected AIS
	Wintermark et al., 2004[31]	60	AIS
user inputs	Ferreira et al., 2010	14	unilateral proximal MCA occlusion
	Wintermark et al., 2008[30]	55	suspected AIS
	Bisdas et al., 2007	18	suspected AIS
	Kealey et al., 2004	40	AIS, CO, TIA, SAH
	Sanelli et al., 2004[19]	3	AIS
observer variation	Soares et al., 2009	30	suspected AIS
	Bisdas et al., 2007	18	suspected AIS
	Sanelli et al., 2007[20]	20	suspected AIS, vasospasm, chronic cerebral ischemia
	Sanelli et al., 2007[21]	20	suspected AIS, vasospasm, chronic cerebral ischemia
	Wintermark et al., 2005[29]	46	suspected AIS
	Fiorella et al., 2004	20	not specified
software operational mode	Soares et al., 2009	30	suspected AIS
	Sanelli et al., 2007[21]	20	suspected AIS, vasospasm, chronic cerebral ischemia
	Turk et al., 2007	33	CAS
software design	Ferreira et al., 2010	14	unilateral proximal MCA occlusion
	Kudo et al., 2010[14]	10	AIS
	Kudo et al., 2009[13]	6	healthy volunteers
	Sasaki et al., 2009	20	suspected AIS
	van der Schaaf et al., 2006	10	suspected aneurysms, suspected sinus thrombosis, SAH, intracerebral hematoma
	Kudo et al., 2003[15]	5	healthy volunteers
	Zussman et al., in press	11	suspected AIS
value type	Waaijer et al., 2007	20	CAS

* AIS = acute ischemic stroke; CAS = carotid artery stenosis; CO = carotid occlusion; SAH = subarachnoid hemorrhage; TIA = transient ischemic attack.

and perform multistep mathematical operations to generate perfusion results. Different algorithms, such as the maximum slope algorithm and the deconvolution family of algorithms, generate significantly different CT perfusion results for identical source data.[14] Similarly, different software applications using different corrective functions for tracer delay (an effect that occurs when contrast media reaches tissues of interest more slowly than predicted) yield significantly different CT perfusion results.[4,13,14,22] Different corrective functions for partial-volume effects (inaccurate measurements of contrast media concentration that occur due to the small size or location of cerebral vessels) cause significantly different CT perfusion results.[25] Computed tomography perfusion software that uses a corrective technique called vascular pixel elimination was found to more closely correlate with PET results than software that does not incorporate this technique.[15] As a result, different commercial CT perfusion software postprocessing applications have been shown to produce significantly different CT perfusion results for identical source data.[14,32] Because there is no industry standard for software design, calibration, or validation, quantitative assessment is not comparable across platforms (Fig. 1).

Value Type. The value type refers to absolute versus relative CT perfusion values. For example, when perfusion values for a given region of tissue are directly reported, they are called absolute values. A given region of tissue can also be compared with the corresponding region of tissue on the contralateral cerebral hemisphere, creating a ratio between the 2 hemispheres. When reported, these ratios are called relative values. Waaijer et al.[26] compared absolute and relative values and found that relative values caused less variability in CT perfusion results than absolute values. This suggests that absolute values of CT perfusion are less reliable and reproducible than relative values and should not be used as a basis for decision-making.

Non–Peer-Reviewed Factors. Additional factors have been shown to affect raw CT image data including tube current and voltage, scan mode (cine vs intermittent), scan timing, and the tomographic reconstruction process,

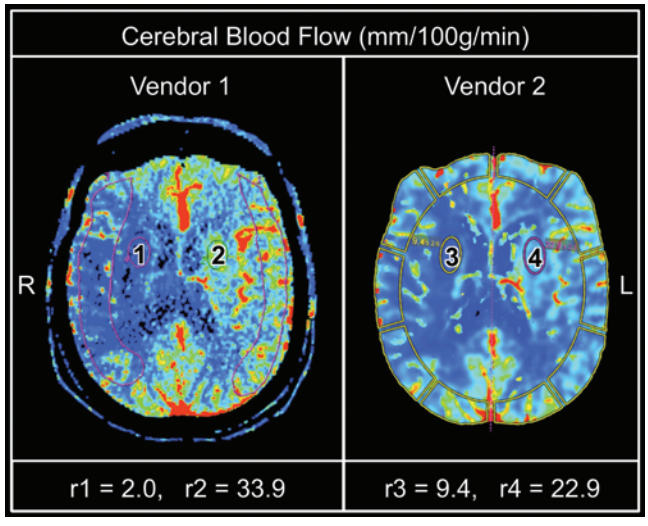

Fig. 1. Different commercial CT perfusion software applications produce significantly different quantitative results for identical source data. The figure shows CBF perfusion color-maps for the same patient data that were reproduced at our institution using 2 different software applications, Vendor 1 **(left)** and Vendor 2 **(right)**. The maps reveal severe ischemia in the region of the right MCA territory. Regions-of-interest (numbered ovals 1–4) were drawn on the perfusion maps, and software platforms returned perfusion results for the tissue enclosed within each oval. Note that quantitative perfusion results for the ischemic tissue (r1 and r3), as well as for the normal contralateral hemisphere (r2 and r4) differed considerably by vendor, although the general trend of decreased CBF in the ischemic tissue was consistent for both vendors. There is no industry standard for software design.

all of which affect CT perfusion results (K. Kudo, unpublished data, 2004). Consensus-based expert recommendations for a CT perfusion image acquisition protocol were recently published,[28] but many institutions have not adopted them.

Additional software design considerations that have been shown to affect CT perfusion results include the presence and type of preprocessing denoising filter, image matrix size, and deconvolution method (K. Kudo, unpublished data, 2004).

Variability in Qualitative CT Perfusion Results

In addition to being quantitative, CT perfusion results are also qualitative. For example, perfusion parametric maps display quantitative CT perfusion values in a color-map overlay that allows qualitative, contextual visualization of an entire brain slice. Computed tomography perfusion color-maps are not standardized and vary by manufacturer, meaning that a given quantitative value will be translated into different colors by different CT perfusion software applications. These parametric color maps are used to qualitatively assess relative variations in CT perfusion metrics. The color scale is not fixed and is operator-adjustable (Fig. 2). Although there is a suggested CT perfusion color scale standard (http://asist.umin.jp/index-e.htm), it is not in general use and has not been incorporated into commercial software.

Discussion

Computed tomography perfusion imaging measures cerebral perfusion and calculates quantitative perfusion results. The typical CT perfusion study has 3 stages: data acquisition, postprocessing, and results interpretation. In the data acquisition stage, the patient is scanned and a contrast agent is injected. Image data gathered during this stage is then transferred to a proprietary vendor workstation for postprocessing. In the postprocessing stage, radiologists use software applications to generate quantitative CT perfusion results. These results are then displayed as quantitative values and qualitative, parametric color-maps for results interpretation. In the results interpretation stage clinicians evaluate CT perfusion values and maps and reformat them to their liking, to aid in clinical decision-making. Sources of variability in CT perfusion are introduced at different stages of a CT perfusion study, and Figure 3 shows the sources of variability identified by this study within the context of the 3 CT perfusion stages.

Several recent studies underscore CT perfusion's clinical potential, but also indirectly highlight the great challenges facing CT perfusion. For example, Murphy et al.[17] studied 30 stroke patients and compared CT perfusion studies (performed at admission) to noncontrast CT studies (performed 5–7 days poststroke). They identified a highly sensitive (95%) and specific (94%) CT perfusion threshold for differentiating between ischemic white matter that ultimately infarcted and ischemic white matter that recovered. Aviv et al.[2] studied 40 stroke patients by comparing admission CT perfusion studies to MR and

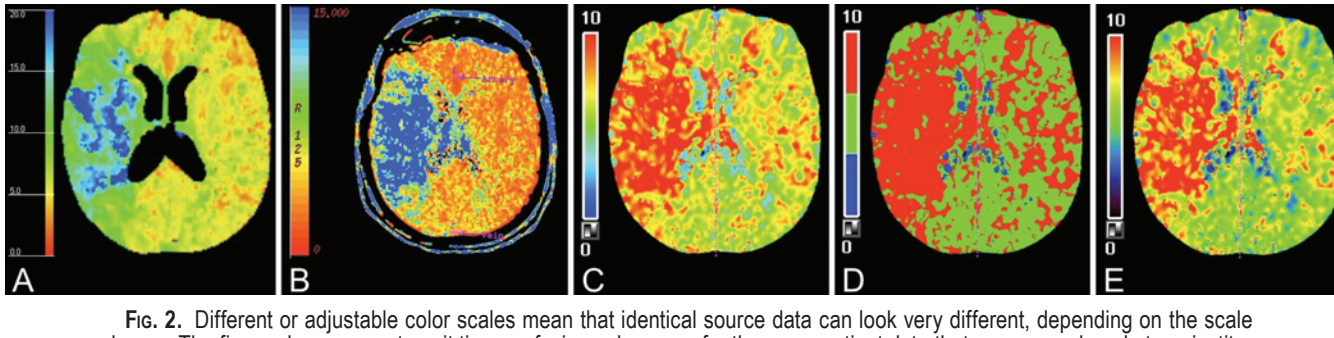

Fig. 2. Different or adjustable color scales mean that identical source data can look very different, depending on the scale chosen. The figure shows mean transit time perfusion color-maps for the same patient data that were reproduced at our institution using different color scale settings. Intervendor color differences are shown: image **A** was generated using vendor 1 software, image **B** with vendor 2 software, and images **C–E** with vendor 3 software. Intravendor color differences are also shown: images **C–E** were generated using 3 different color scales available on the same software platform.

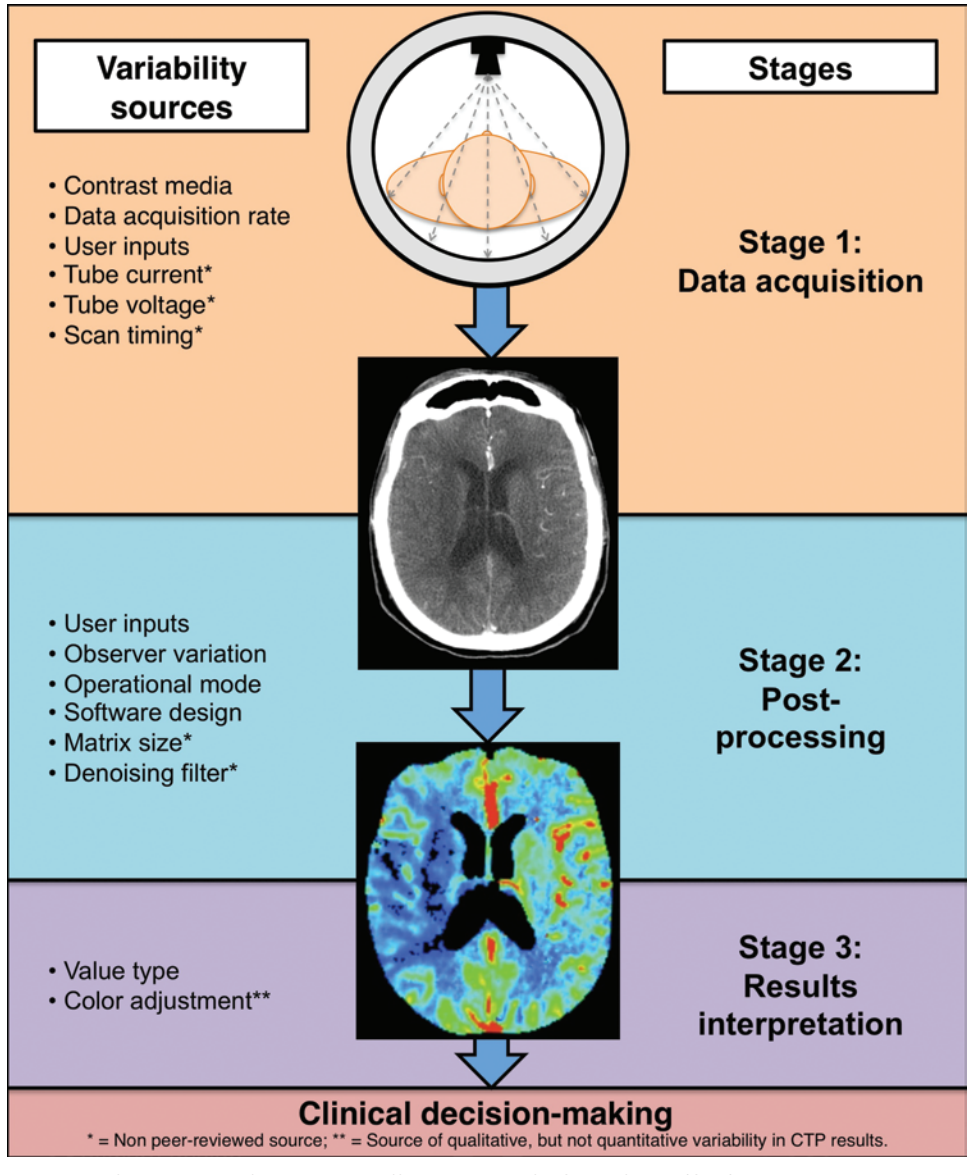

Fig. 3. Illustration of the sources of variability at different stages of a CT perfusion (CTP) study.

CT studies performed at poststroke follow-up. They identified a highly sensitive (77%) and specific (94%) CT perfusion threshold for predicting hemorrhagic transformation in acute stroke patients. These and other studies underscore CT perfusion's great potential because they offer a glimpse of how quantitative cerebral perfusion data might influence decision-making in the context of cerebrovascular disease.

While these studies underscore the potential clinical value of CT perfusion, they also highlight a major limitation of this technique, namely variability and error caused by a lack of standardization. For example, the data of Murphy et al.[17] were analyzed using a single vendor's postprocessing platform, which raises the question of whether the authors would have identified the same results and reached the identical conclusion had a different vendor been chosen for this study. This question may be especially relevant in stroke centers that use multiple vendor acquisition devices and postprocessing platforms to determine whether to administer thrombolytics. Simply put, it is questionable whether CT perfusion results generated by one protocol can be meaningfully compared with CT perfusion results derived using a different protocol.

The clinical significance of the widespread variability in CT perfusion results is difficult to estimate. Few studies have directly examined how CT perfusion affects clinical decision-making or influences patient outcomes,[18] and the clinically acceptable limits of variability in CT perfusion results are unknown. These gaps in the medical literature call attention to the need for future studies to define the role of CT perfusion in acute stroke management. Future studies should take into consideration the widespread variability in CT perfusion results.

For quantitative CT perfusion results, standardization at all 3 stages of CT perfusion studies is warranted, and progress is being made. For example, in 2007, data acqui-

sition (Stage 1) protocols were drafted at an international symposium of stroke imaging experts.[28] Furthermore, the calibration of postprocessing software applications (Stage 2) against a digital, universal standard is increasingly likely, thanks to recent work of the ASIST-Japan group and the STIR consortium (Kudo et al., unpublished data, 2010). It is worth noting that although numerous factors cause variability in CT perfusion results, software design is a large factor, relative to other factors,[32] which makes software standardization especially relevant. For qualitative CT perfusion results, standardized parametric-map representations of perfusion metrics are needed.

This study has several implications for current practice. First, caution should be exercised when interpreting CT perfusion results because they may vary considerably, depending upon a variety of factors. It remains unknown if, and to what extent, this variability may affect clinical decision-making or influence patient outcomes. Second, future studies evaluating CT perfusion should consider the finding that CT perfusion results generated by different techniques are not necessarily interchangeable. Third, standardization efforts at all 3 stages of the CT perfusion study cycle should be pursued.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Zussman. Acquisition of data: Zussman, Talekar. Analysis and interpretation of data: Zussman, Talekar, Flanders. Drafting the article: Zussman, Flanders. Critically revising the article: all authors. Approved the final version of the paper on behalf of all authors: Jabbour. Administrative/technical/material support: Talekar. Study supervision: Flanders.

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See the corresponding article in this issue (E8).

Neurosurg Focus 30 (6):E9, 2011

Editorial

Computed tomography perfusion

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The authors report an interesting review of the literature regarding the utility of CT perfusion in the assessment of acute stroke patients.[1] Specifically, they analyzed sources of variability and error in the acquisition of CT perfusion scans. They identified 23 published original research articles and categorized the 3 stages of a CT perfusion study. They identified 7 sources of potential variability among these 3 CT perfusion stages.

The utility of CT perfusion in the management of acute stroke patients is the subject of considerable current debate. The crux of this debate is whether a subset of patients who are beyond the standard 6-hour time window for the performance of intraarterial thrombolytic techniques can be identified. Computed tomography perfusion offers the allure of delineating a penumbra of at-risk brain in this particular patient population. Without CT perfusion, these patients may be incorrectly labeled as unsalvageable or too risky to treat in an aggressive endovascular fashion. Nonetheless, this current review establishes the potential pitfalls associated with CT perfusion. These 7 sources of variability include the subjective analysis of radiologists in the interpretation of these scans. These interpretations are often made on the basis of qualitative assessments and likely vary from person to person.

The authors conclude that standards need to be established for each of the 3 stages of CT perfusion acquisition. The sheer number of interpretive radiologists and the variability in the equipment and software used to obtain these scans make this task extremely difficult. If and when these techniques can be standardized, the next step would be a quantitative analysis of the efficacy of CT perfusion in identifying patients who could potentially benefit from endovascular therapy. Although these questions are difficult to answer, the potential benefits in the management of this devastating disease are enormous. *(DOI: 10.3171/2011.3.FOCUS1184)*

Disclosure

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Neurosurg Focus 30 (6):E10, 2011

Endovascular stroke therapy: a single-center retrospective review

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Object. Endovascular treatment of acute ischemic stroke delivers direct therapy at the site of an occluded cerebral artery and can be employed beyond the 3–4.5-hour window limit set for intravenous recombinant tissue plasminogen activator. In this paper, the authors report their experience with various endovascular therapies in acute ischemic stroke.

Methods. The authors conducted a retrospective review of their clinical database for acute ischemic stroke in large-vessel cerebral territories that underwent endovascular treatment between May 2005 and February 2009. Endovascular treatment was defined as pharmacological and/or mechanical intervention, angioplasty, stenting, or a combination of these methods. Admission National Institutes of Health Stroke Scale and the modified Rankin Scale scores were recorded. Thrombolysis in Myocardial Infarction (TIMI) scores of 0, 1, 2A, 2B, and 3 were used to define recanalization.

Results. Forty procedures were performed in 39 patients, with 1 patient having sequential bilateral strokes. Nine patients were lost to follow-up after discharge. Strokes in the carotid artery circulation occurred in 82.5% of cases, and those in the vertebral-basilar territory occurred in 17.5%. The Merci device was used in 22 (55%) of 40 procedures, and the Penumbra device in 9 (22.5%) of 40. Angioplasty was performed in 15 (37.5%) of 40 procedures, and intraarterial recombinant tissue plasminogen activator was administered in 23 (57.5%) of 40 procedures. In 23 (57.5%) of 40 cases, multiple recanalization methods were used. The recanalization rate for all methods was 60%. The recanalization rate from TIMI Score 0/1 occlusions was 71.4% (20 of 28). An estimated modified Rankin Scale score of ≤ 2 was obtained in 11 (36.7%) of 30 cases. The overall mortality rate was 26.7% (8 of 30). Intracerebral hemorrhage at 24 hours postprocedure was noted in 17 (42.5%) of 40 cases, 3 (7.5%) of which were symptomatic.

Conclusions. The authors' institution performs endovascular stroke treatment with a safety and efficacy profile comparable to those of other major endovascular stroke therapy studies. Recanalization was associated with an improved clinical outcome. Protocols to maximize efficient triage of patients and better documentation of stroke treatments can assist in further studies. *(DOI: 10.3171/2011.3.FOCUS10267)*

Key Words • **stroke** • **endovascular** • **mechanical** • **ischemic** • **pharmacological** • **stenting**

Previous studies have established the efficacy of intravenous rt-PA to reduce overall disability when administered within 3–4.5 hours of an acute ischemic stroke.[8,12,22] Although rt-PA is the only FDA-approved medical therapy currently available for acute ischemic stroke, it is surprisingly underutilized. It is estimated that less than 2%–5% of patients receive this treatment in most countries, primarily due to delayed admission and the inherent "automatic" exclusion of several patient populations such as the postoperative patient.[2,23] Furthermore, rt-PA has limited efficacy in achieving recanalization in proximal vessel occlusions.[19]

The endovascular management of acute ischemic stroke circumvents some of these shortfalls because this therapy has proven effective up to 6 hours after the stroke[10] and has demonstrated improvement in recanalization rates.[5,10,15,20,24,26,27] Currently a Class I B level of evidence indication is the use of intraarterial thrombolysis in selected patients with major stroke of 6-hour duration due to an occlusion of the middle cerebral artery.[21]

Abbreviations used in this paper: ICA = internal carotid artery; ICH = intracerebral hemorrhage; IMS = Interventional Management of Stroke; MCA = middle cerebral artery; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NMH = Northwestern Memorial Hospital; PCA = posterior cerebral artery; PROACT = Prolyse in Acute Cerebral Thromboembolism; rt-PA = recombinant tissue plasminogen activator; SAH = subarachnoid hemorrhage; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction.

Current endovascular therapies include local pharmacological infusions (usually of a fibrinolytic such as rt-PA), ultrasound-augmented fibrinolysis, and mechanical manipulation by guide wire, snare, angioplasty balloon, stent, and dedicated clot retrieval systems such as the Merci or Penumbra device.[23] The greatest risks of these therapies are vessel damage, thrombus migration, and possible delays in treatment due to a patient's need for a specialized stroke center.[23] In fact, currently a Class I A level of evidence indication is that the availability of intraarterial thrombolysis should generally not preclude the intravenous administration of rt-PA in otherwise eligible patients.[21] In addition, the potential benefit of reperfusion decreases with delayed treatment,[11] and there is a corresponding increase in the risk of symptomatic cerebral hemorrhage.[18] Recent evidence suggests that carefully selected patients, chosen based on perfusion imaging, may receive the maximum benefit from intervention.[3]

Northwestern Memorial Hospital, located in the center of Chicago, is a comprehensive stroke center that treated approximately 60 TIA and 242 ischemic strokes in 2008. The purpose of this study is 2-fold: 1) to assess Northwestern Memorial Hospital's experience in this field as a formal institutional review and 2) to compare our data with major publications.

Methods

Computerized records were reviewed and analyzed for 39 consecutive patients treated between May 2005 and February 2009. All participants provided written and informed consent for release of their clinical data using an institutional review board–approved, Health Insurance Portability and Accountability Act–compliant protocol. Included cases involved strokes of all large-vessel territories that were treated acutely by endovascular methods. Excluded cases were those having central retinal artery occlusions, cerebral venous thrombosis, intracranial angioplasty, stenting done for subacute to chronic cerebral ischemia, any extracranial procedure that did not also include intracranial therapy, and coagulopathies or low platelets.

The data obtained from the medical records included demographic information, vascular risk factors, and medication use. Data also recorded included presenting NIHSS score, ischemic territory, endovascular method, interval between stroke onset and anesthesia prior to endovascular intervention, pre- and postoperative TIMI score, hospital discharge location, mRS score at most recent follow-up, and all-cause mortality.

Initial blood pressures on admission to NMH were recorded. Data were also collected from the neurology resident examination note in all cases as well as an emergency department nurse's triage note, an emergency department paramedic examination note, or an intensive care unit vital sign flow sheet if available for review. However, NIHSS scores were recorded exclusively from the neurology resident notes. If an NIHSS score was not available or was not consistent with the concomitant reported examination, it was estimated using validated methods.[28]

The TIMI score was obtained using a scale described by the IMS-II authors from an ad hoc scale (TIMI scores of 0/1, 2AB, and 3).[15] Contrary to previous studies, we chose to report TIMI scores pertaining to the effect on cerebral perfusion as a whole rather than reporting a TIMI score specific to the occluded vessel.[5,10,15,24,26,27] A TIMI score of 0/1 was reserved for stump occlusions of the ICA, M_1, or basilar system. For example, an M_2 superior branch occlusion would be reported as a TIMI score of 2A should the MCA territory be perfused by less than 50%. Improvement after intraarterial treatment to a TIMI score of 2B would be achieved if the MCA territory perfusion improved to greater than 50%. A TIMI score of 3 was reserved for revascularization that included perfusion to all M_3 and M_4 cortical vessels.

Using the TIMI 2AB classification system, the posterior circulation was scored in a novel way. For instance, a TIMI score of 2A referred to perfusion to the top of the basilar artery and at least one of the PCA branches, whereas a TIMI score of 2B indicated flow involving the basilar tip and both PCA branches. Recanalization was defined as an improvement in grade from TIMI 0/1 to at least a 2A and a TIMI 2A to at least a 2B. The mRS score[29] was recorded as an estimate after reviewing the electronic records of outpatient follow-up visits or readmission notes.

Unless indicated, administration of antiplatelet and anticoagulant agents was prohibited for 24 hours postintervention. Medical management and acute poststroke care after the procedure were consistent with American Stroke Association guidelines.[1] A CT scan was obtained 24 hours after the procedure to rule out the presence of ICH. An ICH was classified using definitions[4] of hemorrhagic infarction Types 1 and 2 and parenchymal hematoma Types 1 and 2. Progress notes (clinical notes) were reviewed to determine whether ICH was symptomatic. If the notes did not clearly state the impact of ICH clinically, the ICH was assumed to be symptomatic.

Results

At NMH, a total of 40 endovascular procedures were performed in 39 patients for acute large-vessel ischemic stroke between May 2005 and February 2009. One patient suffered a recurrent stroke requiring endovascular intervention for both instances. Nine patients were lost to follow-up after being discharged from the hospital. Table 1 summarizes patient baseline characteristics. Table 2 includes information about the NIHSS scores, locations of vascular occlusions, revascularization rate, and clinical outcomes. The mean baseline NIHSS score was 16.7 (median 15, range 5–36) (Table 2). The estimated median interval from stroke onset to anesthesia prior to endovascular stroke therapy was 265.5 minutes. Overall, 82.5% of the strokes were confined to the anterior circulation. The majority were M_1 and M_2 occlusions (47.5%), whereas 25% of patients had ICA or carotid-T occlusions. Only 10% of the occlusions were localized to M_3.

Endovascular therapies varied, and in most treatment cases more than one modality was applied. The Merci device was used in 22 (55%) of 40 procedures and the Penumbra device in 9 (22.5%) of 40. Angioplasty was performed

TABLE 1: Summary of baseline characteristics*

Median Age (yrs)†	Female Sex (%)†	Current Smoker (%)†	Median Index BP (systolic/ diastolic)‡	Prior Aspirin/ Plavix (%)†	Prior AC (%)†	Median Index INR‡	Known A Fib (%)†	Known DM (%)†	Known HL (%)†	Patient History (%)			
										TIA/CVA†	Cardiac Disease†	Renal Disease†	Past Malignancy†
70	59	15.4	S 143.5, D 81.5	41.0	23.1	1.1	38.5	10.3	38.5	15.4	17.9	5.1	15.4

* A Fib = atrial fibrillation; AC = anticoagulation; BP = blood pressure; CVA = cerebrovascular accident; DM = diabetes mellitus; HL = hyperlipidemia; INR = International Normalized Ratio.
† Determined in 39 patients.
‡ Determined in 40 procedures.

in 15 (37.5%) of 40 procedures, and intraarterial rt-PA was administered in 23 procedures (57.5%). In 23 cases (57.5%), multiple recanalization methods were used. Three patients required stents (2 with a Neuroform and 1 with Wingspan stent). Two stents were deployed intracranially, whereas the third was deployed at the carotid bifurcation.

The estimated mRS score was available in all surviving patients, except for 9 lost to follow-up; therefore, analysis was confined to 30 patients (Fig. 1 upper). In this group, the mean age was 64.8 years, and the mean and median NIHSS scores were 17.4 and 15.5, respectively. The follow-up period ranged from 1 to 37 months. Outcome in 11 (36.7%) of 30 patients was reflected by the mRS score 0–2. In 4 patients, lack of information in the outpatient records precluded an accurate rating of the mRS outcome, which presented a challenge in determining whether the mRS score rating was 2 or 3. For analysis' sake, the mRS score was assumed to be 3. The overall mortality rate was 26.7% (8 of 30 patients). Five patients died during the initial stroke while being admitted, and 3 died after discharge from the hospital. Of these patients, 1 died of sepsis 2 months after discharge, another was placed in hospice 6 weeks later, and 1 was placed in hospice 2 years later.

To better compare our results to outcomes in major clinical trials,[2,5,10,15,26,27] we performed subgroup analysis to compute 3-month outcomes (Fig. 1 lower). Of the 39 patients, 9 were lost to follow-up and because 6 were followed up for less than 3 months, their data were excluded from the analysis. For this remaining subgroup of 24, the mean age was 63.1 years, while the mean and median NIHSS scores were 18.45 and 17, respectively. Good outcome was achieved in 37.5% of patients (9 of 24), whereas the overall mortality rate was 29.1% (7 of 24 patients).

Hospital discharge locations were available for all 39 patients: 5 (12.8%) went home, 22 (56.4%) went to acute inpatient rehabilitation, 1 (2.6%) to long-term acute care, 1 (2.6%) to an in-network hospital, 5 (12.8%) to subacute nursing care, and 5 (12.8%) died while in the hospital.

At baseline, 70% of patients had a TIMI score of 0 or 1, and the other 30% had a TIMI score of 2A/2B. After the procedure, 60% of patients achieved a TIMI score of 2AB or 3. In cases of proximal stump occlusion, recanalization from a TIMI score of 0/1 to 2AB occurred in 71.4% (20/28) of the patients, and recanalization from a TIMI score of 0/1 to 3 occurred in 7.1% (2/28) of the patients. For this subgroup of patients, the mean and median NIHSS scores on presentation were 18 and 17, respectively.

Patients with successful revascularization tended to have better outcomes than those in whom revascularization was not successful. In this case series analysis, excluding patients with inadequate follow-up, 9 (47.4%) of 19 patients with successful recanalization had good outcome (mRS score ≤ 2), whereas only 2 (16.7%) of 12 patients without successful recanalization had a good outcome. Similarly, the mortality rate was lower in the revascularized group than in its counterpart, at 26.3% and 33.3%, respectively.

The impact of revascularization of proximal stump occlusions was also evaluated for clinical outcome. Similar conclusions prevailed. Among the 71.4% of the cases that were successfully revascularized (20 of 28 patients), an mRS score of ≤ 2 was achieved in 7 (43.7%) of 16 patients, whereas among those in the nonrevascularized group, an mRS of ≤ 2 was only achieved in 1 (14.3%) of 7 patients. Correspondingly, the revascularized groups had a lower mortality rate, 25% (4 of 16 patients), compared with 42.8% (3 of 7 patients) in the nonrevascularized cases. (Note: 4 patients in the revascularized group and 1 patient in the nonrevascularized group were lost to follow-up, respectively [Table 3].)

TABLE 2: Summary of perioperative data*

Variable	Median NIHSS Score†	Circulation of the ICH		Segment/Artery of Occlusion			Revascularization Rate†	Index TIMI Score 0/1†	Revascularization Rate in TIMI Score 0/1 Cases‡	mRS Score ≤2§	Mortality Rate§	SICH by 24 hrs†
		Anterior†	Posterior†	M_1/M_2†	M_3†	ICA, Carotid-T†						
% of pts	15	82.5	17.5	47.5	10	25	60	70	71.4	36.7	26.7	7.5

* All values are presented as percentages except NIHSS scores. Abbreviations: pts = patients; SICH = symptomatic ICH.
† Determined in 40 patients.
‡ Determined in 28 patients.
§ Determined in 30 patients.

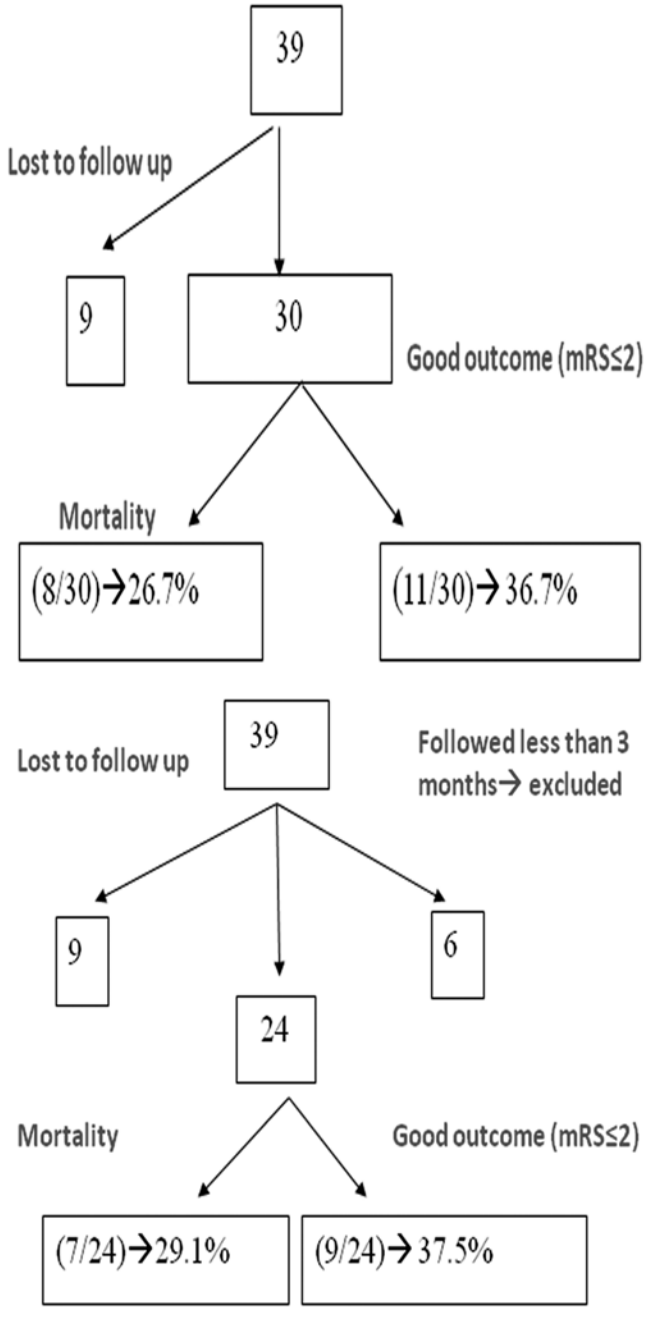

Fig. 1. Diagrams showing outcome in all patients recruited into the study **(upper)** and outcome in patients with 3 months of follow-up **(lower)**.

In 17 patients (42.5%), 24-hour CT scanning revealed ICH; 3 patients (7.5%) were symptomatic (Table 2). Of these 3 patients, 1 developed ICH and SAH after intravenous rt-PA. In this patient, endovascular methods were palliative to decrease clot burden, and subsequently, the patient underwent surgical evacuation of the hematoma and died during the index hospitalization (Fig. 2A). The second patient suffered an intraprocedural perforation, underwent decompressive craniectomy, and was lost to follow-up (Fig. 2B). The third patient suffered a contralateral parenchymal hematoma Type 2 ICH after a skull base carotid stenting procedure was performed for acute stroke. Prior to the emergence of the ICH, postprocedure MR imaging revealed an interval development of a new infarction contralateral to the original stroke. This patient was also lost to follow-up (Fig. 2C).

TABLE 3: Outcome in patients with and without successful recanalization

Index TIMI Score & Outcome	Percentage of Patients*	
	w/ Recanalization	w/o Recanalization
all TIMI scores		
mRS score ≤2	47.4	16.7
mortality rate	26.3	25.0
w/ TIMI scores 0/1		
mRS score ≤2	43.7	14.3
mortality rate	25.0	42.8

* Four patients in the revascularized group and 1 patient in the nonrevascularized group were lost to follow-up.

Overall, 3 (7.5%) of 40 patients had definite procedure-related SAH. One had a concomitant ICH and was discussed in the previous paragraph. The other 2 patients had asymptomatic SAH. An mRS score of 4 was estimated in 1 patient at 2-month follow-up, and an mRS score of 0 was estimated in the other patient at 4-month follow-up.

Discussion

In our population overall, 36.7% of the patients had an outcome represented by an mRS score of ≤ 2 at various follow-up times; 37.5% of the patients had an outcome represented by an mRS score of ≤ 2 at the 3-month follow-up. These results exceed the outcomes of the Penumbra Phase 2 trial[7] (25.0%) and the MERCI Trial,[27] but they are similar to those reported in the Multi MERCI trial (36.0%).[24] Of note, our mRS ≤ 2 rate was less favorable than those of PROACT II (40.0%),[10] MELT (Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial [49.1%]),[25] and IMS-II (46.0%),[15] all of which disallowed direct mechanical means of thrombolysis.[24] Patients with successful revascularization tended to have better outcomes, as measured by an mRS score ≤ 2, than those without revascularization. Outcome reflected by an mRS score of ≤ 2 was achieved in 47.4% of the patients with revascularization, which exceeded the outcome in the Penumbra trial (29%),[7] and was comparable to rates in the MERCI (46.0%),[27] Multi MERCI (49.1%),[26] and IMS-II (45.6%)[15] trials.

The overall mortality rate in our study was 26.7%, and the 3-month mortality rate was 29.1%. On the one hand, this rate is consistent with that in the PROACT II Trial (25.0%) but is exceeded by the rates reported by MERCI/Multi MERCI (43.5% and 34.0%, respectively) and Penumbra (32.8%)[24] investigators. On the other hand, the mortality rate was lower in the IMS-I/IMS-II[14,15] (16.0%) and MELT studies (5.3%). The encouraging mortality rate seen in the latter trial may be attributed to a lower baseline NIHSS score of 14. Based on the location of the target vessels, the highest mortality rate in our cas-

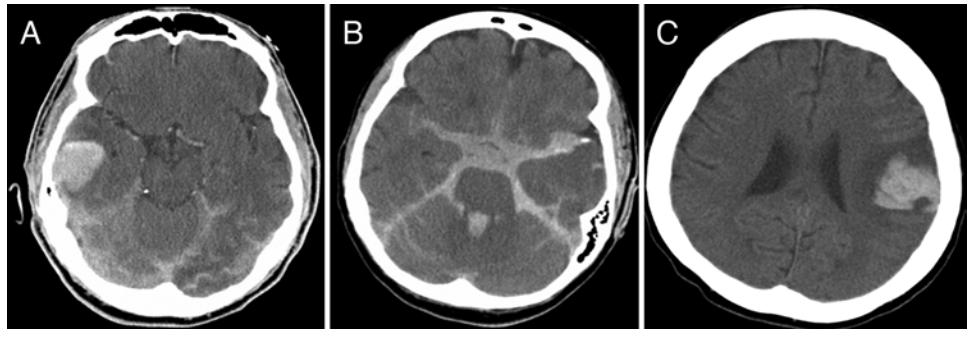

Fig. 2. Imaging studies in different patients. **A:** Intracerebral hemorrhage after intravenous rt-PA followed by endovascular mechanical thrombolysis, surgical evacuation, and craniectomy. The patient died 5 days later. **B:** Perforation of the MCA during intraarterial treatment, followed by surgical evacuation and craniectomy. The patient had a 3-week hospital stay, was discharged to acute rehabilitation, and was thereafter lost to follow-up. **C:** Contralateral parenchymal hematoma Type 2 ICH after right skull base carotid artery angioplasty in which Wingspan stenting was used. The patient had a 2-week hospital stay, was discharged to a subacute facility, and was thereafter lost to follow-up.

es series was associated with the MCA (62.5% [5 of 8]) and the basilar artery (37.5% [3 of 8]). A literature review indicated expected mortality rates ranged from 27% to 78% for the MCA[16] and nearly 90% in the basilar artery.[6,9] Although our data set is limited, it is worth noting that the mortality rate for basilar artery occlusion was less than half (42.8% [3 of 7]) in our case series.

Seventeen patients (42.5%) were found to have ICH on 24-hour postoperative CT scans; 3 patients (7.5%) were symptomatic. This rate has been exceeded by all major endovascular trials to date except for the IMS-I (6.3%).[14] The definition of symptomatic ICH varies across the stroke studies: NINDS (National Institute of Neurological Disorders and Stroke) defined symptomatic ICH as any neurological decline as a result of ICH,[22] whereas the ECASS (European and Australian Cooperative Stroke Study) II,[13] ECASS III,[12] PROACT II,[10] MERCI,[27] Multi MERCI,[26] and Penumbra[5,7] trials defined it as a 4-point increase or higher on the NIHSS.[5,10,12,26,27] In our study, the impact of ICH on clinical status was determined by review of the clinic notes.

Acute stent procedures were performed in 3 patients. Inclusion of these procedures makes our study unique in that previous studies excluded patients with arterial stenosis because it prevented safe passage of a microcatheter.[10] Stenting was not designed to be performed in MERCI, Multi MERCI, or Penumbra trials.[5,26,27] A case example of a supraclinoid dissection treated with stent placement is shown in Fig. 3. Additionally, unlike other intraarterial trials, we included patients with tandem stenosis as long as the extracranial carotid artery was successfully revascularized, which occurred in 10 (25%) of the 40 procedures. Thus, our patients had a mixture of cardioembolic and atherosclerotic occlusions for the treatment of tandem stenosis and an artery-to-artery embolus.

As mentioned earlier, our methods also differ by the definition we used for TIMI revascularization. To our knowledge, all major prior endovascular trials commented on TIMI scores in reference to effect on target vessel treated.[5,10,15,26,27] In PROACT II, the investigators defined successful recanalization as TIMI Score 2 flow in at least one of the M_2 segments (should M_1 be the treated vessel).[10] The same definition was followed in the IMS-II and Penumbra trials.[5,15,24] Both MERCI and Multi MERCI trials were unique in this regard as recanalization was defined as TIMI Score 2 flow in both M_2 segments when treating a more proximal target.[24,26,27] Our series included 4 patients with M_3 occlusions. Such patients were excluded from comparable studies.[5,10,15,26,27] At baseline, these patients had a TIMI score of 2B, and revascularization was not achieved. Excluding those patients from analysis reduces the percentage of nonrevascualized cases with good outcome (mRS score ≤ 2) to 11.1%, which likely reflects the generally better outcomes in patients with M_3 occlusions relative to proximal occlusions.

Our institution is capable of undertaking diffusion/perfusion imaging; however, quantifiable measurement of mismatch is pending. As noted in the DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) study and subsequent analysis, perfusion-weighted imaging can greatly help in selecting the most appropriate patients for intervention.[3,17] In our series, perfusion-weighted imaging was used in 25 (62.5%) of 40 cases, and we determined that there was a mismatch in 17 (68%) of these 25 patients. Unfortunately, a large proportion of our patients lost to follow-up were in this category, precluding any meaningful analysis.

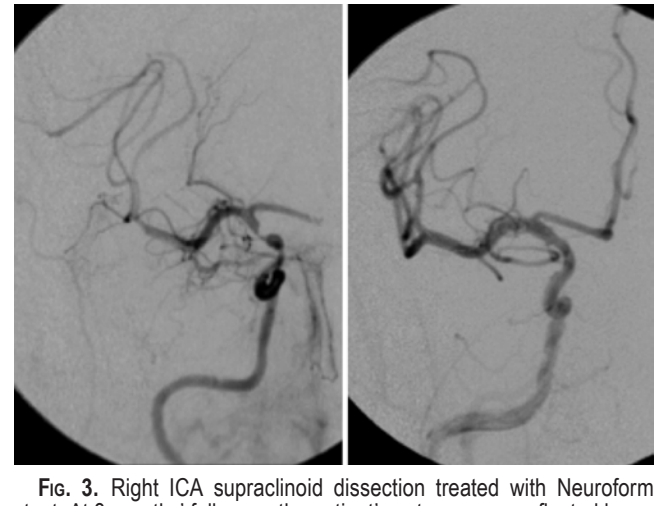

Fig. 3. Right ICA supraclinoid dissection treated with Neuroform stent. At 8-months' follow-up the patient's outcome was reflected by an mRS score of 1.

The other 15 patients, who did not undergo perfusion imaging, were selected for endovascular therapy based on several factors and findings including elapsed intravenous treatment window, clinical decision making, noninvasive angiography, flow void interpretation from MR imaging, or dense artery signs on head CT scanning. There was only one use of combined intravenous plasminogen activator therapy with intraarterial therapy, and this clinical outcome is described in Fig. 2A.

This study is limited by its retrospective nature and by the fact that it is a single-center study. Another limitation in our review is estimation of mRS score from follow-up clinic or readmission notes. To our knowledge, there are no standardized or validated methods for obtaining such mRS scores. To minimize our overestimation of outcome, the 4 patients to whom an mRS score between 2 or 3 could not be reliably assigned due to ambiguous documentation were assumed to be in the higher grade. This approach to assigning values resulted in an overall mRS < 2 rate of 36.7%. Finally, our endovascular therapies varied, and in most treatment cases different endovascular modalities or devices were applied. While our approach resembles most practices at stroke centers, it is not easily comparable to prior studies, in which one treatment modality was used at a time.

Conclusions

Our center is performing endovascular stroke therapy with a safety and efficacy profile that is consistent with other major endovascular studies. To successfully continue with future analysis, we have established a registry of endovascular cases with standardized medical history forms, follow-up scales, and standardized follow-up.

Disclosure

Dr. Bernstein reports a financial relationship with Boehringer Ingelheim.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bendok, Day, Hurley, Alberts, Bernstein, Dabus, Shaibani. Acquisition of data: Bendok, Day, Hurley, Dabus, Shaibani. Analysis and interpretation of data: Bendok, Day, Rahme, Alberts, Bernstein, Dabus, Shaibani. Drafting the article: Bendok, Day, Chmayssani, Rahme. Critically revising the article: Bendok, Chmayssani. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Day, Hurley. Study supervision: Bendok, Day, Alberts.

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See the corresponding article in this issue (E10).

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Editorial

Endovascular stroke therapy

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In this edition of *Neurosurgical Focus*, Day et al.[1] review the Northwestern Memorial Hospital experience with the endovascular treatment of acute ischemic stroke. Overall, the authors establish that their center performed stroke treatment with a safety and efficacy rate comparable to that reported in other major trials. Using a variety of endovascular techniques, including both transarterial medical therapy and various mechanical devices, the authors achieved a good outcome in 36.7% of their patients. This review adds to the growing body of evidence that recanalization is the best predictor of improved outcomes.

Neurosurgeons and neurologists remain entrenched in the battle against acute ischemic stroke. The last decade has witnessed a number of advances in both medical and surgical interventions for stoke. These advances include novel pharmacological thrombolytic agents and mechanical devices employed transarterially. Indeed, the authors of this particular study used many of these novel techniques. The future will likely witness more dramatic endovascular advances for the treatment of this disease. Specifically, we are now witnessing the advantages of stent therapy in the setting of acute ischemic stroke. Retrievable stents also hold great promise. This technology may enable us to mechanically disrupt a thrombus and retrieve the stent, avoiding the risk of antiplatelet therapy.

The authors also touch on an issue of great interest to both interventionalists and neurologists—specifically, the use of diffusion- and perfusion-weighted imaging in assessing the potential utility of endovascular therapy in the management of acute ischemic strokes. By delineating which patients have viable brain tissue, we may be able to treat a larger population of patients who present outside of the standard therapeutic time window. These imaging techniques will need further refinement and evaluation. For instance, one issue remains the length of time that it takes to obtain and analyze these images. As our experience with these modalities increases, this factor will likely diminish in importance.

The authors highlight an issue that remains problematic: the occurrence of intracerebral hemorrhage following endovascular therapy. The authors reported 17 cases in their series, but only 3 were clinically symptomatic. As the technology continues to advance, mechanical thrombolytic techniques and devices will undoubtedly supplant transarterial medical therapies, diminishing the rate of intracerebral hemorrhage. While this study largely confirms the safety and efficacy of endovascular techniques for acute ischemic stroke, much work remains to be done in the fight against this disease. *(DOI: 10.3171/2011.2.FOCUS1168)*

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Hemodynamic instability following carotid artery stenting

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Object. Postprocedural hypotension and bradycardia are important complications of carotid artery stenting (CAS) and are referred to as hemodynamic instability (HI). However, the incidence and impact of HI on the short-term prognosis of patients have been of a large debate.

Methods. Twenty-seven patients were selected based on NASCET criteria, and they underwent CAS between September 2008 and September 2009. Continuous electrocardiography monitoring and supine blood pressure (BP) monitoring were performed before and after stent deployment and on the following day to detect HI, defined as systolic BP lower than 90 mm Hg or a heart rate lower than 60 bpm. Patients were asked to perform a Valsalva maneuver before and after stent deployment. The Valsalva ratios (VRs) along with other demographic and procedural data were documented and compared between patients with and without incidence of HI.

Results. Seventeen patients (63%) developed HI after CAS. The degree of stenosis was found to have a significant correlation with occurrence of HI ($p < 0.006$). No other risk factor or demographic data showed any correlation with HI. The VRs were significantly lower in the HI group compared with the non-HI group, indicating a significant autonomic dysfunction ($p < 0.003$). During follow-up, 1 patient (4.3%) developed major stroke, and the remaining patients were symptom free.

Conclusions. Hemodynamic instability occurs frequently after CAS, but it seems to be a benign phenomenon and does not increase the risk of mortality or morbidity in the short term. A VR at rest less than 1.10, baseline autonomic dysfunction, and degree of carotid artery stenosis can be used as measures for predicting HI after CAS.
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Key Words • **carotid artery stenting** • **hemodynamic instability** • **Valsalva ratio**

Cerebrovascular accidents (CVAs) are associated with high rates of mortality and morbidity and impose a great burden on the economy, especially in developing countries.[17] Carotid artery stenosis is thought to be responsible for about 20%–30% of all strokes.[17,18] Although carotid endarterectomy (CEA) has been the gold-standard treatment for carotid stenosis, carotid artery stenting (CAS) has been proposed as a valid and reliable procedure for the treatment of carotid artery stenosis, especially in patients who are at high risk for general anesthesia and surgery.[12,21] Postprocedural hypotension and bradycardia are important complications of CAS and are referred to as hemodynamic instability (HI).[6] The pathophysiology of HI, which is also observed after CEA, is thought to be due to manipulation of the carotid sinus during stent deployment.[4] The incidence and impact of HI on the short-term prognosis of patients have been of large debate in the literature. Attempts have been made to identify the predictive risk factors for the occurrence of HI.[4]

Carotid artery stenting has recently been performed in a few centers throughout Iran.[8] To our knowledge, there are no investigations in the literature regarding the incidence and adverse effects of HI after CAS. We aim to assess the incidence of HI in our patients, its possible predictive factors, and its impact on mortality and morbidity during short-term follow-up.

Methods

Every patient who was a candidate for CAS at Shiraz University Hospitals between September 2008 and September 2009 without exclusion criteria was included in this study. Twenty-seven patients were selected based on NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators)[12] criteria as follows: those

Abbreviations used in this paper: BP = blood pressure; CAS = carotid artery stenting; CEA = carotid endarterectomy; CVA = cerebrovascular accident; ECG = electrocardiography; HI = hemodynamic instability; MI = myocardial infarction; TIA = transient ischemic attack; VR = Valsalva ratio.

who were symptomatic with 70% or more carotid artery stenosis and those who were asymptomatic with stenosis of more than 80% as determined by color Doppler ultrasonography. The degree of stenosis of all lesions was measured by digital estimation during pre- and postprocedural angiography. Written consent was obtained from all patients.

A bolus dose of aspirin (325 mg) and clopidogrel (300 mg) was administered to patients before the procedure. All medications including antihypertensive drugs were given on the morning of the procedure. Two interventionists (one of whom was a cardiologist) performed all carotid stent implantations. A complete history, including neurological and physical examinations, baseline electrocardiography (ECG), and supine blood pressure (BP), was obtained in all patients. After mild sedation with 2–3-mg intravenous midazolam, CAS was performed through a transfemoral approach. Complete 4-vessel brain angiography was performed before the procedure in each patient. All patients received an intravenous dose of 1 mg atropine. Different brands of stents were used, including WallStent (Boston Scientific), Crystallo Ideale (Invatec), and Acculink (Medlink). All stents were equipped with embolic protection devices: Filter EZ (Boston Scientific), Spider (Medlink), and MoMa (Invatec).

Exclusion criteria were the presence of hemodynamic instability and low BP at baseline, atrial fibrillation, recent transient ischemic attacks (TIAs) and CVAs occurring in the past week, and an inability for the patient to hold his or her breath for 30 seconds.

Hemodynamic instability was defined as: 1) any episode of hypotension (that is, systolic BP lower than 90 mm Hg or a decrease of 50 mm Hg or more from the baseline BP) after stent deployment or balloon inflation; or 2) any episode of bradycardia after stent deployment or balloon inflation described by a heart rate lower than 60 bpm, an R-R interval of greater than or equal to 25 msec, or a decrease of more than 30 bpm from the baseline heart rate according to ECG findings.

During the operation, patients were asked to perform a Valsalva maneuver by forceful expiration with an open glottis in supine position for 15 seconds against a resistance of approximately 40 mm Hg. This was performed by asking the patients to blow into a blunted tube with a pressure recorder on its end. The patient's heart rate and BP were obtained before and immediately after the Valsalva maneuver. We also assessed the Valsalva ratio (VR) by dividing the length of the longest R-R interval on the ECG after the Valsalva maneuver by the shortest R-R interval during the maneuver and within the 45 seconds of peak heart rate. A VR of 1.1 or less was defined as a definite impaired autonomic function, that between 1.11 and 1.20 was defined as borderline, and that of 1.21 or more was defined as normal.

In all cases of HI, whether symptomatic or asymptomatic, an intravenous infusion of 300–400 ml of 9% saline was administered, and isolated bradycardia was managed using 0.5–1 mg atropine. In cases in which there was no response to initial treatment, intravenous dopamine drips starting with 5 μg/kg/min were begun and titrated until HI resolved. Persistent HI in patients was defined as unresponsiveness to treatment after 1 hour or requirement of dopamine drips for maintenance of hemodynamic status after the procedure and transferring to coronary care unit or ward.

The next day, the patient's hemodynamic status and ECG results were reviewed, and abnormal findings, heart rate, BP, and VR were documented. Complete neurological examination to evaluate any new abnormal finding was performed in all patients by the same examiner.

All patients were contacted 1 month after CAS and were reexamined by the same interventionists as before. Any adverse outcomes were recorded, and a new color Doppler ultrasonography study was performed.

All available data from the carotid lesion morphology, degree of stenosis, and presence of calcification or tortuosity along with the location of lesion, risk factors for cardiovascular problems, history of a previous coronary artery disease or myocardial infarction (MI), and history of previous stroke or TIA, were gathered. Data are expressed as the means ± SDs, and variables were analyzed using the Pearson chi-square test and the Fisher exact test. A p value < 0.05 was considered statistically significant.

Results

Twenty-seven patients underwent successful CAS without any adverse neurological events. Seventeen were men (63%) and 10 were women (37%). The mean patient age was 69 ± 10.4 years (range 49–85 years). Among the patients, 4 (14%) suffered from significant bilateral carotid artery stenosis, while the remaining patients had unilateral lesions. The mean degree of stenosis was 88% ± 6.5% (range 75%–99%). Atherosclerosis risk factors are presented in Table 1.

According to our definition of HI, 17 patients (63%) developed the condition. Isolated bradycardia without hypotension was not reported in any case. Ten patients (37%) showed no signs of HI.

For patients with no HI, a mean decrease of 9 ± 12.7 mm Hg in baseline systolic BP was observed after stent deployment, while the mean decrease in the HI group was significantly higher (55 ± 18 mm Hg). The overall mean decrease in systolic BP during stenting in all patients was 38 mm Hg (Table 2). Twenty-six patients (96%) continued to maintain some degree of hypotension regardless of the occurrence of HI the day after stenting. Six patients (22%) developed persistent HI requiring dopamine infusion for a mean of 16 ± 6.2 hours after stenting. All patients were symptom free at the time of discharge with no adverse outcomes.

A comparison of demographic and procedural data between the HI and non-HI groups is given in Table 1. Among all available data, the degree of carotid artery stenosis was the single predictive factor and was statistically significant for the occurrence of HI ($p = 0.006$). Regarding the site and characteristics of the lesions, 26 patients (96%) had involvement of the carotid bifurcation, 8 patients (26%) had calcification, 22 patients (81%) had an eccentric lesion, 4 patients (15%) had significant clotting over the lesion, and 20 patients (74%) had a soft lesion.

TABLE 1: Characteristics in 27 patients who underwent CAS

Variable	Value*			p Value†
	Total	HI Group	Non-HI Group	
mean age (yrs)	69 ± 10.4 (49–85)	69 ± 10.3 (50–85)	70 ± 11 (49–85)	0.99
sex				0.99
male	17 (63)	11 (64.7)	6 (60)	
female	10 (37)	6 (35.3)	4 (40)	
hypertension	18 (66.7)	12 (70.6)	6 (60)	0.683
hyperlipidemia	11 (40.7)	7 (41.2)	4 (40)	0.99
diabetes mellitus	10 (37)	6 (35.3)	4 (40)	0.99
smoking	5 (18.5)	5 (29.4)	0 (0)	0.124
family history of MI or stroke	5 (18.5)	4 (23.5)	1 (10)	0.621
history of stroke or TIA	10 (37)	6 (35.3)	4 (40)	0.99
mean degree of stenosis (%)	88.3 ± 6.5 (75–99)	91 ± 4.7 (80–99)	83.5 ± 6.6 (75–95)	0.006
bilat lesion	4 (14.8)	1 (5.9)	3 (30)	0.128
mean systolic BP at rest (mm Hg)	161 ± 30.7 (95–230)	160 ± 32.5 (95–230)	163 ± 28.8 (120–210)	0.902

* Values represent the number of patients with percentages in parentheses, unless otherwise indicated. Mean values are presented as ± SDs with the ranges in parentheses.

† Fisher exact test. $p < 0.05$ is statistically significant.

However, none of these characteristics were significantly different between the HI and non-HI groups ($p > 0.05$).

The mean VR at rest was 1.057 ± 0.12 (range 0.82–1.40). Twenty patients (74%) had a VR of 1.10 or less, and 2 (7%) had a VR of 1.21 or greater. The remaining patients (19%) had a VR in the borderline zone (between 1.11 and 1.20). Seventeen patients developed HI during stenting, and a decrease of 0.044 in VR was seen in all patients. While the mean VR at rest was 1.057 ± 0.12, the mean VR after stenting was 1.013 ± 0.12, indicating that at least some degree of autonomic dysfunction occurred overall. The mean VR at rest in the HI group was 1.00 ± 0.083 while it was 1.14 ± 0.12 in the non-HI group, which was significant (Table 3). Changes in systolic BP during the Valsalva maneuver at rest were 16 ± 12 mm Hg overall and failed to show any statistical significance between the HI and non-HI groups ($p = 0.604$). However, the decrease in BP after the Valsalva maneuver in the HI group was slightly greater than that in the non-HI group (13 ± 11 mm Hg in the non-HI group compared with 18 ± 12 mm Hg in the HI group).

Only 23 patients could attend follow-up visits in person. The other 4 patients were contacted by phone and underwent careful history taking. No adverse events such as death, MI, minor or major stroke, TIA, or any hospital admissions were reported. The mean follow-up period was 4.5 months after the procedure. Except for 1 case of a major CVA, no other patient developed any adverse

TABLE 2: Comparison of BP and heart rate between the non-HI and HI groups*

Variable	Mean ± SD (range)			p Value†
	Non-HI Group	HI Group	Total	
SBP at rest (mm HG)	163.1 ± 28.8 (120 to 190)	160.3 ± 32.5 (95 to 230)	161.37 ± 30.7 (95 to 230)	0.902
SBP after Valsalva maneuver (mm Hg)	149.8 ± 26.9 (120 to 190)	142.2 ± 32.3 (90 to 220)	145 ± 30 (90 to 220)	0.505
SBP post–stent deployment (mm Hg)	154.1 ± 30.6 (120 to 195)	105.1 ± 25.1 (60 to 179)	123.2 ± 35.9 (60 to 195)	0.000
SBP the day after the procedure	120 ± 27	104.4 ± 17.2	110 ± 22.5	0.000
SBP at follow-up	125.6 ± 21.9 (85 to 160)	129 ± 17.3 (85 to 122)	127.8 ± 18.6 (85 to 160)	0.243
HR at rest (bpm)	82.3 ± 10.7 (71 to 100)	87.4 ± 15.1 (60 to 122)	85.5 ± 13.6 (60 to 122)	0.243
HR after stenting (bpm)	93.8 ± 18.3 (67 to 125)	93.5 ± 24.1 (50 to 150)	93.6 ± 21.8 (50 to 150)	0.863
SBP at rest − SBP after Valsalva (mm Hg)	13.3 ± 11 (−10 to 28)	18.1 ± 12.5 (3 to 50)	16.3 ± 12 (−10 to 50)	0.604
SBP at rest − SBP after stenting (mm Hg)	9 ± 12.7 (−17 to 25)	55.2 ± 18 (20 to 90)	38.1 ± 27.8 (−17 to 90)	0.000

* HR = heart rate; SBP = systolic BP.

† Fisher exact test. $p < 0.05$ is statistically significant.

TABLE 3: Comparison of the VR throughout the study between the non-HI and HI groups

Variable	Mean ± SD (range)			p Value*
	Non-HI Group	HI Group	Total	
VR at rest	1.14 ± 0.12 (0.944–1.10)	1.00 ± 0.08 (0.82–1.11)	1.057 ± 0.12 (0.82–1.40)	0.003
VR after stent deployment	1.07 ± 0.06 (1.00–1.21)	0.97 ± 0.13 (0.63–1.08)	1.01 ± 0.12 (0.63–1.21)	0.083
VR the day after the procedure	1.07 ± 0.13	0.94 ± 0.08	0.99 ± 0.12	0.03
VR at follow-up	1.16 ± 0.09	0.99 ± 0.06	1.05 ± 0.1	0.03

* Fisher exact test. $p < 0.05$ is statistically significant.

events. One patient (4.3%) maintained low BP (85/50 mm Hg) during the follow-up.

Discussion

Hypotension, bradycardia, and asystole have been reported as consequences of distension of the carotid bulb during CAS. In some reports, HI has been associated with neurological sequelae.[3,10,11,20] However, HI does not occur after CAS in all patients; there are numerous debates in the literature regarding the incidence of this phenomenon and possible predictors. In addition, there have been efforts to determine the correlation between HI and increased mortality and morbidity in the short and long term in those who have undergone CAS. In one study of 51 patients in Italy, the presence of a fibrous plaque inside the carotid artery and the degree of stenosis before and after stenting were predictors of postprocedural hypotension and bradycardia. However, the authors could not establish any relationship between the incidence of HI and mortality and morbidity.[13] In another study conducted in the US, significant postprocedural hypotension was noticed, but the condition was not associated with long-term adverse neurological outcomes.[14]

Qureshi et al.[16] performed a multicentric study including 71 cases of CAS. They reported incidences of hypotension and bradycardia to be 22.4% and 27.5%, respectively. A history of MI was found to be a predictive factor for postprocedural hypotension and bradycardia. Leisch et al.[9] reported on the proximity of stenosis to the carotid bifurcation as the most important predictor of HI. Other predictors were identified as existence of contralateral stenosis (> 60%), length of the stenosis, and balloon-to-artery ratio. Our results did not confirm their findings regarding contralateral stenosis as a predictive risk factor for HI. Although Qureshi et al.[16] and Alpman et al.[2] found that ischemic heart disease was frequently associated with postprocedural hypotension, our study failed to prove such a claim, and no relationship was found between the occurrence of HI and the presence of ischemic heart disease.

In 2006, a study on 500 CAS procedures performed in the US showed that HI occurred in 210 procedures (42%), and persistent HI defined as hypotension that only responded to vasopressors occurred in 84 patients (17%). Those with persistent HI were at a significantly higher risk of periprocedural adverse outcomes including MI, stroke, or TIA.[5]

The incidence of HI varies greatly in different studies from 1.7% to 42%. The incidence of HI in our study was roughly 63%, which is closer to the incidence reported by Gupta et al.[5] The reason for the differences among these studies can be attributed to different definitions of HI. None of the demographic data or risk factors in our patients showed any correlation with susceptibility to hemodynamic instability. Our results suggest that the degree of carotid artery stenosis is highly related to occurrence of HI ($p = 0.006$).

It has previously been shown that VR can be of value during bedside detection of autonomic dysfunction, especially in patients with cardiovascular disease.[1,7,19] To our knowledge, no study has evaluated the role of VR in predicting HI after CAS. Multivariate analysis of our data showed that there was a significant difference between the HI and non-HI groups with respect to the values of VR at rest and after stenting ($p < 0.003$).

Individuals in the HI group had significantly lower VRs at rest and before the procedure, and these patients maintained their low values throughout the next day. It can be assumed that patients with lower VRs at rest are more prone to HI after stenting, and this can play a major role as a predictive factor for occurrence of HI. The VR can be a very useful bedside method for prediction of HI after stent deployment; however, obtaining the value can sometimes be difficult depending on the patient's cooperation. The VR decreased in all patients; however, a significant difference was found between the HI and non-HI groups.

According to our data, a patient with a VR of 1.10 or less at rest will probably develop HI after CAS, with a sensitivity of 94% and a specificity of 60%. The positive predictive value of VR for prediction of HI was 80%, and the negative predictive value was 85%. Having the VR at hand preprocedure can help to determine the high-risk group and prevent HI by proper administration of atropine and inotrope preoperatively.

Although our findings failed to correlate HI with short-term survival and there seems to be no association between the occurrence of HI after stenting and mortality or morbidity, the small size of the patient population may have biased the conclusion. Other studies also confirmed the absence of a correlation between HI and short-term survival or morbidity as we claimed in our study, but those studies also suffered from a small patient population.[15]

Study Limitations

The most important limitation was our small patient population, which could affect the results, especially

those regarding the risk factors that might be considered as predictive factors for HI and the possible effect of HI on mortality and morbidity.

Conclusions

Hemodynamic instability occurs frequently after CAS, it but seems to be a benign phenomenon and does not increase the risk of mortality or morbidity in the short term. A VR at rest less than 1.10, baseline autonomic dysfunction, and degree of carotid artery stenosis can be used as measures for prediction of HI after CAS.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kojuri. Acquisition of data: all authors. Analysis and interpretation of data: Kojuri, Zamiri. Drafting the article: Kojuri. Critically revising the article: Kojuri. Statistical analysis: Kojuri, Zamiri. Administrative/technical/material support: Kojuri, Zamiri. Study supervision: Kojuri.

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Contrast stasis on noncontrast computed tomography as a predictor of stroke postthrombolysis

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Multimodal endovascular intervention is becoming more commonplace for the acute intervention of ischemic stroke. Hyperdensity in a portion of the treated territory is a common finding on postthrombolytic noncontrast CT (NCCT), but its significance is poorly understood. The authors conducted a single-institution, retrospective chart review of patients who had intraarterial thrombolysis of the anterior circulation between 2010 and 2011 with evidence of hyperdensity on NCCT following recanalization. Eighteen patients had evidence of postoperative contrast stasis causing hyperdensity on NCCT. One hundred percent of the patients had MR imaging evidence of completed strokes postoperatively in the same distribution as the stasis. Stasis on NCCT after intervention had a sensitivity and specificity of 82% and 0% for predicting stroke, respectively. Furthermore, the positive predictive value was 100%. The presence of contrast stasis on postthrombolytic NCCT correlates well with stroke seen on subsequent MR imaging. *(DOI: 10.3171/2011.4.FOCUS1141)*

Key Words • thrombolysis • stroke • perfusion • magnetic resonance imaging

Stroke is the third leading cause of death in the US, with its prevalence on the rise.[15] Given that a large percentage of patients arrive late at the hospital outside the conventional window[15] for treatment, increased attention has been paid to appropriate imaging techniques for assessing tissue at risk prior from endovascular intervention.[1,3,5,8,9] In ischemic stroke, MR perfusion and CT perfusion mismatch indicates tissue at risk, and this mismatch has been used increasingly to extend the intraarterial thrombolytic treatment window beyond traditional time constraints. Specifically, CT perfusion demonstrating a region of increased mean transit time and decreased cerebral blood flow with preserved cerebral blood volume signifies tissue at risk and has been used by multiple institutions as indications for treatment in the presence of concomitant neurological deficits with varying results.[2,6,13] Diffusion-weighted imaging is an MR imaging modality that demonstrates acute stroke based on water diffusion. Perfusion-weighted imaging can be performed via MR imaging or CT and shows cerebral perfusion based on blood flow, blood volume, and transit time. Although both DW MR and PW CT or MR imaging mismatch has been shown to underestimate penumbrae with an increased margin of error when imaging is performed further from the ictus,[10] Hassan et al.[6] demonstrated in a retrospective review no statistically significant difference in strokes as evaluated by CT perfusion or time-guided methods for selecting patients with stroke.

A major risk of endovascular recanalization is intracranial hemorrhage. It is significant enough that much attention has been paid to the improvement of imaging techniques to differentiate infarction from penumbra, or tissue at risk. After intervention, hyperdensity on NCCT can be particularly concerning because of its similarity to hemorrhage, hindering accurate diagnosis and appropriate care (Fig. 1). At the same time, we propose that this hyperdensity from contrast stasis, frequently found on postthrombolytic NCCT, may in fact be indicative of a completed stroke that will spatially correlate with an MR imaging DW sequence (Fig. 2). While not necessarily as definitive as true DW imaging, it should give the practitioner information regarding the size and location of residual stroke without putting the critical patient through a time-consuming MR imaging study.

Methods

Institutional review board approval was obtained for this study. A single-institution, retrospective chart review of all stroke admissions treated endovascularly between January 2010 and January 2011 was performed. Specific

Abbreviations used in this paper: DW = diffusion-weighted; MCA = middle cerebral artery; NCCT = noncontrast CT; PW = perfusion-weighted.

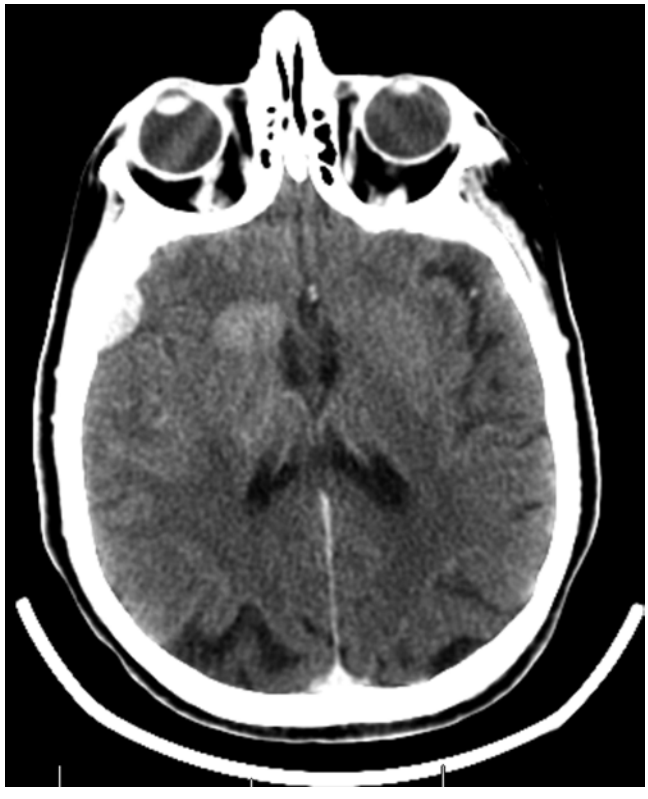

Fig. 1. Noncontrast head CT obtained in a 63-year-old woman who presented with acute left hemiplegia due to right MCA occlusion and then underwent intraarterial thrombolysis with recanalization of the MCA, demonstrating contrast stasis in the right lentiform nucleus and putamen.

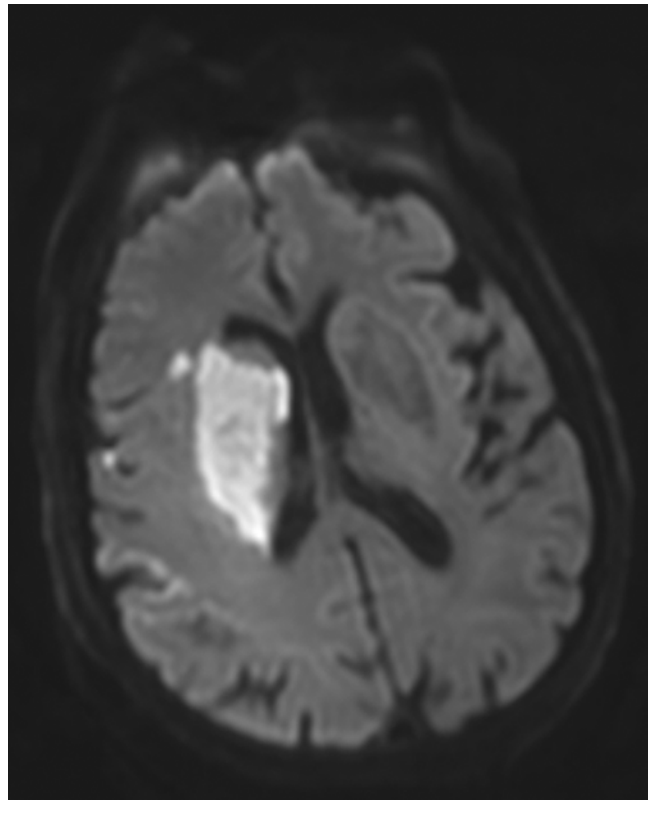

Fig. 2. Postthrombolytic DW image obtained in the same patient referred to in Fig. 1, demonstrating a region of restricted diffusion that is spatially similar to the hyperdensity seen on the previous postthrombolytic NCCT.

patients analyzed were those who underwent endovascular intervention that demonstrated angiographic recanalization and NCCT done immediately after thrombolysis. Hyperdensity seen on this NCCT, based on subjective determination by a neuroradiologist, was compared with DW imaging findings obtained on postoperative Day 1–4 for the spatial stroke relationship. An on-site neuroradiologist performed the imaging evaluation. Excluded patients were those with thrombolysis of the posterior circulation and those without postoperative MR imaging studies.

Results

Twenty-two patients, 12 females (54%) and 10 males (45%), underwent NCCT studies immediately after thrombolysis. The mean patient age was 67 years (ages 36–85 years; Table 1). Sixty percent of at-risk territories were in the right MCA distribution, whereas the remaining 40% were in the left. The anterior cerebral artery territory was at risk in 4 patients as well. Recanalization was achieved in all 22 patients. Postoperatively, 18 patients (82%) had NCCTs demonstrating hyperdensities consistent with stasis in the territory recanalized. Postoperative MR imaging demonstrated stroke in 100% of the patients. Of those who had hyperdensity on NCCT scanning, there was 100% correlation with the infarct seen on postprocedural MR imaging. Four patients with NCCT studies postthrombolysis lacked evidence of stasis, and all of them demonstrated stroke prior to discharge. Therefore, the overall sensitivity of postintraarterial thrombolytic NCCT correlating with DW imaging findings is 82%, with a positive predictive value of 100%. At the same time, since some type of stroke developed in all patients, the specificity cannot be calculated and the negative predictive value is 0. Notably, petechial hemorrhage did develop in 4 patients (23%), as seen on postprocedure MR imaging, which was not clinically significant.

Discussion

Hyperattenuation or hyperdensity on NCCT after thrombolysis is a frequent finding, although its significance is not well understood. It is thought to result during angiography from the injection of contrast into a territory with a completed stroke where the blood brain barrier is disrupted.[7] As the intraarterial contrast leaks through loose endothelial tight junctions into the extravascular spaces in infarcted tissue, hyperdensity forms.[4]

One of the most concerning complications of endovascular intervention is vessel rupture and/or hemorrhage. Multimodal reperfusion therapy has been shown to have an incidence of intraparenchymal hemorrhage as high as 39% in patients who have undergone thrombolysis.[12] In our series, that number was 23%, if attributed entirely to the intervention. Hemorrhage is concerning on NCCT because of its similarity in Hounsfield units to contrast,

TABLE 1: Imaging findings before and after multimodal endovascular recanalization*

Case No.	Age (yrs)	CT Perfusion/Angiography	NCCT w/ Hyperdensity	DW MR Imaging w/ Stroke	NCCT & DW Imaging Matching
1	79	lt basal ganglia & external capsule infarct; lt MCA penumbra	+	+	+
2	66	lt lentiform nucleus infarct; lt MCA penumbra	+	+	+
3	77	no infarct; rt MCA penumbra	+	+	+
4	68	rt insular, putamen, corona radiata infarct; rt MCA penumbra	+	+	+
5	65	no infarct; rt MCA penumbra	−	+	−
6	56	rt insular infarct; rt MCA penumbra	+	+	+
7	36	lt basal ganglia infarct; lt basal ganglia penumbra	+	+	+
8	67	no infarct; rt MCA penumbra	+	+	+
9	81	rt putamen infarct; rt MCA penumbra	+	+	+
10	62	rt lentiform nucleus infarct; rt MCA penumbra	+	+	+
11	62	lt insular infarct; lt MCA penumbra	+	+	+
12	78	lt frontotemporal infarct; lt ACA/MCA penumbra	+	+	+
13	72	rt corona radiata infarct; rt MCA penumbra	+	+	+
14	52	lt basal ganglia infarct; lt MCA penumbra	+	+	+
15	57	no infarct; lt ACA/MCA penumbra	−	+	−
16	85	no infarct; rt MCA penumbra	+	+	+
17	61	no infarct; rt MCA penumbra	+	+	+
18	60	no infarct; lt ACA/MCA penumbra	+	+	+
19	64	no infarct; rt ACA/MCA penumbra	+	+	+
20	66	lt ACA infarct; lt MCA penumbra	−	+	−
21	85	no infarct; rt MCA penumbra	+	+	+
22	84	no infarct; rt MCA penumbra	−	+	−

* ACA = anterior cerebral artery.

and MR imaging is beneficial in differentiating these two fluids. Moreover, the presence of contrast within the reperfused territory tends to rapidly dissipate on sequential imaging.

Mericle et al.[11] proposed a classification scheme to determine the prognostic significance of a postoperative hyperdensity, trying to differentiate blood from contrast. In a retrospective review of outcomes in 10 patients, the poorest predictor was for a hyperdensity > 150 HU, which is more likely compatible with blood extravasation.

The diagnosis of lesions mimicking intraparenchymal hematoma after multimodal endovascular stroke intervention is not straightforward given the similar appearance of contrast stasis on CT. In a series of 10 consecutive patients recanalized with intraarterial thrombolysis, the relevance of hyperdense postoperative lesions was evaluated by Wildenhain et al.[14] Sixty percent (6 of 10) of these patients demonstrated hyperdense lesions, which resolved in 2 patients, persisted as strokes in 2, and were asymptomatic in 2.

Jang et al.[7] evaluated 94 NCCTs from patients with strokes treated using endovascular thrombolysis. Thirty-one (33%) had hyperdensities, 18 of which (58%) demonstrated hemorrhagic transformation.[7] In the present study the radiographic incidence of hemorrhagic transformation was 23% (4 patients). None of these patients required surgical evacuation; however, the course of their hospital stay was lengthened.

In these studies, MR imaging has not been routinely followed after multimodal endovascular intervention to determine the prognostic significance of stasis after recanalization and stroke. To the best of our knowledge, the present report is the first to correlate hyperdensity on NCCT with the core of the stroke on postprocedure MR imaging.

In our case series, 18 patients had NCCT demonstrating postrecanalization stasis. The sensitivity and specificity of stasis on NCCT correlating with stroke after intervention were 82% and 0%, respectively. Given that all of the recanalized patients had MR imaging evidence of stroke, the negative predictive value was 0% and the positive predictive value was 100%. While the territory in question showing stasis on NCCT matched the findings on postoperative stroke, without a larger population including more patients without diffusion restriction on MR imaging after intervention, it would be too difficult to assess the specificity and negative predictive value. Still, in the presence of an NCCT demonstrating stasis in the territory reperfused, in the absence of an expected degree of mass effect, one could surmise that this contrast stasis should correlate well with postprocedural DW MR imaging.

One benefit to the correlation of contrast stasis on NCCT and DW imaging findings on MR imaging postrecanalization is that the practitioner may be able to forego putting the patient through MR imaging. Postprocedure, patients are often in a critical state requiring strict blood

pressure control and often ventilatory support. Having the patient in a time-consuming MR imaging session while being monitored from a control room poses some risk to the patient, as does transport to and from the MR imaging suite. Moreover, many of these patients have a history of poor cardiac status and have pacemakers or other devices that prevent them from undergoing MR imaging. In addition, there is significant financial cost for MR imaging, which can also be avoided with NCCT immediately postprocedure.

One obvious flaw in this study is the small number of patients. With only 22 patients total, all of whom had stroke on MR imaging, and 18 patients with contrast stasis, the findings could be skewed in favor of a correlation between contrast stasis and diffusion findings. As stated previously, however, the goal of this study was not for NCCT to completely replace MR imaging, but to illustrate a correlation between the two that can be used by a practitioner in the appropriate setting.

Conclusions

Noncontrast CT is a valuable tool for immediate postthrombolysis evaluation. The presence of a hyperdense region in an area that has been reperfused, without significant mass effect, most likely correlates with an area of diffusion restriction on MR imaging and signifies a stroke. Magnetic resonance imaging possesses greater sensitivity to differentiate blood products from contrast and therefore should be considered the gold standard in the postthrombolytic setting. We do not attempt to replace the value of postthrombolysis MR imaging but instead give new significance to the value of the hyperdensity that is often seen on postthrombolytic NCCT.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Symptomatic intracranial arterial disease: incidence, natural history, diagnosis, and management

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Symptomatic intracranial arterial disease is associated with a high rate of recurrent ischemic events. The management of this condition is controversial, with some advocating medical therapy as a sole means of treatment and others recommending endovascular therapy in addition to best medical management. In rare cases, surgical intervention is considered. A thorough review of the available literature was performed, and treatment recommendations based on these data are provided. *(DOI: 10.3171/2011.3.FOCUS1138)*

Key Words • **intracranial stenosis** • **cerebral ischemia** • **balloon angioplasty** • **extracranial-intracranial bypass**

Symptomatic intracranial arterial disease is a common cause of ischemic stroke, but the optimal management of this condition remains incompletely defined. Options include medical therapy, endovascular treatment with angioplasty with or without stent placement, and surgical intervention for direct or indirect revascularization. In this review we provide evidence supporting or refuting the use of each of these potential therapies. Special emphasis was placed on available data regarding endovascular and surgical treatment of sICAD.

Epidemiology and Risk Factors

In the US, sICAD accounts for approximately 8%–9% of all ischemic strokes,[62,81] resulting in approximately 65,000 strokes per year.[49] Its incidence, however, exhibits racial and ethnic differences. In Asian populations, between 30% and 50% of ischemic strokes are due to sICAD.[83–85] In African Americans and Hispanics, a significantly higher proportion of strokes are attributable to intracranial atherosclerosis than in Caucasians, despite an equal incidence of the extracranial atherosclerotic stroke subtype among the 3 racial/ethnic groups.[62]

Atherosclerosis, in association with traditional stroke risk factors, accounts for the majority of sICAD.[6,35,78] The common nonmodifiable risk factors of sICAD are age, male sex, and race.[6,35,62,78] The most common modifiable risk factors are hypertension, hyperlipidemia, ischemic heart disease, and diabetes mellitus.[6,35,71,78] The less common causes of sICAD include moyamoya disease,[64] sickle cell disease,[3,59] infectious meningitis,[50,58] vasculitis,[9] dissection,[11] and radiation therapy.[61]

Natural History

There is a high risk of recurrent strokes, which are often disabling, in patients with sICAD. Two large prospective trials—the WASID study and the Groupe d'Etude des Stenoses Intra-Craniennes Atheromateuses symptomatiques (GESICA) study[40,54]—have documented recurrence rates of 14% and 19% over 2 years, with the majority of strokes occurring in the 1st year. Analysis of the WASID data has identified female sex, National Institutes of Health Stroke Scale score > 1, enrollment ≤ 17 days after ischemic event, and ≥ 70% stenosis ($p = 0.004$) as independent risk factors for recurrent stroke.[40] In the WASID study, 73% of patients with recurrent strokes had ischemic lesions in the territory of the symptomatic stenotic artery.[20] Importantly, 91% of the recurrent strokes

Abbreviations used in this paper: ACA = anterior cerebral artery; EC-IC = extracranial-intracranial; ECA = external carotid artery; ICA = internal carotid artery; NIH = National Institutes of Health; NINDS = National Institute of Neurological Disorders and Stroke; OEF = oxygen extraction fraction; PICA = posterior inferior cerebellar artery; SAMMPRIS = Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; sICAD = symptomatic intracranial arterial disease; SONIA = Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis; SSYLVIA = Stenting of Symptomatic atherosclerotic Lesions in the Vertebral or Intracranial Arteries; STA-MCA = superficial temporal artery–middle cerebral artery; TCD = transcranial Doppler; TIA = transient ischemic attack; WASID = Warfarin-Aspirin in Symptomatic Intracranial Disease.

were nonlacunar and 44% were disabling. Also, nearly half of the strokes in the remaining 27% of patients were due to a previously asymptomatic intracranial arterial stenosis.

Optimal Diagnostic Imaging

Digital subtraction angiography is the gold standard for diagnosing intracranial stenosis. Other commonly used modalities include TCD ultrasonography, MR angiography, and CT angiography. A rigorous comparison of the diagnostic accuracy of TCD ultrasonography and MR angiography with DS angiography was provided by the SONIA trial, a prospective, multicenter study designed in collaboration with WASID.[21] In this study, both TCD ultrasonography and MR angiography were found to have high negative predictive values (86% and 91%, respectively), but low positive predictive values (36% and 59%, respectively). The study concluded that both modalities could reliably exclude intracranial stenosis, but if found, would need confirmation with DS angiography. The sensitivity and specificity of CT angiography studies of intracranial stenosis vary from 78% to 100% and 82% to 100%, respectively.[7,34,57,67] The negative predictive value of CT angiography varies from 84% in the SONIA trial to 99.8% in recent retrospective studies.[7,21] These data suggest that, in centers with experienced neuroradiologists, CT angiography could be an accurate and useful diagnostic tool for sICAD.

Medical Management

Anticoagulation Versus Antiplatelet Therapy

Initially, the use of warfarin to prevent recurrent ischemic events in patients with sICAD was a common clinical practice.[22] This treatment paradigm was supported by several retrospective studies, which demonstrated that anticoagulation may be more effective than antiplatelet therapy for prevention of recurrent stroke.[12,73,79] However, this practice was challenged by the results of WASID, a large, prospective, double-blind, multicenter randomized control trial.[13] In this trial, patients with TIAs or nondisabling stroke in whom angiographically demonstrated stenosis of 50%–99% was found in any major intracranial artery were randomized to receive aspirin or warfarin and followed for a mean of 1.8 years. Among 569 patients enrolled in this study, there was no difference (22.1% in the aspirin group vs 21.8% in the warfarin group) in the composite primary end point (ischemic stroke, brain hemorrhage, or death from any vascular causes other than stroke). Importantly, patients treated with warfarin had a higher incidence of adverse events (death and major hemorrhage), necessitating premature termination of patient enrollment. Another multicenter randomized trial examined the efficacy of nadroparin calcium, a low-molecular-weight heparin, in Asian patients with ischemic stroke within 48 hours of symptom onset.[82] Of 603 patients recruited, 353 had moderate or severe stenosis of large arteries (300 with intracranial stenosis only, 11 with extracranial stenosis only, and 42 with both intra- and extracranial stenosis) confirmed by carotid duplex scan, TCD, or MR angiography. These 353 patients were randomized to receive either 3800 U nadroparin calcium subcutaneously twice daily or 160 mg aspirin daily for 10 days, followed by 80–300 mg aspirin daily (in all enrolled patients) for 6 months. The primary end point, good outcome at 6 months (defined as Barthel Index ≥ 85), did not differ between the 2 groups.

Choice of Antiplatelet Drug

Although the American Heart Association/American Stroke Association guidelines recommend single antiplatelet therapy for all patients with acute ischemic stroke,[2] there have been no studies comparing a single antiplatelet agent to placebo for secondary stroke prevention in patients with sICAD. However, in a multicenter, double-blind, placebo-controlled trial (Trial of cilostazol in Symptomatic intracranial arterial Stenosis [TOSS]), investigators evaluated dual antiplatelet therapy with aspirin and cilostazol, a phosphodiesterase-3 inhibitor, in 135 patients with sICAD.[44] The primary outcome measure was progression of M_1 or basilar artery stenosis as measured by MR angiography. The cilostazol/aspirin treatment group showed both less progression (6.7% vs 28.8%) and greater regression (24.4% vs 15.4%) of stenosis. However, major limitations of this study include a high dropout rate, small sample size, short follow-up, and large proportion of mild stenosis. A follow-up trial, TOSS-II, initiated to compare the effect of cilostazol versus clopidogrel monotherapy, has recently been completed.

Risk Factor Modification

During the WASID trial, multiple risk factors for stroke were monitored at baseline and throughout the 2-year follow-up period.[10] Although significant lowering of total cholesterol, low-density lipoprotein, and glycated hemoglobin was seen over the study period, blood pressure did not change. On multivariate analysis, a mean systolic blood pressure ≥ 140 mm Hg ($p = 0.0009$), no alcohol consumption ($p = 0.002$), and cholesterol ≥ 200 mg/dl ($p = 0.048$) were associated with an increased risk of stroke, myocardial infarction, or death from vascular causes other than stroke. These same factors were also significantly associated with ischemic stroke alone. A closer look at the relationship of blood pressure and recurrent stroke risk demonstrated a continuous increase in risk with increasing systolic and diastolic blood pressure.[76] The significance for systolic blood pressure was largely driven by the highest blood pressure group (systolic ≥ 160 mm Hg). A common clinical practice regarding blood pressure management following sICAD is to withhold antihypertensive therapy, allowing for permissive hypertension and prevention of hemodynamic ischemic events in the territory of the stenotic artery. The aforementioned relationship between higher blood pressure and increased recurrent stroke risk suggests that this practice is not beneficial and may instead be harmful.

Endovascular Treatment

With rapid advances in endovascular technology,

along with the documented high recurrence rate in prospective studies such as WASID, the use of endovascular therapy for patients with sICAD has become increasingly common (Fig. 1). Options include angioplasty alone, balloon-expandable stents, and angioplasty followed by placement of self-expanding stents. However, all published studies examining the safety and utility of these endovascular treatments for patients with sICAD represent case series, often with limited data about long-term outcome and restenosis rates. No randomized trials comparing these treatments against medical therapy have thus far been reported, although one such study is currently underway.[18] In this section, we will review this literature and highlight specific study limitations. A summary of pertinent literature has been provided in Table 1.

Primary Angioplasty

Balloon angioplasty for intracranial stenoses was first reported in 1980.[69] In current practice, the technical success rate (defined as reduction of stenosis to < 50%) of angioplasty is more than 80%, and restenosis rates range from 0% to 30%.[45,52] Retrospective single-center studies have reported a 30-day rate of stroke or death varying between 0% and 50%.[4,14,15,28,32,33,45,52,53,55,56,72] However, procedures that were performed in an elective manner were associated with lower complication rates (4%–6%),[15,53,56] suggesting that this wide variation in complication rates could be due to a difference in the timing of treatment after the ischemic event. Only limited long-term clinical outcome data are available. The largest study, a retrospective multicenter review of 120 patients, has reported an annual stroke rate of 4.4% (3.2% in the territory of stenosis).[53] However, the actual stroke rate is still uncertain, given the retrospective nature of this study and the lack of adjudication of events by neurologists.

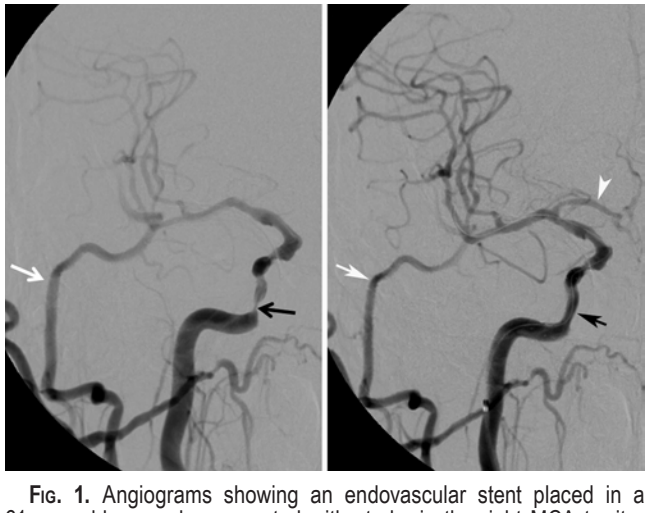

Fig. 1. Angiograms showing an endovascular stent placed in a 61-year-old man who presented with stroke in the right MCA territory. **Left:** Severe stenosis of the vertical petrous segment of the ICA was identified *(black arrow)*. Flow limitation with filling of ECA branches *(white arrow)* simultaneously with intracranial branches was present. Note the absence of filling of the ACA. **Right:** After angioplasty and placement of a self-expanding stent (Wingspan, Boston Scientific), near-complete restoration of normal luminal diameter was achieved *(black arrow)*. The guidewire is visible crossing the stenosis and terminating in an M_2 branch. Improved flow is evidenced by the presence of the A_1 segment of the ACA *(white arrowhead)* and filling of the intracranial branches ahead of the ECA *(white arrow)*.

Angioplasty and Stent Placement

A recent meta-analysis showed that the 1-year stroke and death rates were significantly lower with angioplasty and stent placement (14%) than with angioplasty alone (20%).[65] Technical success rates were also higher in the angioplasty and stent placement group (95%) than in the group with angioplasty alone (80%). However, angiographic restenosis rates were similar between the techniques (11.1% and 14%, respectively). Early reports on intracranial stent placement were single-center series that demonstrated high technical success and low complication rates.[17,24,25,36,37,41,46,48,51,60,90] The larger, more recent studies additionally suggest that the rate of stroke after stent insertion in patients with 70%–99% stenosis may be substantially lower than the rate of stroke in patients in the WASID study who had 70%–99% stenosis. Data exist for 2 categories of stents: balloon-expandable and self-expanding stents.

Balloon-Expandable Stents. The initial studies of intracranial angioplasty and stent placement with balloon-mounted stents were retrospective case series in which high technical success rates (90%–98%) were reported.[17,36,37,48,51,90] Thereafter, an industry-sponsored multicenter Phase I trial of a balloon-expandable bare-metal stent (Neurolink, Guidant Corp.) for intracranial stenosis provided the first prospective data. This trial, SSYLVIA, was a nonrandomized, multicenter study that evaluated the safety and performance of primary stent placement in 61 patients with the following forms of stenosis: ≥ 50% intracranial arterial stenosis (43 patients), vertebral pre-PICA stenosis (12 patients), or vertebral ostium stenosis (6 patients).[68] Delivery of the stent was successful in 58 (95%) of 61 patients. Four (7.2%) of 55 patients with intracranial or pre-PICA stenosis (defined as intracranial in WASID) had a stroke at 30 days; there were no deaths. The frequency of stroke within 1 year (including the 30-day rate) was 6 (10.9%) of 55. All strokes were in the territory of the treated artery. The incidence of angiographically documented recurrent stenosis (≥ 50%) was 35% at 6 months. Factors that were significantly associated with restenosis included diabetes, postprocedure diameter of stenosis > 30%, and small vessel diameter. This device (the Neurolink stent) was not marketed.

A later study by Jiang et al.[38] reported a 7.2% rate of stroke or symptomatic brain hemorrhage at 1 year after stent placement in patients with ≥ 70% intracranial stenosis. However, the stent used in this study is not available in the US. Studies have also reported the use of coronary drug-eluting stents in the cerebral circulation, with the aim of reducing in-stent stenosis.[1,31] However, because of their stiffness, the currently available coronary stents are difficult to deliver consistently in the tortuous cerebral circulation. More recently, single-center studies have reported the initial experience with 2 new balloon-mounted stents specifically designed for intracranial use. One study evaluated the use of the Apollo stent (MicroPort Medical) in 46 patients and demonstrated a technical

TABLE 1: Literature review and summary of various management strategies for patients with sICAD*

Study No.	Authors & Year(s)	Type of Study	No. of Cases	Treatment Method	Technical Success Rate (%)†	Stroke Incidence (%)		Restenosis Rate	Comments
						At 30 Days	At 1 Yr		
1	Kasner et al. (WASID), 2006	prospective, multicenter RCT	569	aspirin or warfarin	NA	NA	NA	NA	probability of stroke at 1 yr: 11%
2	multiple[4,14,15,28,32,33,45,52,55,56,72]; 1993–2003	retrospective, single center	10–70	primary angioplasty	75–100	0–50	0–14	0–30	early stroke rate for elective procedures: 4%–6%
3	Marks et al., 2006	retrospective, multicenter	120	primary angioplasty	60	6	NR	NR	16 had angioplasty & stent insertion; annual stroke rate 4.3%
4	Siddiq et al., 2008	retrospective, multicenter	95	primary angioplasty	85	8.4	12	39	
5	multiple[17,36,37,48,51,90]; 2003–2005	retrospective, single center	18–106	balloon-expandable stents	90–98	2–10	2–10	0–13	
6	Siddiq et al., 2008	retrospective, multicenter	98	balloon-expandable stents	96	9.2	13	34	
7	SSYLVIA study, 2004	prospective, multicenter	61	balloon-expandable stents (Neurolink)	95	7	11	35	
8	Jiang et al., 2007	prospective, single center	46	balloon-expandable stents (Apollo)	91	7	11	28	
9	Kurre et al., 2008	prospective, single center	14 (21)‡	balloon-expandable stents (Pharos)	86	14	NR	NR	
11	Bose et al., 2007	prospective, single center	45	self-expanding stents (Wingspan)	98	5	9	8	
12	Fiorella et al., 2007; Albuquerque et al., 2008	prospective, multicenter	78	self-expanding stents (Wingspan)	99	6	NR	32§	
13	Zaidat et al., 2008	prospective, multicenter	129	self-expanding stents (Wingspan)	97	10	NR	25	
14	multiple[74,80]; 1984 & 2009	retrospective, single center	11–105	direct bypass	97–100	0–3	NR	NA	only sICAD
15	multiple[27,70,75,87]; 1976–2003	retrospective, single center	65–403	direct bypass	87–99	0–6	NR	NA	intracranial arterial disease w/ multiple origins
16	EC–IC Bypass Trial, 1985	prospective, multicenter RCT	1377	direct bypass	96	4.5	20	NA	approx 30% of patients w/ sICAD
17	Komotar et al., 2009	retrospective, single center	12	indirect bypass	NR	27	42	NA	17% had increased perfusion to ischemic area on SPECT scans

* Approx = approximately; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

† Technical success was defined as residual stenosis < 50% after angioplasty or stent placement, or patent bypass.

‡ The technical success rate and stroke incidence are reported for the 14 patients who underwent elective intracranial stent placement. Clinical outcome in the remaining 7 patients with acute ischemic stroke who underwent urgent intracranial stent insertion was variable, depending on the severity of the ischemic event.

§ The restenosis rate was obtained from the follow-up study by Albuquerque et al., and the remaining data were obtained from Fiorella et al. Both papers are from the same study.

success rate of 91.7%. However, delivery of the stent was limited in some cases by vessel tortuosity, and there was a relatively high rate of restenosis (28%).[39] The other study used the Pharos intracranial stent (Micrus) in 21 patients. Seven of these patients received urgent intervention after acute stroke for hemodynamic instability and progressive worsening of stroke or after thrombolysis. The remaining 14 patients underwent elective treatment after a TIA or minor stroke. In these 14 patients, a technical success rate of 85.7% and a procedure-related complication rate of 28.5% was observed.[43]

Self-Expanding Stents. The Wingspan stent (Boston Scientific)—a bare-metal, self-expanding stent designed specifically to treat intracranial stenosis—was approved by the FDA in 2005 for use under a humanitarian device exemption in patients with intracranial stenosis "who are refractory to medical therapy." This approval was based on a European/Asian study of 45 patients with symptomatic 50%–99% stenosis who had recurrent stroke on antithrombotic therapy. The main results of the study were that the stent was successfully delivered in 44 (98%) of 45 patients, the 30-day rate of stroke or death was 4.4%, and the 12-month rate of ipsilateral stroke or death was 9.3%. Only 3 (7.5%) of 40 patients had restenosis at 6 months, and none were symptomatic.[8] Of the 45 patients, 29 had 70%–99% stenosis. Of these 29 patients, 3 (10.3%) had a stroke in the territory or died within 1 year.

Thereafter, 2 multicenter registries provided additional data on the Wingspan stent. The first report included 78 patients with 82 symptomatic intracranial stenoses (50%–99%) from 5 centers. A technical success rate of 98.8% and a periprocedural rate of 6.1% for major neurological complications were observed.[23] The second report was the NIH Wingspan registry of 129 patients with 70%–99% symptomatic intracranial stenosis at 16 centers.[89] The technical success rate was 96.7% and the frequency of any stroke, intracerebral hemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14% at 6 months. These data compare favorably with the outcome in the WASID study and form the basis of the ongoing randomized trial evaluating angioplasty and stent treatment (using the Wingspan system) versus best medical management (SAMMPRIS trial). Follow-up data from the Wingspan registries demonstrate a restenosis (≥ 50% on follow-up angiogram) rate of 25%–32%.[5,89] However, the restenosis is usually asymptomatic.[47,89] An interesting phenomenon is that the incidence of restenosis appears to be higher in younger patients, especially those with supraclinoid carotid artery stenosis,[77] and this raises a question about the underlying occlusive vasculopathy in this population. The location of stenosis and demographic characteristics are similar to those in patients with North American moyamoya phenomenon,[26] thereby suggesting that these patients may have a similar underlying occlusive vasculopathy but lack the proliferative signals that result in moyamoya collateral formation.

Extracranial-Intracranial Bypass

Based on several retrospective case series which demonstrated high bypass patency rates and low incidence of perioperative complications in patients with ischemic cerebrovascular disease,[27,70,80,87] the STA-MCA bypass became a commonly used therapeutic approach in the 1970s and 1980s for patients with sICAD that was refractory to medical treatment. However, after the discouraging results of the International Cooperative Extracranial-Intracranial Bypass Trial were published in 1985,[19] the STA-MCA bypass, and less common techniques for establishing a direct EC-IC bypass (for example, radial artery or saphenous vein high-flow bypass), became infrequently used for sICAD. Some groups have suggested that assessment of cerebral hemodynamics with sophisticated imaging techniques may identify a subgroup of patients with sICAD who have hemodynamic impairment that would benefit from surgical revascularization.[16,63,88] Others have begun to explore potentially less morbidity-causing indirect revascularization techniques to treat patients with sICAD.[42] In this section, we will review the published literature on both direct and indirect revascularization for sICAD.

Direct Bypass

Several single-institution case series examining the technical success and perioperative safety of direct EC-IC bypass for ischemic cerebrovascular disease have been published. The majority evaluated patients with a variety of cerebrovascular conditions including sICAD (but also ECA occlusion, moyamoya disease, and/or carotid artery dissection), whereas a minority specifically examined patients with sICAD. In series that reported on EC-IC bypass for ischemic cerebrovascular disease including sICAD, the overall bypass patency, perioperative morbidity, and perioperative mortality rates vary from 87% to 99%, 0% to 6%, and 0% to 8%, respectively.[27,70,75,87] Very few studies have exclusively examined the safety and efficacy of direct bypass in patients with sICAD. Weinstein et al.[80] reported a series of 105 patients who underwent STA-MCA bypass procedures for sICAD, documenting 97% bypass patency, 2.8% perioperative morbidity (from stroke), and 1% perioperative mortality. The long-term outcome after surgery (annual stroke rate of 1.5%) appeared to be better than the natural history of medically treated patients with sICAD. More recently, Tsai et al.[74] reported a series of 11 patients who underwent STA-MCA bypass for sICAD (all MCA stenosis or occlusion). These authors documented 100% bypass patency, 0% perioperative morbidity, and 0% perioperative mortality. The late stroke rate in long-term follow-up was not reported. Importantly, all the aforementioned studies were retrospective, and none included adjudication of cerebrovascular events by neurologists.

The landmark International Cooperative Extracranial-Intracranial Bypass Trial[19] remains the largest prospective third-party adjudicated study examining the safety and efficacy of STA-MCA bypass for patients with ischemic cerebrovascular disease including sICAD. Patients enrolled in this study included those with a history of recent TIAs or minor ischemic strokes and angiographic evidence of one of the following: 1) stenosis or occlusion of the MCA or its branches; 2) stenosis of the ICA at or above the C-2 vertebral body (that is, at a place inaccessi-

ble to carotid endarterectomy); or 3) ICA occlusion. Overall, approximately one-third of the patients included in this study had sICAD. Patients were randomized to STA-MCA bypass or nonsurgical management. All patients received 325 mg aspirin perorally 4 times per day throughout the trial unless contraindicated or not tolerated. The primary study end points were postrandomization fatal or nonfatal stroke. The STA-MCA bypass patency was found to be 96%. The incidence of perioperative cerebral or retinal ischemic events and major strokes was 12.2% and 4.5%, respectively, and the perioperative mortality rate was 1.1%. Importantly, the incidence of fatal and nonfatal strokes was higher in patients randomized to STA-MCA bypass versus those randomized to medical therapy alone. This trend was also noted in patients with sICAD, particularly in those with intracranial stenosis rather than occlusion. Specifically, the incidence of fatal and nonfatal stroke for patients with severe ICA or MCA stenosis was 40.2% in the surgical group versus 30.5% in the medical group. This finding has been attributed to postbypass stasis at the stenotic arterial segment (probably the result of competing antegrade flow from the native artery vs retrograde flow from the arterial bypass) that would promote thromboembolic complications. These overwhelmingly negative results significantly reduced the use of the STA-MCA bypass for patients with sICAD in whom medical therapy had "failed."

One of the main reasons for failure of the International Cooperative Extracranial-Intracranial Bypass Trial was thought to be the absence of cerebral hemodynamic assessment to help identify patients with reduced cerebral perfusion pressure in whom STA-MCA bypass may be more beneficial.[16,63,88] Subsequently, several quantitative methods have been developed to examine cerebral hemodynamic impairment in patients with ischemic cerebrovascular disease (for a review, see Grubb et al.[30]). Two prospective observational studies in which PET was used for assessment of hemodynamic impairment have shown that patients with recently symptomatic ischemic cerebrovascular disease and increased OEF have a markedly elevated risk of subsequent ipsilateral ischemic stroke (compared with those with normal OEF).[29,86] However, only 10 of the 121 patients included in these 2 studies had sICAD (the rest had ICA occlusion). Therefore, it is difficult to draw conclusions regarding the utility of hemodynamic assessment in this patient population. Given the paucity of cerebral hemodynamic data for patients with sICAD, along with the aforementioned increased risk associated with STA-MCA bypass for patients with severe ICA or MCA stenosis,[19] and the recently announced premature stopping of the Carotid Occlusion Surgery Study (a randomized controlled trial comparing STA-MCA bypass with best medical therapy for patients with recently symptomatic ICA occlusion and increased OEF[30]), it is unlikely that direct EC-IC bypass will be proven effective for patients with sICAD—even for those who have "failed" medical therapy and who have documented impaired cerebral hemodynamics.

Indirect Bypass

Recently, Komotar et al.[42] examined the role of indirect surgical bypass as a method of promoting angiogenesis and enhancing cerebral blood flow in patients with sICAD. In their series, 12 patients with sICAD and impaired cerebral hemodynamics were treated with indirect bypass: 11 underwent encephaloduroarteriosynangiosis, and 1 received bur holes with dural and arachnoid incisions. Perioperative morbidity was 27%; there were no perioperative deaths. Also, follow-up data showed that only 2 patients had increased perfusion in previously hypoperfused areas, and 5 patients suffered repeat ischemic infarction. In comparison with a meta-analysis of 4 studies of patients with symptomatic ICA occlusion and severe hemodynamic failure who were treated medically, it was observed that indirect surgical revascularization provided no protection against subsequent ischemic stroke. Based on this small retrospective case series, indirect surgical revascularization for patients with sICAD does not appear to be indicated and lacks therapeutic potential.

Conclusions

Current evidence suggests that aspirin is the preferred antithrombotic option to prevent recurrent ischemic events in patients with sICAD. Treatment of modifiable risk factors is also recommended. Consideration for angioplasty and stent placement in select patients with sICAD is also reasonable; however, at present there are no randomized trials proving its efficacy. One such trial—the SAMMPRIS[18] trial—is currently underway. If results from this trial are positive, a new era of widespread use of endovascular therapy for patients with sICAD may ultimately emerge. Regarding surgical revascularization, available literature that includes only 1 large randomized multicenter trial does not support the use of direct bypass for patients with sICAD. In particular, direct bypass for patients with symptomatic severe ICA or MCA stenosis appears not only ineffective but also seems to be harmful.

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Applications of stenting for intracranial atherosclerosis

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Intracranial atherosclerosis presents a therapeutic challenge to medical and surgical physicians alike. Despite maximal medical therapy, the stroke rate from this disease is still high, especially when arterial stenosis is severe and patients are symptomatic. Open surgical therapy has yet to be shown to be a more efficacious treatment than medical therapy alone, largely due to the relatively high rates of perioperative complications. Angioplasty has a similar fate, with the risk of periprocedural complications outweighing the overall benefit of treatment. With the advent of stents for use in intracranial vasculature, new hope has arisen for the treatment of intracranial atherosclerosis. The NEUROLINK system, the drug-eluting stents Taxus and Cypher, the flexible Wingspan stent, the Apollo stent, and the Pharos stent have all been used in various prospective and retrospective clinical studies with varying technical and clinical results. The authors' objective is to review and loosely compare the data presented for each of these stenting systems. While the Wingspan stent appears to have somewhat of an advantage with regard to technical success in comparison with the other stenting systems, the clinical follow-up time of its studies is too short to properly compare its complication rates with those of other stents. Before we continue to move forward with stenting for intracranial stenosis, a randomized prospective trial is ultimately needed to directly compare intracranial stenting to medical therapy.
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Key Words • **intracranial arteriosclerosis** • **stent** • **stroke**

Stroke is one of the leading causes of morbidity and mortality in the US population,[3] and along with TIAs, afflicts approximately 900,000 people annually.[18] Intracranial atherosclerosis comprises 70,000–90,000 of these cases.[26] While medical therapy with aspirin has been shown to be safe and effective in treating symptomatic intracranial arterial stenosis in more than 50% of cases,[4] the rate of recurrent ischemic stroke ipsilateral to the stenotic artery is still approximately 12% at 1-year follow-up. Unfortunately, surgery has, to date, not shown much promise in treating this disease.[7] Similarly, angioplasty provides only a temporary solution to a permanent problem and is associated with its own pitfalls, such as acute and chronic restenosis of the treated vessel and arterial dissection.[5,23] The advent of flexible stents that could be deployed in intracranial vessels has greatly expanded the endovascular repertoire.[10,29] Properly placed stents not only favorably alter intravascular dynamics, but also they have the potential to reverse blood vessel stenosis, thereby increasing tissue perfusion, remodel deformed vasculature, and prevent recurrence of cerebrovascular pathology. We will review the numerous attempts to demonstrate the effectiveness of different stents for the treatment of intracranial atherosclerosis.

Abbreviations used in this paper: MCA = middle cerebral artery; TIA = transient ischemic attack; WASID = Warfarin-Aspirin Symptomatic Intracranial Disease.

NEUROLINK Stent

Although the NEUROLINK System (Guidant Corp.) is no longer in use, it was initially approved by the FDA under a Humanitarian Device Exemption in 2002 and was the first of many intracranial stents studied for the treatment of intracranial atherosclerosis. A multicenter, nonrandomized prospective trial named SSYLVIA (Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries) tested the flexible, balloon-mounted NEUROLINK stent, composed of 316 L stainless steel, in 61 patients with at least 50% symptomatic stenosis of the extracranial vertebral arteries or intracranial arteries.[27] Of the 61 treated arteries, 18 (30%) were extracranial vertebral and 43 (70%) were intracranial. Technically successful stent deployment occurred in 58 patients (95%), and procedural success, defined by study parameters as less than 50% poststent stenosis, occurred in 54 patients (89%). At 30 days, no deaths and 4 strokes (7%) were observed. One of the strokes was a subarachnoid hemorrhage that did not result in any neurological deficits, while the other 3 were major ipsilateral strokes. All 3 of the ischemic strokes were of the posterior circulation.

At 6-month angiographic follow-up, significant restenosis greater than 50% was detected in 18 patients (30%). Of the 37 stented intracranial arteries, 12 (32%) exhibited significant restenosis, and of the 14 stented extracranial

vertebral arteries, 6 (43%) exhibited significant restenosis. Symptomatic restenosis, stroke, or TIA was present in 7 (39%) of the 18 patients with significant restenosis at follow-up. Fifty-five patients returned for 1-year clinical follow-up, during which time an additional 4 patients (7%), not including the 4 patients who had strokes within the first 30 days, experienced strokes in the distribution of the treated stenotic vessel resulting in 1 death. Two of the 4 delayed strokes were of the anterior circulation, and the other 2 were of the posterior circulation. Cumulatively, 6 (75%) of 8 strokes documented within 1 year were of the posterior circulation, which correlates with the higher stroke rate seen in vertebrobasilar stenosis when compared with intracranial stenosis of the anterior circulation.[25] Despite these initial results, further studies with the NEUROLINK stent were not conducted, perhaps due to advances in stent technology that were developed shortly after these data were published.

Drug-Eluting Stents

The introduction of drug-eluting stents greatly decreased the restenosis rate of coronary artery stents in the treatment of coronary artery disease.[13,28] In an attempt to duplicate those reductions in restenosis in the treatment of intracranial atherosclerosis, Abou-Chebl et al.[1] treated a small series of patients by placing balloon-mounted, drug-eluting stents in the intracranial arteries. This was the first published series describing the use of drug-eluting stents in humans after an initial study of sirolimus-coated Cypher stent (Cordis Corp.) deployment in canine basilar arteries showed promising results.[21] The group prospectively selected 8 patients with symptomatic intracranial stenosis that was greater than 70% and refractory to medical management. The authors used coronary drug-eluting stents to treat the patients' diseased vessels. Half of the patients received the Cypher stent and the other half received the paclitaxel-coated Taxus stent (Boston Scientific). There were 2 periprocedural complications (25%), one (12.5%) of which was symptomatic but unrelated to the stent, being a retinal embolism during guide catheter removal. The mean preprocedural stenosis of 84.4% was reduced to a mean postprocedural stenosis of 2.5%. At a mean clinical follow-up of 11 months, there were no recurrent ischemic events. Of the 5 patients with a mean angiographic follow-up of 10 months, none had significant (> 50%) restenosis. Notably, only 1 patient showed any degree of restenosis with 29% stenosis on imaging at 12.6-month follow-up. While the number of patients was too few to make any generalized statements, this study showed the viability and safety of drug-eluting stents in a carefully selected patient set.

A second study with similar patient selection criteria (that is, their conditions were symptomatic and refractory to medical treatment with at least 50% stenosis of the affected intracranial artery), also examined the technical feasibility and restenosis rates of the same 2 drug-eluting stents, Cypher and Taxus, for the treatment of intracranial atherosclerosis.[24] Of the 21 patients in whom stent placement was attempted, technical success was achieved in 18 (86%) with a reduction in mean stenosis from 68% preprocedure to 14% postprocedure. One patient (6%) had a stroke in the 1st month after stent placement. At a mean clinical follow-up of 14 months, a total of 3 patients (17%) suffered a stroke (2 patients) or died (1 patient), including the patient who had a stroke within the first 30 days. Angiographic follow-up at a mean time of 6 months was obtained in 7 patients and showed that 1 patient (14%) was asymptomatic despite having significant restenosis greater than 50%. Delayed stent thrombosis with drug-eluting stents is a known risk in the cardiac literature[15] and was reported in a case in which late thrombosis developed 16 months after intracranial stenosis treatment with a Taxus stent.[14] Ultimately, due to the lack of flexibility of drug-eluting stents, given the tortuous nature of intracranial vasculature and the lack of long-term prospective data on large patient set, the use of drug-eluting stents for the treatment of intracranial stenosis has been largely abandoned.

Wingspan Stent

In 2005, the FDA approved the use of a self-expanding stent made of a nickel and titanium alloy, nitinol, known as the Wingspan stent (Boston Scientific) for patients with at least 50% intracranial stenosis despite antithrombotic medical therapy. Figure 1 shows an illustration of the Wingspan stent along with the Gateway Percutaneneous Transluminal Angioplasty balloon catheter, which is used to predilate the atherosclerotic segment of the artery prior to stent deployment. Initial periprocedural results using the Wingspan stent were reported by Fiorella et al.[8] in a multicenter, prospective study involving 78 patients with 82 intracranial vessels with at least 50% stenosis. Of the 78 treated patients, 76 were symptomatic with 48 strokes and 28 TIAs, and 54 had at least 70% intracranial stenosis; medical therapy failed in 59. Technical success was achieved in 81 (98.8%) of the 82 stenotic vessels. In the remaining case in which the treatment failed, the patient returned at a later date for successful treatment with the Wingspan stent. The average 75% preprocedural stenosis was reduced to an average 27% postprocedural stenosis. Diffusion-weighted MR images obtained in 38 patients

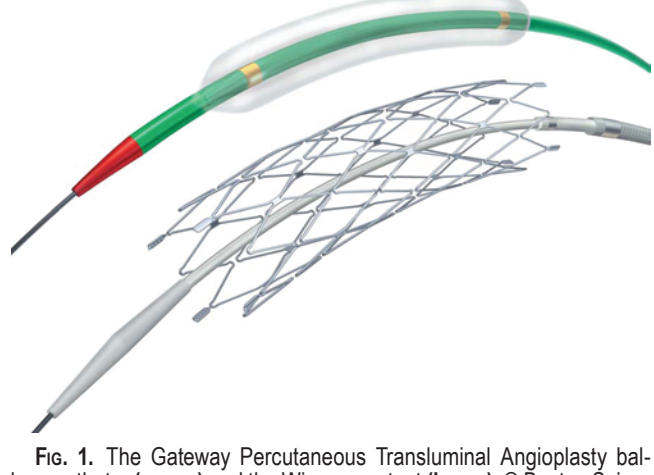

Fig. 1. The Gateway Percutaneous Transluminal Angioplasty balloon catheter **(upper)** and the Wingspan stent **(lower)**. © Boston Scientific. Reprinted with permission.

within 72 hours posttreatment showed 13 new ischemic lesions (34%), 3 (8%) of which were symptomatic. Including those 3 symptomatic patients who had new imaging findings, a total of 5 (6%) of the 78 treated patients had periprocedural complications, including 4 deaths (5%). One of the deaths occurred during a procedure in which the basilar artery was perforated by the guidewire. The other 3 deaths occurred on postprocedural Days 5, 15, and 16. The overall results from this preliminary study showed an impressively high technical success rate accompanied by an acceptably low complication rate, indicating that the Wingspan stent was a marked improvement over its predecessors.

Shortly thereafter, a prospective, multicenter study using the Wingspan stent with intermediate follow-up selected 45 symptomatic patients whose conditions were refractory to medical therapy with at least 50% stenosis of an intracranial vessel of a caliber 2.5–4.5 mm.[2] Technical success was achieved in 44 patients (98%) with a reduction in vessel stenosis from a mean of 75% pretreatment to a mean of 32% posttreatment. Two patients (4%) had large ipsilateral strokes and died within the first 30 days. At 6-month clinical follow-up, 2 more patients had strokes, one ipsilateral and the other contralateral, for a cumulative combined stroke or death rate of 9% (4 of 45). Further physician-reported outcomes outside of the study protocol at an average of 13 months posttreatment showed another patient with an ipsilateral stroke. At 6-month angiographic follow-up in 40 patients, the mean stenosis of 28% was not significantly different from the degree of stenosis immediately after stent deployment. However, 3 patients (7.5%) had significant restenosis of at least 50% at follow-up, all of whom were asymptomatic. Additional procedural adverse events included vasospasm in 5 patients and MCA branch occlusion in 1 patient without any permanent clinical sequelae. Four access site complications, including 3 hematomas and 1 infection, required further treatment, but all ultimately resolved. This study was limited by the number of enrolled patients and its relatively short follow-up time, but it made a strong case for the potential benefits of Wingspan stent treatment of symptomatic intracranial atherosclerosis in which medical therapy failed. A later study by Levy et al.[22] in a similar group of patients reported a higher rate of in-stent restenosis of approximately 30% compared with 7.5% and a higher rate of symptomatic restenosis of 7% compared with none. While symptomatic restenosis unarguably warrants treatment, the lack of long-term outcome data on asymptomatic restenosis makes it a much murkier clinical scenario.

The WASID study showed that decreased time from qualifying clinical event to study enrollment and a high degree of stenosis were powerful predictors of stroke in the territory of the stenotic artery.[4] The 1-year territorial stroke rate was higher in patients who had their qualifying events less than 30 days from study enrollment (23%) than in patients who had their events more than 30 days from study enrollment (10%). Not surprisingly, patients with severe arterial stenosis (≥ 70%) had a higher 1-year territorial stroke rate (18%) than patients without severe arterial stenosis (7%). Zaidat et al.[30] enrolled 129 patients with severe intracranial stenosis (≥ 70%) for endovascular treatment with the Wingspan stent and followed their outcomes for 6 months. This study had a 97% technical success rate with a significant immediate postprocedural increase in the arterial diameter, from 82% preprocedural to 20% postprocedural mean arterial stenosis. Angiographic follow-up was obtained in 52 patients (40%) and showed restenosis of at least 50% in 13 patients (25%). Of those patients with significant restenosis, only 2 (15%) were symptomatic. Eight patients in the study (6%) had periprocedural (< 24 hours) events, defined as any stroke or death. The 2 patients who died both suffered from pontine strokes, one ischemic and the other hemorrhagic. At 30 days, a total of 12 patients (9%) had events, including 4 deaths, and at 6 months, the cumulative event rate was 14%. While the results from this study were not as impressive as its predecessor's, the discrepancy was likely due to the greater degree of neurovascular compromise in this study's patients. Like its predecessors, this study was limited by its lack of long-term follow-up but again demonstrated the Wingspan stent to be effective at its job description.

A recently published single-center, retrospective study by Guo et al.[12] looked at the application of the Wingspan stent specifically for MCA stenosis which, due to the structure and location of the MCA, is often a technically demanding disease to treat. Building on previous smaller studies of other stenting systems for MCA stenosis that showed high technical success rates and reasonably low complication rates,[16,20] the authors hypothesized that the more flexible Wingspan stent would be able to face the challenges presented during stenting of the proximal MCA and ultimately improve clinical outcomes. The study enrolled 53 patients with at least 50% stenosis of the M_1 segment of the MCA who were symptomatic despite standard medical therapy. The procedure was technically successful in 52 (98%) of 53 patients, reducing the mean pretreatment stenosis of 77% to a mean 18.2% posttreatment stenosis. Including the 1 technical failure, 4 patients (7.5%) experienced complications, 2 (4%) of which resulted in permanent neurological deficits. Among the 32 patients with angiographic follow-up at 6 months, none had significant restenosis greater than 50%. All 52 patients who underwent successful stenting were clinically evaluated at 6 months and received transcranial Doppler ultrasonography measurements of MCA flow velocities. The relatively short follow-up limits our ability to assess possible delayed in-stent stenosis or other long-term complications, but nonetheless this study certainly supports for the technical capabilities of its interventionalists and the versatility of the Wingspan stent.

Apollo Stent

The Apollo stent (MicroPort Medical) is a balloon-mounted, flexible 316 L stainless-steel stent device that was tested by Jiang et al.[17] in a single-center prospective trial. The study enrolled 46 patients with 48 intracranial arterial stenoses greater than 50% on angiography. The stenoses were symptomatic, defined as TIAs or minor strokes within 90 days of stent placement. Technical success was achieved in 42 patients (91%) with all 4 failures attributed to tortuosity of the target stenotic vessel. At 30 days, 4 (9%)

of the 46 patients experienced strokes, 3 (7%) of which were symptomatic due to perforating artery compromise on postprocedure Day 1. All patients were available for a median follow-up of 24 months. After 30 days, 1 patient had a stroke in the distribution of the stented artery, and 2 patients had ischemic strokes in an untreated arterial distribution. A total of 6 (14%) of the 42 patients who were successfully treated had strokes within the clinical follow-up period. Of the 25 patients who underwent angiographic follow-up at a median time of 7.4 months, 7 patients (28%) had restenosis of the treated vessel, resulting in 1 symptomatic restenosis (4%). While the study was underpowered to detect a statistically significant advantage of stenting over medical therapy, it did show that the Apollo stent has the potential to be effective in the treatment of symptomatic intracranial atherosclerosis given good preprocedural selection. Not surprisingly, the likelihood of technical failure increased with increasing target vessel tortuosity, although technical success surely depended on the biomechanical limitations of the device itself along with the skill and expertise of the operators.

Pharos Stent

Derived from a coronary stent, the balloon-mounted Pharos stent (Micrus Endovascular), previously known as the Lekton Motion stent, showed some promise of future success in 2 small studies. The first, a retrospective multicenter study by Freitas et al.,[9] examined the efficacy of the Pharos stent in 32 patients with at least 50% intracranial stenosis, all of whom were symptomatic despite medical therapy except 2 asymptomatic patients. Technical success was achieved in 31 patients (97%) with 2 periprocedural complications (6%), one of which was symptomatic. Immediate postprocedural results showed complete stenosis reduction in 24 patients (75%) and partial reduction in 8 patients (25%) to less than 20% residual occlusion. At 30-day clinical follow-up, including the immediate postprocedure events, 5 patients (16%) suffered stroke or died. Of the 3 deaths (9%), 2 were attributed to medication noncompliance, leading to stent thrombosis and multisystem failure following a hypertensive episode while the cause of death of the third patient was unknown. At a mean clinical follow-up of 10 months, no additional strokes or deaths were reported. At mean angiographic follow-up of 10 months in 23 patients, 3 patients (13%) had significant restenosis greater than 50% while 1 patient (4%) had nonsignificant restenosis of less than 10%; all were asymptomatic. The average poststent stenosis at angiographic follow-up was 5%, down from an average 69% prestent stenosis. This initial study demonstrated the technical feasibility and short-term viability of the Pharos stent, although the 30-day mortality rate, which may have been a consequence of patient selection, was higher than that in other comparable studies.

A second single-center study out of Germany enrolled 21 symptomatic patients with at least 70% intracranial arterial stenosis for treatment with the Pharos stent.[19] Interestingly, 7 (33%) of these patients were treated in the setting of an acute stroke. Technical success was achieved in 19 patients (90%); both treatment failures were due to complex courses of the stenotic vessels. One of these patients was subsequently successfully treated with 2 Wingspan stents. Both technical failures occurred in the electively treated cohort. The reduction in median stenosis was from 85% pretreatment to 20% posttreatment. Within the first 30 days after stent placement, 4 (29%) of the 14 electively treated patients experienced complications, 2 (14%) of which resulted in permanent neurological sequelae. One of the patients had a major stroke despite subsequent open surgical bypass. Another patient who received a basilar artery stent had a minor stroke of a pontine perforator. For the 2 patients who did not have permanent deficits, one experienced immediate postprocedural stent thrombosis that resolved with endovascular recanalization and the other suffered a brainstem TIA with complete clinical recovery after 24 hours. One of the patients died at 3 months for a total of 3 electively treated patients (21%) who suffered a stroke or died at a mean clinical follow-up of 7 months. Of the 7 patients urgently treated for acute strokes, 2 (29%) died within the first 30 days and another 2 patients went on to develop strokes by a mean clinical follow-up of 10 months for a cumulative stroke or death rate of 57% in the urgently treated group. Despite the small number of patients in the urgently treated cohort, it is apparent from this study that stenting in the setting of acute stroke is extremely risky and warrants thorough consideration before being undertaken.

The Future of Stenting for Intracranial Atherosclerosis

Gröschel et al.[11] performed a meta-analysis of 31 studies involving 1177 procedures for high-grade (mean 78%) symptomatic (98%) intracranial arterial stenosis. The outcomes varied widely across the studies with procedural success rates ranging from 71% to 100%, periprocedural complication rates ranging from 0% to 50%, and restenosis greater than 50% ranging from 0% to 50%. The rate of periprocedural stroke or death was significantly higher ($p = 0.006$) in the treatment of posterior circulation stenosis (12.1%) than in the treatment of anterior circulation stenosis (6.6%). The rate of periprocedural complications did not differ ($p = 0.470$) between treatments with balloon-mounted (9.5%) and self-expandable (7.7%) stents. The clinical follow-up after the procedures ranged from 3 to 21 months with a median follow-up of 6 months. The total restenosis rate was 14.4%, of which 32.7% were symptomatic, that is, TIA, stroke, or death. While there was a statistically significant difference ($p < 0.001$) in any restenosis between treatment with balloon-mounted (13.8%) and self-expandable (17.4%) stents, there was no statistically significant difference ($p = 0.080$) in symptomatic restenosis between the 2 treatments (41.6% [balloon-mounted] vs 12.5% [self-expandable]). The cumulative probability of stroke or death was approximately 12%, indirectly comparable to that of medical therapy in the WASID study. Based on these data, there is not a strong argument for or against the benefit of endovascular stenting therapy over conventional medical therapy for the treatment of intracranial stenosis. However, the lack of a prospective randomized trial comparing the 2 therapies makes it difficult to draw a definitive conclusion.

Table 1 compares the technical success rates immediately after the procedure and the complication rates at clinical follow-up across difference stents. The Wingspan stent can be seen to have the highest technical success rates, likely due to its more flexible nature when compared with its counterparts. While the Wingspan stent does also appear to have lower complication rates, the mean clinical follow-up for those studies is shorter, making the comparison somewhat uneven. Another obvious confounding factor is that since the operators in each trial are different, their experience and skill levels are obviously not the same. We can safely assume that all of the interventionalists are skilled, but their experiences with the individual stents may have varied considerably, making it difficult to compare stents across different studies. However, the question that looms the largest after all of these studies is whether the complications associated with stenting are justified by the benefits. While some studies fare favorably against the results of the WASID study, others do not. Without a prospective, 2-arm study that directly compares stenting to medical therapy, we cannot answer fairly.

As device delivery and stent technology continue to improve at an explosive rate, it is difficult to make direct comparisons between the different types of stents. Balloon-mounted stents are typically much stiffer and harder to deliver through tortuous anatomy than self-expanding stents, but they only require crossing the lesion once. Self-expanding stents, while flexible and potentially easier to deliver, typically require crossing the lesion with 2 devices, the first being a balloon used for predilation followed by the stent, theoretically increasing the chance of incurring a thromboembolic event. As alloy composition, stent architecture, and device maneuverability continue to improve, technical success and complication rates between stents will likely blur into one another. In Fig. 2, we show an example of a patient with proximal MCA atherosclerosis who was successfully treated at our institution with a balloon-mounted coronary stent.

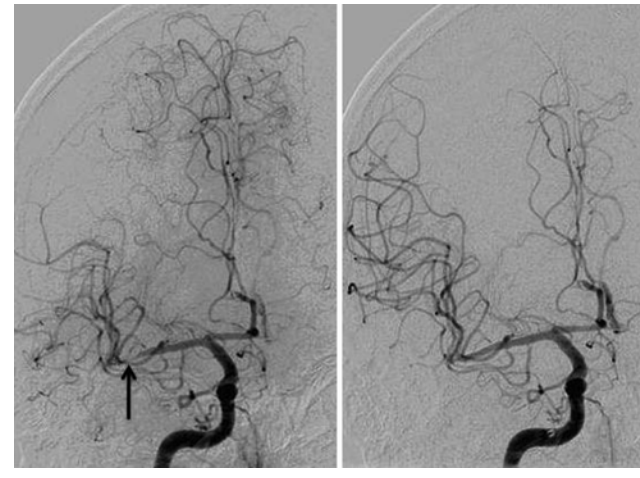

Fig. 2. Angiograms obtained in a patient at our institution with severe right M_1 segment MCA stenosis (**left**, *arrow*) that was successfully stented with a balloon-mounted coronary stent **(right)**. Note the improved flow in the MCA circulation after stent placement as evidenced by increased filling of the distal MCA branches relative to the anterior cerebral artery branches.

Given the FDA approval of the Wingspan stent under a Humanitarian Device Exemption supported by initial studies demonstrating its high technical success rate and good safety profile[2,8] and data showing that severe, symptomatic intracranial atherosclerosis portends a poor prognosis despite maximal medical therapy,[4] a well-conceived randomized trial prospectively comparing stenting with standard medical management has the potential to establish landmark clinical guidelines in stroke treatment.[6] The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial is currently recruiting with

TABLE 1: Comparison of technical success and complication rates among different stents*

Stent	Authors & Year	No. of Pts	Min Stenosis (%)	Tech Success Rate (%)	Restenosis Rate >50% (%)	Mean Clinical FU (mos)	Complication Rate (%)†				
							Tech/ Procedural	Asymp Stroke	Symptomatic Stroke	Death	Cumulative
NEUROLINK	Freitas et al., 2007‡	61	50	95	30	12	3	2	11	2	15
drug-eluting	Holmes et al., 2004	8	70	100	0	11	25	12.5	12.5	0	25
drug-eluting	Huang et al., 2009	21	50	86	14	14	0	0	11	6	17
Wingspan	Johnston, 2002	45	50	98	7.5	6	22	0	9	0	9
Wingspan	Lee et al., 2005	129	70	97	25	6	6	0	11	3	14
Wingspan	Levy et al., 2004§	53	50	98	0	6	6	4	4	0	8
Apollo	Qureshi et al., 2003	46	50	91	28	24	9	2	12	0	14
Pharos	Qureshi et al., 2006	32	50	97	13	10	6	0	6.5	9.5	16
Pharos	Sacco et al., 1995	21	70	90	5	8	0	10	19	14	43

* Asymp = asymptomatic; FU = follow-up; Min = minimum; Pts = patients; Tech = technical.

† Technical/procedural complications may overlap with asymptomatic and symptomatic stroke and death. The cumulative complication rate is the total of asymptomatic and symptomatic stroke and death rates only and does not include technical/procedural complications that did not result in stroke or death.

‡ Eighteen of 61 treated patients had extracranial atherosclerosis.

§ The patients in this study were treated only for M_1 stenosis.

¶ Seven of the 21 patients were treated in the setting of acute stroke, 4 of whom had complications.

a goal of 764 patients at 60 academic and community centers across the US (http://www.sammpris.org/). Its inclusion criteria include, but are not limited to, patients 30–80 years old with a modified Rankin Scale score not greater than 3 who experience a TIA or minor stroke fewer than 30 days prior to enrollment, attributable to at least 70% stenosis but less than 100% occlusion of a major intracranial artery (carotid, M_1, vertebral, or basilar) diagnosed by transcranial Doppler ultrasonography, MR angiography, or CT angiography, and confirmed by subsequent catheter angiography. The enrollees will be randomized into one of 2 arms, either medical therapy alone or intracranial stenting plus medical therapy, and will be followed clinically for 1–3 years. Medical therapy, as defined by the SAMMPRIS study parameters, is aspirin 325 mg daily for the entire course of enrollment, clopidogrel 75 mg daily for 90 days following enrollment, and aggressive blood pressure and cholesterol management by each study center neurologist to keep the blood pressure lower than 140/90 mm Hg and lower than 130/80 mm Hg in patients with diabetes and low-density lipoprotein cholesterol less than 70 mg/dl. We eagerly await the results of this trial and anticipate that its conclusions will be of great importance to stroke neurologists and neurointerventionalists alike.

Conclusions

The role of intracranial stenting in the treatment of intracranial stenosis, the management of its complications, and the long-term clinical and angiographic effect it affords patients has yet to be fully delineated. However, stenting has been clearly shown to be a versatile weapon in our ever-expanding arsenal of therapeutic strategies for a disease with potentially devastating consequences. While some studies have shown promising results, we are limited by the lack of prospective, randomized controlled data directly comparing intracranial stenting to standard medical therapy. Until such results are available, we can continue to be cautiously optimistic that the use of intracranial stents will reduce the acute and chronic morbidity and mortality of intracranial atherosclerosis.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors.

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Endovascular recanalization of symptomatic flow-limiting cervical carotid dissection in an isolated hemisphere

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Object. Internal carotid artery dissection (ICAD) is a common cause of stroke in young patients, which may lead to major transient or permanent disability. Internal carotid artery dissection may occur spontaneously or after trauma and may present with a rapid neurological deterioration or with hemodynamic compromise and a delayed and unstable neurological deficit. Endovascular intervention using stent angioplasty can be used as an alternative to anticoagulation and open surgical therapy in this setting to restore blood flow through the affected carotid artery.

Methods. The authors present the cases of 2 patients with flow-limiting symptomatic ICAD leading to near-complete occlusion and without sufficient collateral supply. Both patients had isolated cerebral hemispheres without significant blood flow from the anterior or posterior communicating arteries. In both cases, the patients demonstrated blood pressure–dependent subacute unstable neurological deficits as a result of the hemodynamic compromise resulting from the dissection.

Results. Both patients underwent careful microwire-based selection of the true lumen followed by confirmatory microinjection and subsequent exchange-length microwire-based recanalization using tandem telescoping endovascular stenting. In both cases the neurological state improved, and no permanent neurological deficit ensued.

Conclusions. The treatment of ICAD may be difficult in patients with subacute unstable neurological deficits related to symptomatic hypoperfusion, especially in the setting of a hemodynamically isolated hemisphere. Anticoagulation alone may be insufficient in these patients. Although there is no widely accepted guideline for the treatment of ICAD, the authors recommend stent-mediated endovascular recanalization in cases of symptomatic flow-limiting hemodynamic compromise, especially in cases of an isolated hemisphere lacking sufficient communicating artery compensatory perfusion. *(DOI: 10.3171/2011.2.FOCUS1139)*

Key Words • **carotid artery** • **dissection** • **isolated hemisphere** • **stent** • **stroke** • **trauma** • **hypoperfusion**

Internal carotid artery dissection occurs spontaneously or in the setting of trauma and can lead to ischemic and hemorrhagic stroke through thromboembolic complications or hemodynamic compromise. Internal carotid artery dissection accounts for a small proportion of strokes overall but is a more common cause of stroke in the younger population. The natural history is not very well understood. Some reports point to stroke due to ICAD that is unexpectedly benign in some cases,[15,23,29] while others have suggested possible major transient or permanent disability.[17,25,34,38,40,43] In a series of 260 patients with nontraumatic intracranial arterial dissections, Yamaura[45] reported an overall mortality rate of 26% and poor outcomes in 5%, with the mortality rate reaching 49% in patients with carotid artery lesions. Traumatic dissections have been reported to occur in 1% of patients with blunt injury mechanisms to the neck,[37] and spontaneous dissections may be triggered by seemingly innocuous events, including violent coughing, nose blowing, and forceful neck rotations.[38] In spontaneous dissections, collagen tissue abnormalities such as Marfan syndrome or fibromuscular dysplasia may be associated with ICAD.[5,6,14] Internal carotid artery dissection may present with a wide variety of neurological symptoms including headache, carotidynia, oculosympathetic palsy, hemiparesis, and hemiplegia.[21,43]

Patients with ICAD are routinely treated using anticoagulation therapy at most institutions, despite a lack of evidence from well-designed studies supporting this treatment's efficacy.[31] Anticoagulation alone has been shown to be effective in a number of case series,[16,21,42] although strokes may occur despite anticoagulation,[3] and the treatment is usually contraindicated in the setting of trauma with concomitant injuries. Endovascular stent placement has been proposed in patients with worsening neurological condition and in cases in which anticoagulation is contraindicated.[1,3,8–12,20,22,26,27,30,32]

Abbreviations used in this paper: ICA = internal carotid artery; ICAD = ICA dissection; MCA = middle cerebral artery.

Patients with poorly developed or absent communicating arteries and a cerebral hemisphere supplied solely by the index ICA, a configuration found in 18%–44% of the population,[24,35,44] are in a high-risk group for the imminent stroke after ICAD due to hemodynamic compromise during the subacute period. In this report, we present the cases of 2 patients with isolated hemispheres in whom symptomatic dissection of the ICA led to near-complete occlusion of the vessel. In both cases, the dissection resulted in blood pressure–dependent transient neurological deficit, which was treated by endovascular revascularization. We reviewed the relevant literature, and we discuss the rationale of endovascular treatment of ICAD in the setting of hypoperfusion in the affected hemisphere.

Case Reports

Endovascular Technique

Both patients underwent catheter angiography of the cervical and intracranial vasculature. Intravenous heparin was administered to achieve an activated clotting time of longer than 250 seconds. An 8 Fr guide catheter (Brite Tip) coaxially over a 5 Fr vertebral 125-cm catheter was placed in the common carotid artery via a femoral vascular sheath (Avanti, Cordis Corp.). A microcatheter was used coaxially over a 0.014-in microguidewire to gently probe, identify, and enter the true arterial lumen under real-time high-resolution digital roadmap angiography. This was then navigated past the site of dissection into the petrous intracranial distal portion. A microinjection was performed to ensure continued presence in the true lumen and good outflow. At this point, a 300-cm exchange-length microguidewire was passed through the microcatheter with its tip positioned in the petrous segment and was used for advancing the stent delivery catheter. A Nitinol shape-memory alloy self-expanding stent (Precise Stent, Cordis Corp.) was used in this study and was advanced over the microwire until its tip reached the distal portion of the dissection at the junction of the cervical and petrous portions of the ICA. The first stent was deployed from distal to proximal. A subsequent stent was deployed in tandem overlapping fashion until the proximal inflow zone was covered and recanalized. Patients were maintained on a regimen of clopidogrel (75 mg orally per day) for 6 weeks and aspirin (325 mg orally per day) indefinitely.

Case 1

History and Examination. This 49-year-old man skated inadvertently into a wall and suffered blunt trauma. He did not notice any problems at the time, such as neck pain, external abrasions, or cervical fractures. Three days later, he noted sudden onset of right arm weakness, along with difficulty in speaking and finding words. He was hospitalized with these complaints at an outside institution, and MR imaging/MR angiography demonstrated dissection of the left ICA with good flow to intracranial vessels. His symptoms resolved spontaneously after systemic anticoagulation with intravenous heparin was initiated. He was discharged from the hospital 3 days later and was placed on a regimen oral warfarin together with enoxaparin. Again, 3 days later he suddenly felt dizzy while sitting, noted an unsteady gait, paresthesias to bilateral lower extremities, and return of speech difficulties. He presented to the hospital with dysphasia and right hemiplegia. Additional MR imaging/MR angiography findings were compared with those obtained 5 days earlier and revealed extension of the dissection with virtually no intracranial blood flow visualized through the left MCA. There was no sign of a lesion or stroke on diffusion-weighted MR imaging sequences.

Treatment. Catheter-based digital-subtraction angiographic studies demonstrated the previously suspected left carotid artery dissection (Fig. 1). Persistent flow was noted through the dissected segment of the left ICA, although it was sluggish (compared with the filling of branches of the external carotid artery) due to the dissection flap, which was under pressure and consequently compressing the true lumen. In addition, injection of the right ICA did not reveal anterior communicating flow or perfusion to the left MCA and no retrograde flow into the left A_1 segment of the anterior cerebral artery after injection of the right ICA. An SL-10 microcatheter (Boston Scientific Corp.) was advanced into the high petrous segment of the ICA after the true lu-

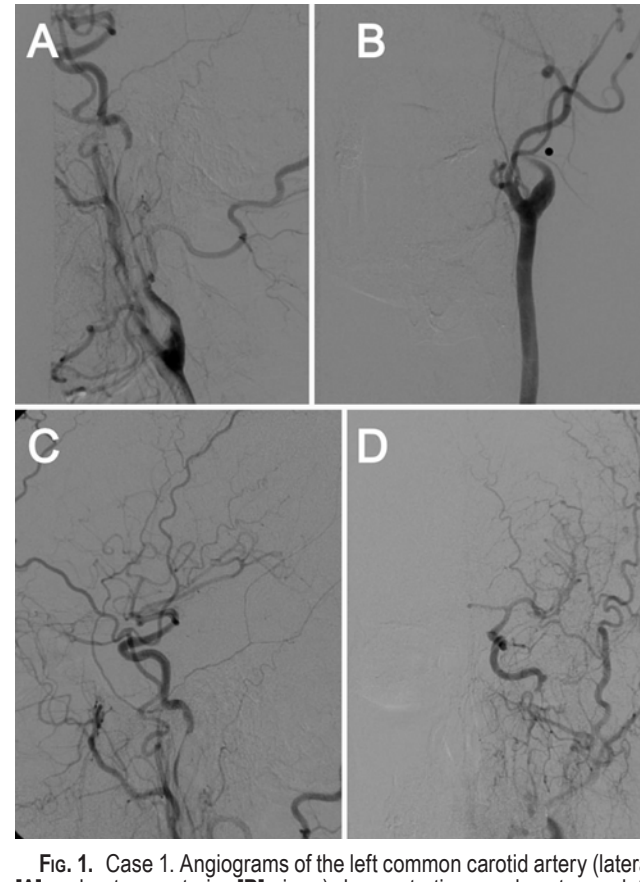

Fig. 1. Case 1. Angiograms of the left common carotid artery (lateral **[A]** and anteroposterior **[B]** views) demonstrating an almost complete occlusion of the ICA with poor, sluggish intracranial filling through the compressed true lumen and minor collateral vessels of the external carotid artery (lateral **[C]** and anteroposterior **[D]** views).

men of the dissection had been selected with an Agility 14 microwire (Cordis Corp.). Patency and antegrade flow in the petrous ICA was confirmed by microcatheter contrast injection (Fig. 2). The microwire was exchanged for a supersoft 300-cm-long wire (Stabilizer, Cordis Corp.) inserted through the microcatheter and advanced into the supraclinoid segment, followed by 5 × 40–mm Precise Stent deployment from the proximal portion to the junction of the cervical and petrous ICAs. The stent delivery microcatheter was withdrawn, and an angiographic run revealed very poor flow through the stent and worsening of the proximal component of the inflow zone of the dissection. There was concern that perhaps the first stent had been deployed in the false lumen, thus sealing the carotid artery shut. Nonetheless, since there was constant access through the true lumen with the exchange-length microwire, and since confirmation was made initially of being within the true lumen via microcatheter injections, the decision was made to deploy a second proximal overlapping stent to connect the true lumen to its proximal portion. Accordingly, a second 6 × 40–mm stent was guided in overlapping fashion over the stabilizer wire that was kept in the supraclinoid segment and was delivered with a small overlap with the proximal portion of the stent ending in the distal portion of the left ICA bulb without crossing into the bifurcation. This second stent successfully tacked the inflow zone of the dissection, which had been inflated in an accordion-like manner and thus had worsened the lumen, and this resulted in full restoration of left ICA flow (Fig. 2).

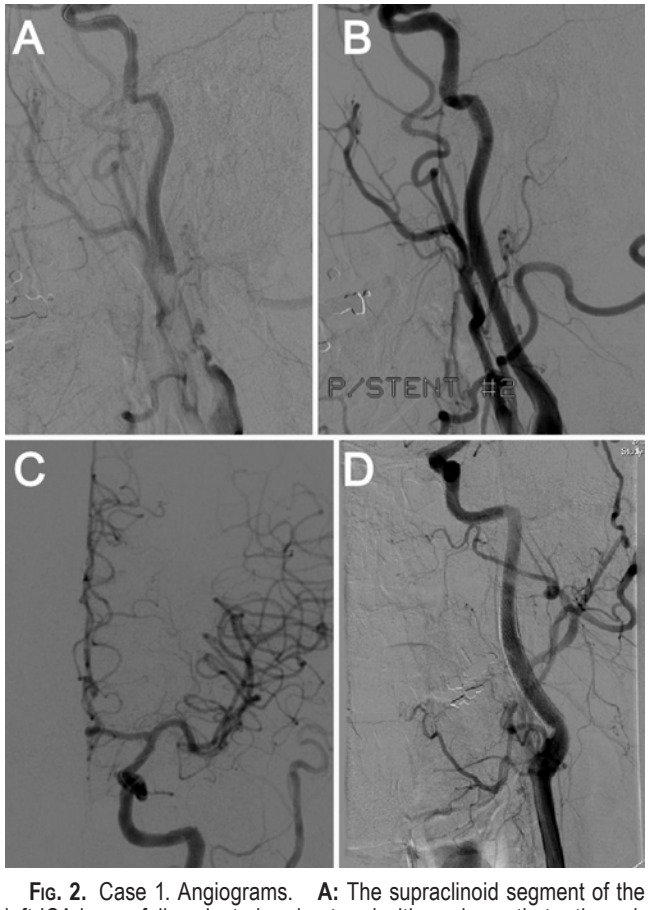

Fig. 2. Case 1. Angiograms. **A:** The supraclinoid segment of the left ICA is carefully selected and entered with a microcatheter through the true lumen of the ICAD, and a self-expanding Precise stent is deployed. Very poor flow is noted through the stent, with worsening of the proximal component of the inflow zone of the dissection. **B:** A second stent is delivered in tandem with a small overlap enabling the tacking down of the ICAD inflow zone. **C:** Resumption of flow is seen in the distal left ICA and improved left-sided intracranial perfusion. **D:** Follow-up angiogram obtained 6 months later demonstrating a good and stable stent position with preservation of the vessel lumen.

Posttreatment Course. The patient tolerated the procedure without deficit and became insensitive to blood pressure variation. He was discharged from the hospital on the 3rd postintervention day and was placed on a regimen of dual antiplatelet therapy. Follow-up angiography at 6 months demonstrated persistent patency of the stented left ICA segment with no evidence of stenosis. The patient remains asymptomatic at 6 years postintervention with patent stents on CT angiography (Fig. 2).

Case 2

History and Examination. This 64-year-old man complained of a severe headache that had persisted for the past 3 weeks. Magnetic resonance imaging of the brain revealed a left frontal deep-seated hemorrhage. Subsequently, diagnostic catheter angiography was performed at an outside institution, after which the patient became aphasic and hemiplegic. The patient was started on a heparin drip. Additional MR imaging/MR angiography revealed multiple left cerebral emboli and decreased flow in the anterior cerebral artery and MCA on the left and no flow in the proximal left ICA with minimal distal reconstitution. The patient was transferred for further management and underwent microcatheter-based recanalization and stenting of the left ICA (Fig. 3).

Treatment. An 8 Fr guide catheter was placed in the left common carotid artery, and an S-10 microcatheter used over a Transend EX microwire (Boston Scientific) to identify the true lumen of the left ICA dissection. The wire was then removed, and the SL-10 microcatheter was gently advanced without microwire support until it reached the supraclinoid segment. From this location, a contrast microinjection revealed that the microcatheter remained in the true lumen as evidenced by good distal flow in the petrous and supraclinoid segments (Fig. 4). An exchange-length microwire was advanced into the intracranial ICA over the microcatheter, with the latter being exchanged for a Precise 5 × 40–mm stent, which was positioned with its distal end in the transition zone of the petrous and cervical segments. After stent deployment, a test injection through the guide catheter revealed excellent resumption of flow into the left ICA. Examination of the transition zone between the stent and the native vessel and the lower portion revealed a persistent area of irregularity in the anterior portion suggestive of incomplete coverage of the inflow zone of the dissection. Accordingly, the decision was made to deploy a second 5 × 40–mm tandem proximal overlapping stent. This led to coverage of irregularity at the transition zone, and there was now excellent flow through the left ICA in the cervical portion.

Posttreatment Course. After the intervention, the pa-

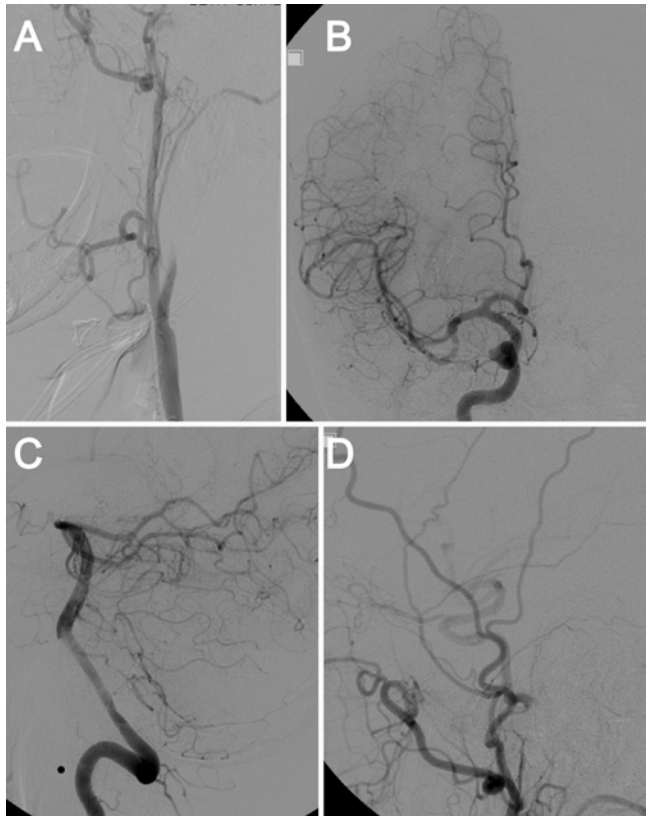

Fig. 3. Case 2. **A:** Angiogram of the left common carotid artery demonstrating a complete occlusion of the ICA. **B:** Injection of the right carotid artery (anteroposterior view) demonstrating no cross-flow through the anterior communicating artery. **C:** The left vertebral artery (lateral view) showing only minimal flow through the left posterior communicating artery. **D:** Additional blood supply to the distal left supraclinoid ICA (lateral view) stems from collateral flow through the left ophthalmic artery.

tient was awake, alert, and aphasic but following simple commands. He had some movement in the right upper and lower extremities on the bed. His neurological examination improved to moderate weakness on the right side. He continued to be intermittently confused and disoriented. He was discharged home and was placed on a regimen of clopidogrel and aspirin. Follow-up at 6 months showed improvement in the dysphasia and hemiparesis, and a CT angiogram (the patient refused catheter angiography) demonstrated persistent patency of the stented left ICA segment and no evidence of stenosis (Fig. 4).

Discussion

Carotid artery dissection may result in occlusion or severe narrowing of the affected vessel and subsequent hypoperfusion of the distal territory or thromboembolism causing transient ischemic attacks or stroke. In patients with an incomplete circle of Willis and vascular supply to one hemisphere that is entirely dependent on the dissected ICA, the resultant ischemic territory may encompass the entire hemisphere. Aggressive endovascular and microsurgical measures may be necessary to salvage neurological function and minimize stroke morbidity in

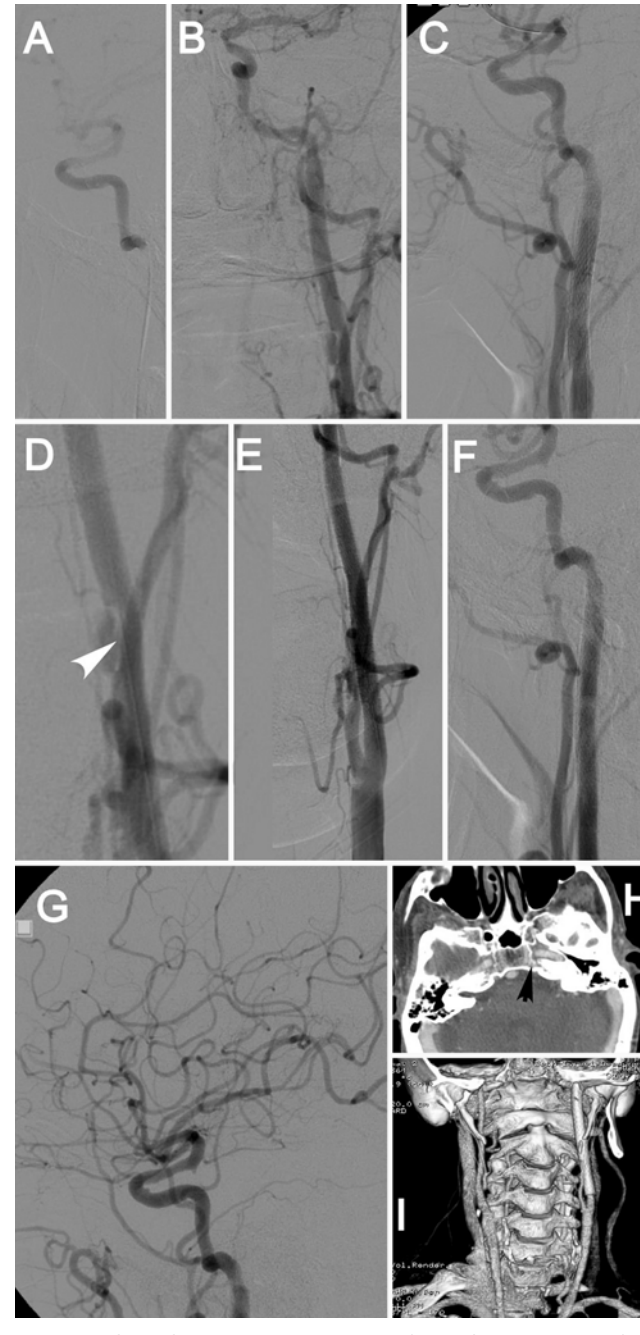

Fig. 4. Case 2. **A:** The true lumen of the ICAD is successfully selected as shown by microcatheter injection in the left ICA (lateral view). **B and C:** A self-expanding Precise stent immediately restores flow in the left ICA (anteroposterior **[B]** and lateral **[C]** views). **D:** A flap at the inflow zone persists after deployment of the stent *(arrowhead).* **E and F:** A second tandem overlapping stent is deployed, restoring the vessel profile completely (anteroposterior **[E]** and lateral **[F]** views). **G:** Injection of the left ICA (lateral view) showing resumption of a normal flow pattern intracranially. **H:** A CT angiogram obtained at the 6-month follow-up reveals good contrast material flow in the petrous portion of the left ICA *(arrow).* **I:** A 3D reconstruction confirms stable placement of both stents with flow in the proximal cervical left ICA.

this extreme situation.[25] Internal carotid artery dissection has been held accountable for up to 20% of strokes in a younger population; its incidence has been reported to be 2.6–2.9 per 100,000 population.[19,39] Internal carotid artery dissection results from an intimal tear with spread of the circulating blood into the vessel wall that progresses into a subintimal dissection and subsequently to a narrowing of the lumen or pseudoaneurysm formation.[21] The extracranial portion of the ICA is affected much more commonly; 90% of dissections occur in the cervical segment of the ICA, and the dissection usually terminates at the level of entry into the carotid canal.[21,27] As was the case in Case 1, hyperextension and lateral rotation of the neck is thought to lead to stretch of the carotid artery over the upper cervical vertebral bodies.[42] Our experience with Case 2 demonstrates that endovascular procedures, including diagnostic angiography and interventional procedures, may lead to ICAD.[7,18]

Although periorbital headache is the most common presenting symptom of ICAD, ischemic or thromboembolic infarction is the most severe clinical sequela. In 80% of the cases, retinal and/or cerebral ischemia has been reported (20%–30% of transient ischemic attacks and 40%–60% of complete stroke).[21] Transcranial Doppler ultrasonography studies have demonstrated frequent microemboli[41] in accordance with imaging studies, revealing that strokes due to ICAD are predominantly thromboembolic in origin.[23,41] Strokes following ICAD are embolic in the majority of cases, but hemodynamic compromise is also another considerable proportion.[29,43] In our Case 1, the deficit was not fixed but rather fluctuated directly in relation to cerebral perfusion pressure. A decrease in the systolic blood pressure below 120 mm Hg dynamically prompted the development of a reversible neurological deficit. Cohen et al.[9] reported that angiographic parenchymography or perfusion MR imaging can be used to determine the extent of salvageable ischemic penumbra to select the patients who would potentially benefit from a revascularization. Hemodynamically significant stenosis and pseudoaneurysm formation develops in a number of patients despite anticoagulation, increasing the risk of flow-related infarction and distal embolization.[33,36]

Internal carotid artery dissection is not a fixed lesion and should be viewed as a dynamic entity. Clinical and radiological findings may change within hours, as occurred in our patients. The timing and type of treatment in patients with ICAD remain controversial, and there are no controlled studies for the treatment comparing anticoagulation or other invasive procedures. Liu et al.[27] reported the indications for stent placement for ICAD as follows: 1) dissection-induced stenosis that has not responded to a course of medical therapy; 2) ischemic or thromboembolic symptoms; 3) dissection in a patient with contraindications for anticoagulation therapy; and 4) iatrogenic dissection with severe stenosis. Contraindications for anticoagulation have to be considered on a case-by-case basis as the interventional therapy usually involves anticoagulation and dual antiplatelet therapy.

The development of hemorrhagic transformation or progression of the dissection has been reported in patients who have undergone anticoagulation therapy, but there are also other reports of good results in patients treated with anticoagulation.[5] Although there are no accepted guidelines for the ICAD treatment, whether anticoagulation or stent deployment, we believe that stenting would be very appropriate in patients with a rapidly deteriorating neurological status in the acute, clinically dynamic phase of dissection with an underlying hemodynamic rather than simple thromboembolic etiology. In a previous study, we treated 10 cases of ICAD with endovascular stenting and reported good neurological outcomes.[32] In 7 of these patients, there were intracranial infarctions, and none of them developed hemorrhagic transformation after treatment. The major difference of this study from the previous one is the treatment of ICAD in the isolated hemisphere that has the main blood supply from the side affected by ICAD. Neither case demonstrated hemorrhagic transformation likely because the cerebral tissue remained viable and not infarcted.

Timing of the reperfusion is also very important. Salvage of the penumbra at risk might not be feasible without early reperfusion. Ischemic cerebral tissue may potentially benefit from thrombolysis between 3 and 6 hours, and there is increasing evidence that noninfarcted but hypoperfused portions of ischemic brain tissue might remain viable and regain function even after 12 hours.[28] The timing of endovascular revascularization and stent placement depends on the clinical condition of the patients, and guidelines regarding this facet of the management of these patients are lacking. The literature contains reports of stent deployment over time periods ranging from emergency procedures to interventions performed 3 months after the onset of symptoms.[2,4,9,13,22,27] We do not advocate primary carotid artery stenting for all cases of carotid artery dissection, but we believe that early stenting may provide a better chance for reperfusion of the critical penumbra. We also believe that stenting could be combined with antithrombolytic therapy in select cases demonstrating hypoperfusion with poor reserve, or in cases of bilateral carotid or carotid and vertebral dissections, given the unpredictable dynamic nature of ICAD progression to occlusion in certain cases. Nonetheless, the clinical decision process must be individualized for each patient, and its risks and benefits need to be clearly explained to the patient and the patient's family or health care proxy.

Endovascular stenting has some readily apparent advantages over surgical treatment, including immediate restoration of flow in the artery leading to early reperfusion of the ischemic brain areas, and the patient may be kept only on a regimen of antiplatelet agents. Recent studies have reported only low rates of complications including distal embolization, perioperative stroke, or new deficits attributable to stent deployment despite performing angioplasty of the deployed stent.[30,32] Atherosclerotic stenoses require angioplasty with higher balloon pressures to treat the underlying often calcified atherosclerotic lesion. The absence of such underlying atherosclerosis in most ICAD cases makes balloon angioplasty very seldom needed; instead, the radial force of the appropriately sized self-expanding stent can be relied on to restore the native vessel caliber.[32]

The most common disadvantages and limitations of

endovascular therapy include the apparent difficulty to correctly identify, microcatheterize, and canalize the true lumen of the ICA and the potential need for deployment of more than one stent in a telescoping fashion to cross the often long distance of the dissection. A note of caution must be stated with respect to the often-worsening angiographic appearance after deployment of the distal stent. Provided that the true lumen was initially confirmed and an exchange-length microwire was kept in place throughout in the true lumen, the endovascular operator must not panic or withdraw the exchange microwire, but rather forge ahead and deploy additional tandem overlapping proximal stents until the proximal dissection inflow zone is tacked down, access to the false lumen is sealed off, and the healthy segments of the affected carotid artery are reconnected. The transient worsening of the flow after distal stent deployment is usually the result of the windsock-like dissection flap becoming bunched up proximally as it is squeezed back like a tube of toothpaste, leading to further compression and a worsening angiographic appearance compared with that seen before intervention. Our long-term follow-up imaging suggests that these long constructs in nonatherosclerotic vessels remain widely patent at follow-up and do not seem to share the same risk of restenosis seen in stent therapy for atherosclerotic disease.

Conclusions

The 2 patients presented in this report underwent endovascular stenting after a thorough discussion about other noninvasive options had been conducted and the failure of medical therapy had been determined. They underwent recanalization in the setting of minimal diffusion-weighted imaging changes on MR imaging and dense hemodynamically dependent deficits. The hemodynamic isolation of the hemisphere supplied by the affected ICA warranted a rather aggressive therapy. In both cases, restoration of carotid artery flow resulted in the return of neurological function with little residual deficit, and the treated ICA was seen to remain patent after a 6-month follow-up period.

Internal carotid artery dissection causing occlusion or near-occlusion with intracranial embolism is an important cause of severe and potentially life-threatening hemispheric ischemia. Stenting may be an appropriate method to alter the clinical course in select patients during the acute, clinically dynamic phase of dissection. We believe that endovascular stent deployment is a feasible and effective method to treat subacute ICAD with complete or near-complete occlusion, especially in the absence of adequate collateral flow. Stenting should be considered in patients in whom radiographic evidence of an imminent irreversible stroke is evident, such as in those with isolated cerebral hemisphere ipsilateral to the dissection.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Malek. Acquisition of data: Malek. Analysis and interpretation of data: Malek, Atalay. Drafting the article: Schirmer, Atalay. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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Therapeutic hypothermia in acute ischemic stroke

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Induced hypothermia has been used for neuroprotection in cardiac and neurovascular procedures. Experimental and translational studies provide evidence for its utility in the treatment of ischemic cerebrovascular disease. Over the past decade, these principles have been applied to the clinical management of acute stroke. Varying induction methods, time windows, clinical indications, and adjuvant therapies have been studied. In this article the authors review the mechanisms and techniques for achieving therapeutic hypothermia in the setting of acute stroke, and they outline pertinent side effects and complications. The manuscript summarizes and examines the relevant clinical trials to date. Despite a reasonable amount of existing data, this review suggests that additional trials are warranted to define the optimal time window, temperature regimen, and precise clinical indications for induction of therapeutic hypothermia in the setting of acute stroke. *(DOI: 10.3171/2011.4.FOCUS1154)*

Key Words • hypothermia • stroke • brain cooling method • clinical trial • vascular disorders

Therapeutic hypothermia was first described in the Edwin Smith Papyrus, the oldest medical text known to man. History books have since repeatedly documented efficacy in the resuscitation of cold-water drowning victims. In the 1930s, Dr. Temple Fay, an American neurosurgeon, pioneered the use of hypothermia in the treatment of neurological disease.[8] The concept was first applied to patients with intractable pain, and later to intracranial processes such as traumatic brain injury, abscesses, and cerebritis. In the 1950s, hypothermia was effectively used in cardiac arrest victims and during cardiac bypass surgery.[1,38] Shortly thereafter, the model was applied to intracranial aneurysm surgery, to create a bloodless operative field and allow for controlled tissue dissection. Hypothermic circulatory arrest has since been effectively used to treat complex aneurysms that are not amenable to standard techniques.[25] Half a century later, the medical community demonstrated that therapeutic hypothermia could be used as an effective neuroprotective agent for out-of-hospital cardiac arrest survivors.[1,9,17,32,34] To date, hypothermia is the only treatment modality proven to have neuroprotective effects in clinical trials of global cerebral ischemia such as cardiac arrest[1,17,22] and newborn hypoxic encephalopathy.[40] These findings have generated enthusiasm for the use of hypothermia as a neuroprotectant in focal ischemic stroke. Successful implementation, however,[40] thus far has been marred by clinical trials with small sample size, prolonged time to intervention, and concern for potential side effects. In the following article we explore the current development of hypothermia as a neuroprotectant in acute ischemic stroke. The review focuses on therapeutic delivery methods, mechanisms of action, potential side effects, and complication avoidance, and then examines existing data from clinical trials (means are expressed ± SD throughout).

Abbreviations used in this paper: ATP, ATPase = adenosine triphosphate, adenosine triphosphatase; COOL AID = Cooling for Acute Ischemic Brain Damage; EAA = excitatory amino acid; ICP = intracranial pressure; MCA = middle cerebral artery.

Pathophysiological Indications

Therapeutic hypothermia is defined as an intentionally induced, controlled reduction of a patient's core temperature below 36°C. Further classification delineates mild (34°C–35.9°C), moderate (32°C–33.9°C), moderate/deep (30°C–31.9°C), or deep (< 30°C) hypothermia.[32]

Ischemia produces variable degrees of tissue damage, with apoptosis and cellular death as the final common pathways of a multifactorial process. Brain tissue ischemia leads to ATP depletion within a very short period of time. The exhaustion of ATP triggers membrane depolarization from an uncontrolled influx of ions in the setting of nonoperational Na^+-K^+ ATPase pumps. Changes in membrane potentials release EAAs and promote Ca influx. Excess intracellular Ca initiates mitochondrial injury. Affected mitochondria produce oxygen free radicals, and release cytochrome C, causing activation of caspase-mediated DNA fragmentation and cellular apoptosis. If reperfusion occurs, the injured mitochondria may further contribute to neuronal damage. Likewise, an influx of in-

flammatory mediators and free radicals may exacerbate tissue necrosis on restoration of blood flow.[5,20,23,28,31,48]

Experimental animal studies have demonstrated that hypothermia effectively targets a multitude of ischemia-induced pathways. These processes, which are invariably detrimental to sustained cellular activity, include energy depletion, ion shifts, free radical formation, EAA release, and inflammation.[3,44,47] Hypothermia reduces cerebral oxygen consumption by a rate of approximately 6% per 1°C change in temperature, allowing preservation of potentially viable brain tissue for longer periods of time.[9,47] Lowering brain temperature expedites restoration of ionic homeostasis and impedes ischemia-induced EAA release.[30,35,41,42] Furthermore, free radical formation and inflammatory responses are inhibited during hypothermia.[11] Thus, hypothermia counteracts multiple steps of cellular injury to reduce the recruitment of penumbral tissue into the ischemic core following acute stroke.[23]

Methods of Cooling

Methods of inducing therapeutic hypothermia may be divided into surface, intravascular (core), and selective types. Numerous surface cooling methods use air, volatile liquids, or cold water and/or ice as thermoconductive media. Surface cooling is noninvasive, inexpensive, and easy to implement. Disadvantages include fluctuations in body temperature and a prolonged time to achieve the temperature goal. Intravascular cooling is administered via infusion of ice-cold fluids, or use of devices such as intravascular catheters (with metal or circulating cold water–filled balloon conductors) with electronic feedback temperature control, peritoneal lavage devices, and extracorporeal circulation. The main advantages of core cooling are shorter time to goal temperature and more precise hypothermic control.[15,26,32,39] In recent years, there has been an increased interest in selective brain cooling for the treatment of ischemic stroke. This concept has led to the invention of 2 devices for implementation. Wang et al.[45] conducted a randomized controlled study on induction of hypothermia by using a cooling helmet. The investigators achieved statistically significant decreases in brain temperature in the treatment group while maintaining selective hypothermia for 48–72 hours. The authors did not encounter any of the significant complications classically associated with systemic hypothermia, and concluded that a cooling helmet was safe for implementation by emergency medical services. The Pre-ROSC (return of spontaneous circulation) IntraNasal Cooling Effectiveness (PRINCE) study evaluated a transnasal evaporative cooling device called RhinoChill in cardiac arrest victims.[4] Two hundred patients in whom cardiac arrest was witnessed were randomized to treatment with intra-arrest cooling or standard care. Time to the target temperature of 34°C was shorter in the treatment group. The significant device-related adverse events included periorbital emphysema (1 patient), epistaxis (3), and perioral bleeding (1).

Potential Side Effects and/or Complications

Shivering is the most frequently noted side effect of induced hypothermia. Typical methods of controlling shivering include counter-rewarming, meperidine, buspirone, magnesium, benzodiazepines, opiates, and paralytics. Frequent electrolyte shifts can develop during induction of hypothermia, causing significant hypokalemia, hypomagnesemia, and hypophosphatemia. Opposite electrolyte derangements can occur during the rewarming phase.[32,33] Hyperglycemia has also been described and associated with relative insulin resistance.

Mild to moderate hypothermia can decrease heart rate and cause a reduction in cardiac output by 25%–40%. This effect is counterbalanced by a more significant reduction in metabolic rate, which may produce paradoxical increases in venous oxygen saturation. Contrary to common belief, myocardial contractility may be increased by cold temperatures (35.5°C and below) and induce bradycardia. Cardiac arrhythmias usually develop at temperatures below 30°C, although characteristic electrocardiographic changes (for example, Osborne waves) without clinical consequence can be observed before reaching this threshold. Thrombocytopenia[36] and coagulation abnormalities usually occur at temperatures below 33°C.[29,32,43,46] The most common infectious complication is pneumonia (in up to 50% of cases), and happens frequently in proportion to duration and degree of hypothermia.

Clinical Trials

In the late 1990s, a prospective, observational analysis of the Copenhagen Stroke Study Registry determined that for each 1°C increase in body temperature at admission following acute stroke, the relative risk of poor outcome rose by 2.2.[18,34] Based on these data, Kammersgaard et al.[19] conducted a feasibility and safety trial of hypothermia for stroke patients in 2000. In that study, 17 patients with acute stroke (within 12 hours of symptom onset) were successfully cooled to 35.5°C for 6 hours by using surface cooling techniques; 56 patients were included as controls. The authors concluded that induced hypothermia was not associated with poor outcome, death, or an increased incidence of infectious complications. Shivering was reported as the most common uncomfortable event, and was well controlled by pethidine (meperidine). Encouraging results from this safety and feasibility study prompted trials examining optimal delivery models for, and clinical efficacy of, induced hypothermia (see Table 1).

Schwab et al.[37] reported a temperature gradient (range 1°C–2.1°C) between the core body and brain temperature after severe acute MCA stroke. The authors then evaluated the use of moderate hypothermia (33°C core body temperature) in 25 patients with severe MCA stroke. Cooling was achieved within 14 ± 7 hours after the onset of symptoms by using cooling blankets and cold saline infusions. The purpose of this study was to control ischemic cytotoxic edema by maintaining moderate hypothermia for 48–72 hours. Continuous monitoring of ICP, brain temperature, and cerebral perfusion pressure was performed. During the hypothermia period, ICP was well controlled, although rewarming was associated with rebound intracranial hypertension. The reported survival rate was 56%. This compared favorably with natural his-

TABLE 1: Literature review of clinical trials of hypothermia in acute ischemic stroke*

Authors & Year	Total No. of Patients	Trial Design	Cooling Method	Duration (hrs)
Schwab et al., 1998	25	uncontrolled study	cooling blanket & cold baths	65
Kammersgaard et al., 2000	73	case-control trial	cooling blanket	6
Krieger et al., 2001	19	controlled study	cooling blanket, alcohol, ice water baths	47
Schwab et al., 2001	50	uncontrolled study	cooling blanket, alcohol, & ice	55
Zweifler et al., 2003	10	pilot study in volunteers	cooling pads	5
Georgiadis et al., 2001	6	uncontrolled study	endovascular device	67
De Georgia et al., 2004	40	randomized controlled trial	endovascular device	24
Lyden et al., 2005	18	uncontrolled study	endovascular device	24
Els et al., 2006	25	randomized controlled trial	endovascular device	48
Guluma et al., 2006	10	uncontrolled study	endovascular device	24
Martin-Schild et al., 2009	20	uncontrolled study	endovascular device or surface cooling	24
Hemmen et al., 2010	59	randomized controlled trial	endovascular w/ or w/o alteplase	24
Wang et al., 2004	14	randomized controlled trial	cooling helmet	48
Castrén et al., 2010	200	randomized controlled trial	transnasal cooling	NA

* Entries are grouped according to cooling method. Abbreviation: NA = not applicable.

tory data, which suggested a mortality rate of roughly 80%.[2,13,16,37]

In a follow-up trial, Schwab et al.[36] induced moderate hypothermia in 50 patients with malignant hemispheric infarction. Cooling was initiated within 22 ± 9 hours after the onset of stroke symptoms by using surface methods and cold infusions. The target bladder temperature < 33°C was achieved in 6.5 hours (average) and maintained for 55 hours (range 24–72 hours) with passive rewarming for approximately 17 hours. This trial confirmed the previous observation that intracranial hypertension leading to death most frequently occurred during the rewarming phase, and faster rewarming was associated with a more prominent ICP increase. Although the study was not powered to demonstrate efficacy, it yielded a relatively low mortality rate of 38%. Common complications observed in the trial were thrombocytopenia (70%), bradycardia (62%), and pneumonia (48%).

Georgiadis et al.[10] showed the feasibility of using an intravascular approach for the treatment of patients with severe acute ischemic stroke. Their protocol achieved rapid cooling rates (1.4 ± 0.6°C/hour), with good temperature control in 6 patients subjected to moderate hypothermia (33.4°C–32.2°C). The design of the intravascular cooling device included 3 balloons perfused with circulating cold saline located near the tip of a central line placed into the inferior vena cava via a femoral approach. The most commonly observed side effects were pneumonia, arterial hypotension, arrhythmia, and thrombocytopenia.

Traditionally it was believed that hypothermia could be applied only to intubated and sedated patients. A study by Zweifler et al.[49] described a method of mild hypothermia induction (tympanic membrane temperature 34°C–35°C) and maintenance by using a surface cooling device (Arctic Sun Energy Transfer Pads) in healthy, unanesthetized, nonintubated volunteers. Shivering was suppressed with acetaminophen and meperidine. The goal tympanic temperature of 35°C was reached in 90 ± 53 minutes (1.4°C/hour). The most common side effects were nausea, observed in 30% of participants, and elevated systolic blood pressure. Guluma et al.[12] described a method of hypothermia induction in awake, nonintubated patients in whom an intravascular cooling catheter was used. They were able to cool patients to a target core temperature of 33°C by using a combination of buspirone, meperidine, and cutaneous counter-rewarming with a heating blanket to suppress shivering. Moderate hypothermia was maintained for 24 hours, with controlled rewarming achieved over the ensuing 12 hours. This protocol showed good tolerability, with minimal shivering, no rebound hyperthermia, and no oversedation.

At present, alteplase is the only FDA-approved medication for the treatment of acute stroke. The compatibility of potential neuroprotective therapies with thrombolytic agents is therefore critical. Prior to 2001, the safety of hypothermia in stroke patients had been documented, but cooling had not been examined as an adjuvant to alteplase. Much of the concern rested on a theoretical risk of intracerebral hemorrhage, because hypothermia could induce thrombocytopenia and coagulopathy. The COOL AID I trial addressed the safety of administering hypothermia after alteplase thrombolysis in patients with acute ischemic stroke. This study enrolled 19 patients with acute stroke (National Institutes of Health Stroke Scale score of > 15) who received alteplase for thrombolysis. Ten patients were subjected to hypothermia (surface cooling with a cooling blanket and intermittent ice water and whole-body alcohol rubs), and 9 patients served as controls. Hypothermia was implemented within 6.2 ± 1.3 hours of symptom onset. Cooling to a core temperature of 32°C was achieved in 3.5 ± 1.5 hours. Bradycardia (in 5 patients), ventricular ectopy (in 3), hypotension (in 3), melena (in 2), fever after rewarming (in 3), infections (in 4), rapid ventricular rate in a patient with atrial fibrillation

(in 4), myocardial infarction (in 3), and 3 deaths were reported in the hypothermia group. The patients subjected to hypothermia achieved mean modified Rankin Scale scores of 3.1 ± 2.3 at 3 months, versus 4.2 ± 1.6 in non-hypothermic patients. This trial proved the feasibility and safety of combining thrombolytic therapy and hypothermia in patients with acute ischemic stroke.[21]

A subsequent 2004 study, COOL AID II, was designed as a multicenter randomized pilot trial to evaluate the feasibility of intravascular cooling in patients with ischemic stroke. Patients were enrolled within 12 hours of symptom onset. The target core temperature of 33°C was achieved faster (77 ± 44 minutes) than in the previous surface cooling study, and maintained for 24 hours. However, only 13 of the 18 patients randomized to hypothermia achieved the target temperature. Clinical outcomes and rates of infectious complications were similar in both groups, although the study was not powered to detect such a difference. This trial further supported the findings of COOL AID I, and suggested that endovascular cooling was feasible in patients with moderate to severe ischemic stroke in the anterior circulation territory.[6]

Two trials, the Intravascular Cooling for the Treatment of Stroke (ICTuS)[24] and the Intravascular Cooling for the Treatment of Stroke–Longer window (ICTuS-L),[14] further investigated the feasibility and safety of intravenous alteplase combined with intravascular cooling. The latter trial included 59 patients divided into 2 cohorts. The first cohort included patients who presented within 3 hours of symptom onset. All patients in this group received the standard dose of intravenous alteplase, and were then randomized to therapeutic hypothermia or standard medical care. The second cohort of patients presented at 3 to 6 hours of onset and was randomized to 4 groups as follows: Group 1, no treatment; Group 2, treatment with alteplase only; Group 3, treatment with hypothermia only; or Group 4, combined therapy. The hypothermia protocol included endovascular cooling for 24 hours and controlled rewarming for 12 hours. Because of technical difficulties, hypothermia was not achieved in 2 of 28 patients randomized to cooling groups. Although the incidence of pneumonia was higher in the hypothermia groups, there were no statistically significant differences in outcome or death at 3 months among the groups.

Given the high mortality rate associated with large MCA infarctions, Els et al.[7] proposed an aggressive strategy for the treatment of patients with such infarctions, in 2006, that combined hypothermia and decompressive hemicraniectomy. Twenty-five patients with malignant ischemic stroke, defined as an infarction of more than two-thirds of one hemisphere, were randomized to treatment with hemicraniectomy alone or a combination of hemicraniectomy and mild hypothermia (35°C). The hemicraniectomy was performed within 15 ± 6 hours of symptom onset, and cooling was started immediately after surgery (using surface or intravascular techniques). The combination therapy group showed a tendency for better clinical outcome as measured by the National Institutes of Health Stroke Scale at 6 months, although the difference did not reach statistical significance ($p = 0.08$). There was no death associated with hypothermia. The authors attributed this finding to a milder cooling regimen when compared with other studies.

Conclusions

Although there is an increasing body of data supporting the utility of hypothermia in acute stroke, there have been no large-scale randomized studies proving efficacy. Prior investigations have differed with regard to induction methods, target temperature, timing, and adjuvant therapies. Hypothermia remains a promising therapeutic modality. Further trials are needed, however, to define the optimal time window and temperature regimen necessary for maximal treatment efficacy if this technique is to alter the current pattern of acute stroke management in clinical practice.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Mack, Groysman, Emanuel. Drafting the article: Groysman. Critically revising the article: all authors.

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Decompressive hemicraniectomy after malignant middle cerebral artery infarction: rationale and controversies

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Malignant middle cerebral artery stroke carries a very poor prognosis. Significant retrospective data support the hypothesis that decompressive hemicraniectomy decreases mortality rates due to this disease entity. Recently, 3 randomized controlled studies have been published and shed light on these issues and enhance the quality of evidence revolving around this procedure. In this review, the rationale, risks, benefits, and unanswered questions related to hemicraniectomy for acute ischemic stroke are reviewed with an emphasis on how 3 randomized trials have influenced knowledge on this life-saving yet controversial procedure. Further randomized studies are needed to clarify lingering questions regarding age indications and impact on quality of life. *(DOI: 10.3171/2011.3.FOCUS1160)*

Key Words • **hemicraniectomy** • **craniectomy** • **randomized controlled trial** • **malignant stroke** • **patient outcome** • **quality of life**

Large ischemic strokes presenting as malignant cerebral edema account for 1%–10% of all ischemic strokes.[18] Mortality rates have been reported to be as high as 80%,[5] and most of the survivors are left severely disabled. An MCA infarction is the usual culprit, but the anterior and posterior cerebral arteries may additionally be affected. Early death is a result of transtentorial herniation while delayed death is typically due to the medical complications of prolonged hospitalization including pneumonia and pulmonary emboli.[22] Although decompressive craniectomy has been shown to significantly decrease mortality, high morbidity rates among survivors have tempered enthusiasm for this procedure. This reluctance has been most pronounced in elderly patients and those with dominant hemisphere infarcts. The span of the optimal operative time window when surgical decompression is superior to medical management alone is also subject to debate.

Abbreviations used in this paper: MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; RCT = randomized controlled trial.

Predictors of Malignant Cerebral Edema

Severely compressive brain edema is associated with significant mortality and morbidity. From a pathophysiological standpoint, early intervention could minimize secondary ischemia of viable tissue around the infarcted core and possibly prevent herniation. Optimal utility of this procedure would require identifying the population that is most likely to benefit in a way that meets patients' a priori expectations as well as those of their families and caretakers.

With that objective in mind and by using diffusion-weighted MR imaging, Oppenheim et al.[19] reported that a stroke volume greater than 145 cm^3 within 14 hours of onset of stroke symptoms has 100% sensitivity and 94% specificity for predicting the progression to malignant edema. Additionally, in a retrospective multicenter case-control study of 201 patients who suffered a massive MCA stroke, Kasner et al.[12] identified stroke volume greater than 50% of the MCA territory, high white blood cell count, additional involvement of the anterior or posterior cerebral artery, systolic blood pressure higher than 180 mm Hg within 12 hours of stroke onset, and a history

of hypertension or heart failure as additional risk factors for the progression toward malignant edema. Similarly, Krieger et al.[15] found that patients with an NIHSS score of 20 or greater on admission or who present with nausea or emesis are at high risk for developing malignant cerebral edema.

In addition to clinical and radiographic risk factors, serum levels of the astroglial protein S100B have been shown to be predictive of malignant cerebral edema with 94% sensitivity and 83% specificity (for a value of 1.03 μg/L at 24 hours from the ischemic event).[3] This may become a useful monitoring tool at crucial clinical time points at which the development of cerebral edema is believed to be an imminent possibility, once a commercially available bedside kit is available.

Best Medical Treatment

Optimal medical management for malignant edema due to stroke has not been standardized. In the HAMLET (Hemicraniectomy After Middle cerebral artery infarction With Life-Threatening Edema Trial), recommendations for medical management of stroke-related malignant edema included admission to the intensive care unit, osmotherapy with mannitol or glycerol, invasive monitoring of intracranial pressure, blood pressure control, elevation of the head to 30°, and maintenance of normothermia, normoglycemia, and normovolemia. Morbidity and mortality rates are high for this disease entity despite such aggressive measures.

Evidence for Decompressive Craniectomy

Craniectomy for the relief of cerebral edema associated with ischemic stroke was first described in the 1970s[8,14] and is intended to prevent life-threatening herniation. Although the impact on mortality appeared unequivocal in most studies, several controversies lingered and led to recent randomized trials, which are discussed below.

Data Prior to RCTs

Gupta et al.[4] performed a review of the literature in 2004, pooling all the data available up to that point. For the purposes of the review, good neurological outcome was defined as a Barthel Index of 60 or more, mRS score of 3 or less, or Glasgow Outcome Scale score of 4 or less. In the pooled analysis of 139 patients, the authors demonstrated a mortality rate of 24% after decompressive craniectomy with 42% of patients experiencing good neurological outcome. Of note, 80% of patients 50 years of age or older experienced poor neurological outcome (mRS Score 5 or 6 [severely disabled or dead]) following decompression. In the absence of randomized controlled data, questions remained regarding optimal patient selection, timing of therapy, and prognosis.

Randomized Controlled Trials: DECIMAL, DESTINY, and HAMLET

Given the unresolved questions regarding the role of decompressive craniectomy and appropriate patient selection, the following 3 RCTs were conducted, and the results were published recently (Table 1): DECIMAL (DEcompressive Craniectomy In MALignant middle cerebral artery infarcts) in France, published in 2007;[25] DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY) in Germany, published in 2007;[10] and HAMLET (Hemicraniectomy After Middle cerebral artery infarction With Life-Threatening Edema Trial) in the Netherlands,[6] published in 2009.

Study Design

In all 3 trials, patients were randomized to surgical treatment versus best medical management alone. The study design was similar in the 3 studies, but some noticeable differences are worthy of discussion. The 3 trials included patients with an age of 60 years and younger, and defined the primary outcome by the mRS score at 6

TABLE 1: Randomized controlled trials for hemicraniectomy in malignant cerebral edema*

Study Name	Year	No. of Pts	Inclusion Criteria	Time to Tx (hrs)	Primary Outcome Measure	Mortality (%)		Good Outcome	
						Surgical	Medical	Surgical	Medical
DESTINY	2007	32	age 18–60 yrs, NIHSS >18–20, >2/3 MCA territory	36	death at 30 days, mRS score <4 at 6 mos	17.6	53.0	47.0	27.0
DECIMAL	2007	38	age 18–55 yrs	24	mRS score <4 at 6 mos	25.0	77.8	50.0	22.2
HAMLET	2009	64	age 18–60 yrs	96	mRS score <4 at 12 mos	22.0	59.0	25.0	25.0
HeADDFIRST	NA	26	acute unilat MCA territory ischemia	96	death, functional outcome, quality of life, pt perceptions, acute health care use after 21, 90, & 180 days	results pending			
HeMMI	NA	NA	ischemic MCA stroke, GCS Score 6–14/5–9		GCS, NIHSS, mRS, & Barthel Index; functional outcome at 6 mos	recruiting patients			
DESTINY II	NA	NA	age ≥61 yrs, MCA malignant infarct	48	mRS score <5 at 6 mos	recruiting patients			

* GCS = Glasgow Coma Scale; NA = not available; Pt = patient.

months for DESTINY and DECIMAL and 1 year for the HAMLET (Table 2). The primary outcome was dichotomized between an mRS score of 0–3, defined as good outcome, and 4–6, defined as poor outcome. The crucial difference between a score of 3 and a score of 4 is that in the former, individuals still possess the ability to walk and attend to their bodily needs unassisted. A major difference in trial design was the time window for craniectomy. Surgical decompression was initiated within 24 hours of symptom onset in DECIMAL, between 12 and 36 hours in DESTINY, and within 96 hours in HAMLET.

After the completion of the HAMLET, the authors published pooled data from the 3 randomized trials.[7] The meta-analysis only included individuals treated within 48 hours of symptom onset from the HAMLET, thus excluding 11 patients and totaling 109 patients. Fifty-eight patients had been assigned to hemicraniectomy and 51 to medical treatment alone. The primary outcome was changed to include an mRS score of 4 in the good outcome category. The dichotomization was thus made between an mRS score of 1–4 for good outcome and an mRS of 5 or 6 for bad outcome.

TABLE 2: Modified Rankin Scale

Score	Definition
0	asymptomatic
1	no significant disability; able to carry out all usual activities, despite some symptoms
2	slight disability; able to look after own affairs w/o assistance, but unable to carry out all previous activities
3	moderate disability; requires some help, but able to walk unassisted
4	moderately severe disability; unable to attend to own bodily needs w/o assistance, unable to walk unassisted
5	severe disability; requires constant nursing care & attention, bedridden, incontinent
6	dead

Results of the RCTs

Effect on Mortality. The DECIMAL and DESTINY trials were stopped early in 2006 as ongoing data analysis demonstrated significant mortality reduction in the surgical group compared with those receiving medical treatment. All 3 of the European trials showed a significant reduction in mortality in patients belonging to the surgical arm, with an absolute risk reduction of 53% at 6 months in DECIMAL, and 38% at 1 year in HAMLET. DESTINY also showed a 12% mortality rate in surgically treated patients at 30 days, versus 53% in the medical treatment arm. In the meta-analysis, the absolute risk reduction in mortality with surgery was found to be 49.9% (95% CI 33.9%–65.9%), which meant that the number needed to treat to prevent death equaled 2. The authors concluded that surgical decompression within 48 hours of stroke onset reduced the risk of death.

Effect on Severe Disability (mRS Score 5). The DECIMAL, DESTINY, and HAMLET studies showed a statistically significant reduction in severely disabled, bedridden patients (mRS score > 4). In the pooled analysis of the 3 pooled studies, the absolute reduction in risk for a bad functional outcome was 41.9% (95% CI 25.2%–58.6%). As a result, the authors concluded that surgical decompression within 48 hours of stroke onset reduced the risk of significant morbidity.

Effect on Moderately Severe Disability (mRS Score 4). The primary outcome measure in the 3 RCTs defined a good outcome as an mRS score of 3 or less. The goal was to prove a significant reduction in the number of patients unable to attend to their bodily needs or walk unassisted (mRS score of 4). Unfortunately, none of the 3 trials reached statistically significant conclusions favoring a good functional outcome after craniectomy as defined by their primary outcome measure, although there was a trend in this direction in DESTINY and DECIMAL studies. This conclusion may not have reached statistical significance because of the small number of patients included in both trials, since they were prematurely terminated. Additional studies with larger patient groups are needed before drawing definite conclusions.

Disability in Survivors. Separate and pooled analyses of the DECIMAL, DESTINY, and HAMLET trials, while demonstrating an undeniable increase in the number of survivors among surgical patients, also showed an increase in the number of survivors with moderately severe disability (mRS score of 4). This fact necessitates careful discussion with the patient's family and/or power of attorney to be sure that outcomes associated with craniectomy are in keeping with patient wishes. Quality of life issues are difficult to put in proper perspective, but the randomized studies discussed above help clarify some facets of this important subject. Future studies will need to focus more rigorously on the long-term quality of life in survivors. There exists a difficult balance between increasing survival and poor neurological outcome, which inherently includes the subjective assessment of outcome along a continuum.[20,23] Further investigations regarding the neurological outcome of patients after decompression, as well as better standardization of functional outcome measures in larger series, is certainly warranted.

Dominant Hemisphere Involvement

While the fear of complete aphasia was classically the reason behind the refusal to operate on large dominant hemispheric strokes, recent data have suggested that nondominant hemispheric injuries leading to serious depression and neglect can be as disabling as aphasia during the rehabilitation process.[27] Additionally a subset analysis in the DECIMAL trial showed no difference in the mRS scores of survivors with or without aphasia at 1 year; in addition, all surgical survivors agreed with the decisions to undergo surgery when asked retrospectively, including patients still experiencing aphasia.[16] Stroke laterality and its correlation with outcome[4,17,21] have also been the subject of subgroup analysis in the other European trials,[6,7,10,24,25] and controlled and uncontrolled studies have

shown no predicative value for outcome related to laterality. Clearly this issue will continue to warrant debate and should be further studied.

Surgical Technique and Craniectomy Size

Wagner et al.[26] retrospectively reviewed 60 patients who were admitted with malignant MCA infarcts. They studied the impact of craniectomy size, shape, and location on parenchymal hemorrhagic and ischemic lesions, postoperative bleeding, and mortality. Interestingly, they found a 70% rate of hemicraniectomy-associated infarcts and hemorrhage. Bleeding was associated with a small craniectomy size and sharp bone defects. Parenchymal hemorrhage was the only factor that statistically affected mortality rate, with only 55% of patients surviving compared with 80% in the absence of hemorrhage. Their recommendation for craniectomy size was a diameter larger than 12 cm. This conclusion is validated by the fact that some studies suggest that doubling the diameter from 6 cm to 12 cm potentially increases the decompressive volume from 9 to 86 ml.[26,29] Ideally, hemicraniectomy should be performed in the frontotemporoparietal region and reach the floor of the middle cranial fossa. The midline should be spared to avoid injury to the superior sagittal sinus.

Surgical Complications

The outcomes of patients undergoing decompressive craniectomy may be impacted by the complications of the procedure.[23] Reported complications include inadequate decompression,[26] infection,[2] hemorrhage, and the development of contralateral fluid collections.[13] Furthermore, delayed sinking flap syndrome may result in headaches, seizure and focal neurological deficits and is typically cured by replacement of the bone flap.[1] Similarly, hydrocephalus may develop in a delayed fashion.[28]

Time Window for Surgery

The question of the optimal time window for intervention has not yet been completely elucidated. Although the pooled data from the European trials seem to show benefit from early surgery, only a small number of patients (11) was included in the late group in the HAMLET, and definite conclusions cannot be drawn at this time.[23] Additionally, a major systematic review of the literature did not demonstrate a difference in outcome based on timing.[4] Clear definition of a time window for intervention will be essential to creating treatment guidelines. With that purpose in mind, 2 additional RCTs have been initiated. The North American HeADDFIRST (Hemicraniectomy And Durotomy on Deterioration From Infarction Related Swelling Trial), aimed to evaluate patient outcome after hemicraniectomy within 96 hours from symptom onset, and is awaiting publication. The HeMMI trial (Hemicraniectomy for Malignant Middle cerebral artery Infarcts) in the Philippines, is studying patient morbidity and mortality after decompressive surgery within 72 hours from symptom onset and is still in the process of recruiting patients.

Surgical Age Limit

As noted above, randomized trials to date have focused on patients 60 years of age and younger, thus leaving us with very few data regarding patients older than 60 years of age. The HAMLET displayed conflicting results with previous review series,[4] with a trend toward better outcome in the upper age categories (51–61 years). These results raised questions about the existence of an age limit for surgical benefit. The DESTINY 2 trial is currently underway and will shed more light on the impact of surgery in patients older than 60 years.[9]

Conclusions

Pooled analysis of the European trials discussed above provides Class I evidence for the performance of early decompressive craniectomy in the setting of large unilateral infarcts (volume > 145 cm^3) within 48 hours of the ischemic event.[11] Given the potential tradeoff between survival and good neurological outcome, frank discussion with the patient and the family should be held early in the setting of an envisioned need for surgical decompression, while keeping in mind that 2 RCTs reported a trend of reduced disability among survivors. Although the surgical age limit has not yet been fully defined, very few data exist to support hemicraniectomy for patients older than 60 years, although individual circumstances may outweigh paucity of data issues. Further studies are needed to better define quality of life issues at long-term follow-up as well as age limit issues. Ultimately, MCA infarction with malignant edema is a devastating disease for which hemicraniectomy can play a positive role. New strategies are needed to enhance long-term outcomes, which will likely extend across the entire stroke continuum from the acute phase to the rehabilitation period.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bendok, Batjer, Arnaout, Aoun. Acquisition of data: Arnaout, Aoun. Analysis and interpretation of data: Arnaout, Aoun. Drafting the article: Arnaout, Aoun. Critically revising the article: Bendok, Batjer.

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Determination of geographic variance in stroke prevalence using Internet search engine analytics

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Object. Previous methods to determine stroke prevalence, such as nationwide surveys, are labor-intensive endeavors. Recent advances in search engine query analytics have led to a new metric for disease surveillance to evaluate symptomatic phenomenon, such as influenza. The authors hypothesized that the use of search engine query data can determine the prevalence of stroke.

Methods. The Google Insights for Search database was accessed to analyze anonymized search engine query data. The authors' search strategy utilized common search queries used when attempting either to identify the signs and symptoms of a stroke or to perform stroke education. The search logic was as follows: (stroke signs + stroke symptoms + mini stroke – heat) from January 1, 2005, to December 31, 2010.

The relative number of searches performed (the interest level) for this search logic was established for all 50 states and the District of Columbia. A Pearson product-moment correlation coefficient was calculated from the state-specific stroke prevalence data previously reported.

Results. Web search engine interest level was available for all 50 states and the District of Columbia over the time period for January 1, 2005–December 31, 2010. The interest level was highest in Alabama and Tennessee (100 and 96, respectively) and lowest in California and Virginia (58 and 53, respectively). The Pearson correlation coefficient (r) was calculated to be 0.47 ($p = 0.0005$, 2-tailed).

Conclusions. Search engine query data analysis allows for the determination of relative stroke prevalence. Further investigation will reveal the reliability of this metric to determine temporal pattern analysis and prevalence in this and other symptomatic diseases. *(DOI: 10.3171/2011.2.FOCUS1124)*

Key Words • **search engine** • **stroke** • **epidemiology** • **prevalence** • **public health**

Stroke represents one of the leading causes of morbidity and death in the US.[6] An estimated 795,000 new strokes occur each year in the US, making it the third overall leading cause of death in America.[5] Surveillance data has been notoriously difficult to obtain due to sampling ability and reporting bias. In 2007 the Centers for Disease Control and Prevention analyzed the 2005 Behavioral Risk Factor Surveillance System (BRFSS) survey and reported the first state-specific variability in stroke prevalence.[7] The prevalence estimates from the BRFSS are produced from a state-based, random-digit-dial telephone survey, a method that is probably costly and labor intensive.

Recent advances in search engine queries have led to the development of a new metric for disease surveillance to evaluate symptomatic phenomena in the infectious disease literature. Because about 90 million American adults are believed to search online for information about specific diseases or medical problems each year,[2] Internet search engine data represent a potentially valuable source of information about health trends. Recently, an analysis of the frequency of queries related to influenza infection was highly correlated with the percentage of physician visits in which a patient presented with influenza-like symptoms.[3] Essentially, near real-time prevalence data are available using search engine query data. With this in mind, we hypothesized that the use of search engine query data could determine the prevalence of a noninfectious but symptomatic disease: stroke.

Abbreviation used in this paper: BRFSS = Behavioral Risk Factor Surveillance System.

TABLE 1: Interest level and stroke prevalence for 50 states and the District of Columbia for January 1, 2005–December 31, 2010

State	Interest Level	Stroke Prevalence*
Alabama	100	3.2
Alaska	64	2.5
Arizona	82	2.1
Arkansas	90	3.0
California	58	2.6
Colorado	77	1.7
Connecticut	67	1.5
Delaware	68	2.6
District of Columbia	70	3.4
Florida	82	2.8
Georgia	84	2.9
Hawaii	74	2.8
Idaho	76	2.4
Illinois	77	3.0
Indiana	82	2.5
Iowa	73	2.6
Kansas	78	2.3
Kentucky	93	3.1
Louisiana	89	3.3
Maine	79	2.4
Maryland	79	2.1
Massachusetts	71	2.1
Michigan	83	3.0
Minnesota	77	1.7
Mississippi	92	4.3
Missouri	90	3.1
Montana	74	2.1
Nebraska	82	2.2
Nevada	74	3.2
New Hampshire	72	2.6
New Jersey	74	2.1
New Mexico	81	2.2
New York	68	2.4
North Carolina	90	2.8
North Dakota	82	1.8
Ohio	83	2.3
Oklahoma	93	3.4
Oregon	78	2.5
Pennsylvania	82	2.2
Rhode Island	68	2.1
South Carolina	87	2.9
South Dakota	89	2.6
Tennessee	96	3.1
Texas	84	3.0
Utah	87	2.6
Vermont	71	2.1
Virginia	53	2.7
Washington	69	2.4
West Virginia	90	3.0
Wisconsin	76	1.9
Wyoming	67	1.9

* Percentage of respondents ages ≥ 18 years who reported a history of stroke.

Methods

We accessed the Google Insights for Search database (Google, Inc.) to analyze anonymized search engine query data (http://www.google.com/insights/search). This database contains 50 million of the most common search queries on all possible topics, without prefiltering. While billions of search queries occur every day, only those that occur frequently are included in the database. The Internet protocol (IP) address associated with each search query is recorded, allowing the location of each search to be determined to the nearest major city within the US.

Our search strategy utilized common search queries that either a patient or a patient's representative might use when attempting to identify the signs and symptoms of a stroke or to perform stroke education. Our search logic (stroke signs + stroke symptoms + mini stroke – heat) included all dates from January 1, 2005, to December 31, 2010. The term "– heat" was used to exclude all queries relating to heat stroke. We filtered for Web searches only and included all search categories.

The relative number of searches performed for this search logic was established relative to the total number of searches performed on Google over the same amount of time for all 50 states and the District of Columbia. All data were normalized and then scaled (interest level). A Pearson product-moment correlation coefficient was then calculated from the state-specific stroke prevalence data previously reported.[7]

Results

The Web search engine interest level was available for all 50 states and the District of Columbia for the time period from January 1, 2005, to December 31, 2010. Interest level was highest in Alabama and Tennessee (100 and 96, respectively) and lowest in California and Virginia (58 and 53, respectively) (Table 1 and Fig. 1). The Pearson correlation coefficient calculated with previously reported state prevalence rates was determined to be 0.47 ($p = 0.0005$, 2-tailed; Fig. 2).[7]

Discussion

We analyzed a large database of search engine queries to identify searches related to stroke. Previous methods for

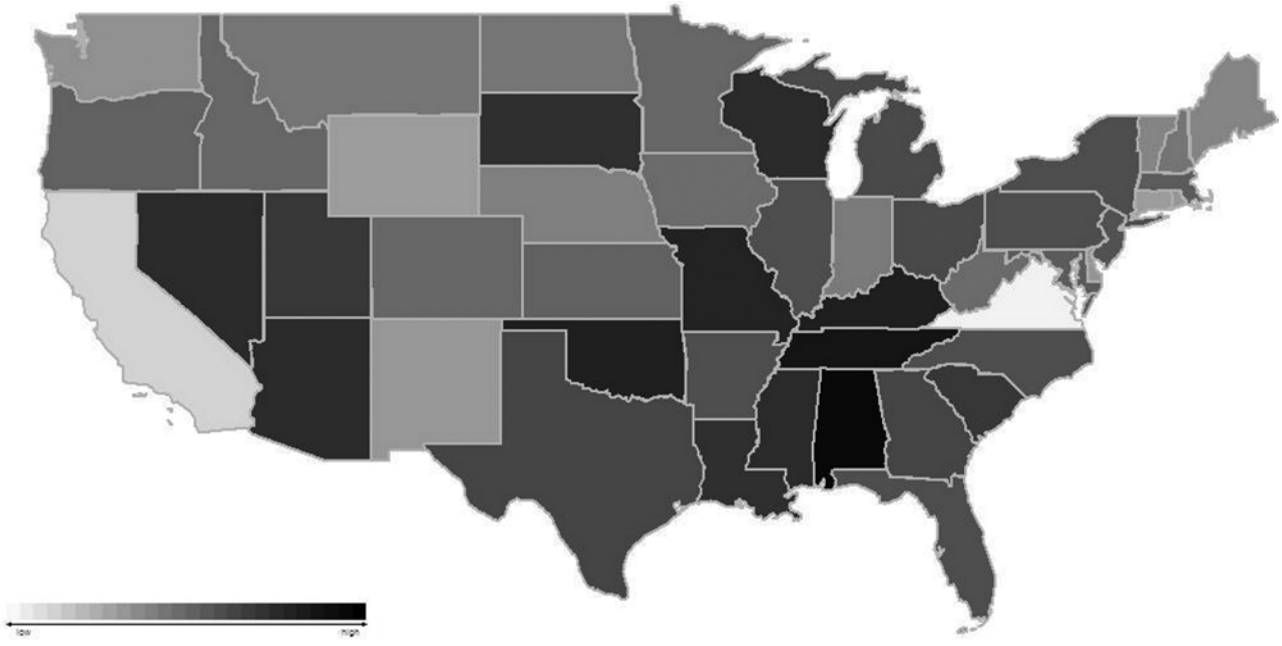

Fig. 1. Map demonstrating the search volume index (interest level) in the US from January 1, 2005, to December 31, 2010.

prevalence analysis, such as survey methods, are time and labor intensive. Based on the previously demonstrated effectiveness of search engine analytics to identify epidemiological data for symptomatic disease, we hypothesized that this tool could be used as a surrogate marker for actual disease prevalence. The Pearson correlation coefficient of 0.47 is moderate but should be interpreted with caution, as outliers can skew data interpretation.[1] The state-specific

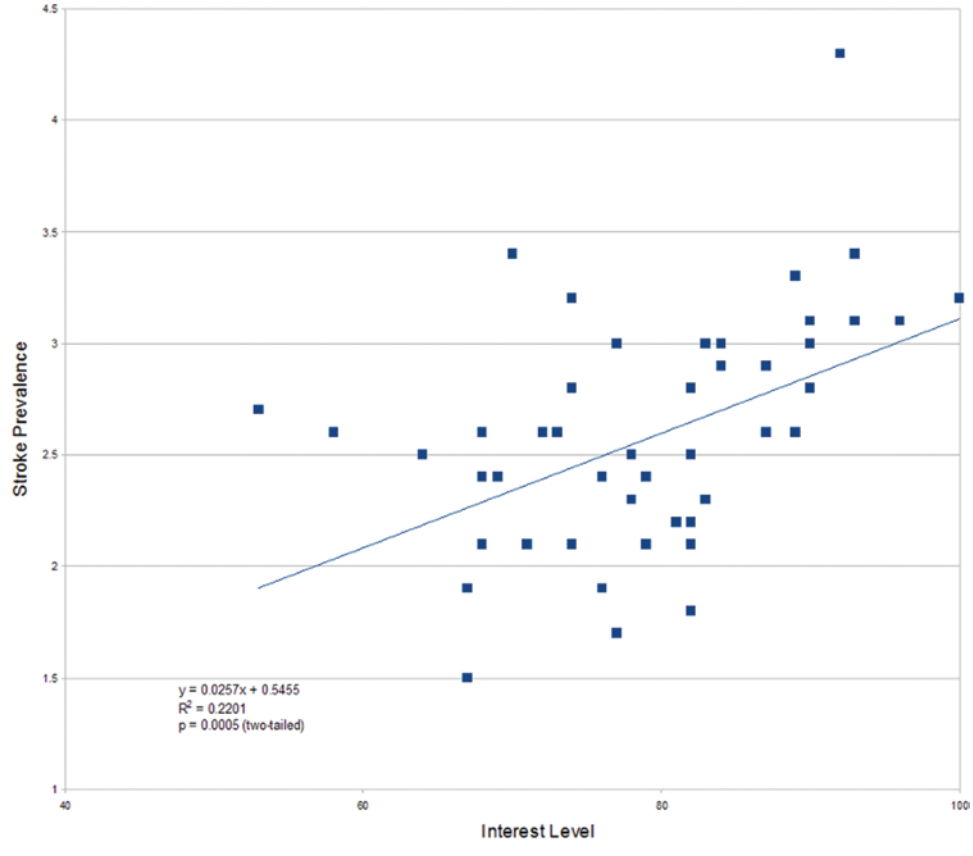

Fig. 2. Scatterplot of interest level in the US from January 1, 2005, to December 31, 2010, and stroke prevalence defined by state/area using the BRFSS, US, 2005 (r = 0.47, p = 0.0005, 2-tailed).

dataset used for comparison is itself estimated and admittedly limited.[7]

Many states with the highest Internet interest estimates are concentrated in the southeast US, such as Alabama, Mississippi, and Arkansas. These correspond to the high rates of stroke prevalence previously observed in this region, which has been traditionally called the "stroke belt."[4] However, certain states outside of this region, such as Oklahoma, Missouri, and West Virginia, also had Internet interest levels among the highest in the country. This finding correlates with the 2005 Centers for Disease Control and Prevention BRFSS survey and can be explained by geographic differences in risk factors associated with stroke, such as race, obesity, diet, diabetes mellitus, and socioeconomic status. When using Internet interest estimates as surrogate markers for disease prevalence, major geographic disparities continue to exist.

In the same manner that patients with symptoms of the flu use a search engine to investigate their symptoms, stroke symptoms are plausibly entered into search engines at the onset of stroke-like symptoms, transient ischemic attack, or stroke. This can be accomplished by either the patients themselves or, depending on the clinical condition, their representative. Additionally, these search queries may be entered at any time after a stroke and do not necessarily depend on patient survival.

Search engine query data represent self-reported disease history in its purest form; it is generated from the patient or their representative of their own accord and in a private setting. A major limitation of this analysis is the user-generated misinterpretation of symptoms as those of stroke. Many different conditions could masquerade as stroke, falsely increasing the estimated prevalence. Another limitation of this methodology is that Internet access is not uniform and, in particular, may not be readily accessible to persons living in nursing homes, prisons, military bases, or other institutions. Internet use also varies widely by sex, socioeconomic background, and English literacy.[6,9] The geographic distribution by state of reported Internet usage for individuals is varied;[8] however, our model normalizes for overall search engine traffic.

The heterogeneity of stroke symptoms precludes the analysis of individual query terms. The disease-specific search, related to stroke, was made the core of our model. The identification of these geographic differences provided a metric to evaluate health disparities, allowing for the potential to direct public health programs related to stroke risk-factor prevention and educational measures in disproportionately affected states.

Conclusions

Search engine query data analysis allows for the determination of relative stroke prevalence in the US. Further investigation will reveal the reliability of this metric to determine temporal pattern analysis and prevalence in other symptomatic diseases.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Walcott. Acquisition of data: Walcott. Analysis and interpretation of data: Walcott, Redjal. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Walcott, Coumans. Study supervision: Coumans.

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Moyamoya disease: a review of histopathology, biochemistry, and genetics

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Object. Moyamoya disease (MMD) is a rare cerebrovascular disorder involving stenosis of the major vessels of the circle of Willis and proximal portions of its principal branches. Despite concerted investigation, the pathophysiology of the disorder has not been fully elucidated. Currently, the major proteins believed to play an active role in the pathogenesis include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), transforming growth factor–β_1 (TGFβ_1), and granulocyte colony-stimulating factor (G-CSF). In terms of the genetics, recent literature suggests a low penetrance autosomal dominant or polygenic mode of transmission involving chromosomes 3, 6, 8, 12, and 17 for familial MMD. This review summarizes the current knowledge on the histopathology, pathophysiology and genetics of MMD.

Methods. A PubMed/Medline systematic study of the literature was performed, from which 45 articles regarding MMD pathophysiology were identified and analyzed.

Conclusions. Moyamoya disease is characterized by the intimal thickening and media attenuation of the proximal vessels of the circle of Willis as well as the development of an aberrant distal vascular network. The primary proteins that are currently implicated in the pathophysiology of MMD include VEGF, bFGF, HGF, TGFβ_1, and G-CSF. Furthermore, the current literature on familial MMD has pointed to a low penetrance autosomal dominant or polygenic mode of transmittance at loci on chromosomes 3, 6, 8, 12, and 17. *(DOI: 10.3171/2011.3.FOCUS1151)*

Key Words • **moyamoya disease** • **histopathology** • **biochemistry** • **genetics**

Initially defined in 1969 by Suzuki and Takaku,[31] moyamoya disease is an uncommon, progressive cerebrovascular disease involving spontaneous occlusion of the vessels of the circle of Willis and its principal branches, with a predilection for the internal carotid arteries.[7] The generally bilateral stenosis coincides with the development of an aberrant network of collateral circulation vessels that leads to hemorrhagic and ischemic strokes. The term "moyamoya" in Japanese means a "hazy puff of smoke," in reference to the characteristic appearance of the collateral vessels on cerebral angiography (Fig. 1).

While MMD is most prevalent in Japan, its presence has been reported in various populations around the world.[1] The disease still appears to be more prevalent in east Asian countries including inland China, which has had an increasing incidence over the past decade.[23] A national study in Japan has reported the incidence of MMD to be 0.35 per 100,000,[37] whereas an analysis of the western US identified a significantly lower incidence of 0.086 per 100,000.[35] Potentially indicative of a genetic component, Asian-Americans in the western US were affected on the order of 0.28 per 100,000, an incidence much more comparable to the Japanese incidence.[35] Also, prevalence in females is slightly higher than that in males with a ratio of 1.8:1.[3]

Moyamoya disease can be organized as follows: ischemic, hemorrhagic, epileptic, and other;[6] however, no specific pathophysiological distinctions have been established between these presentation categories. More commonly the disease is organized into adult and pediatric subtypes. Children are more likely to suffer from ischemia, while adults do not have a specific predilection for ischemic or hemorrhagic complications.[9,13,19] Furthermore, pediatric patients suffer significantly greater cognitive impairment.[17] This review includes a discussion of the pathophysiology of MMD with an emphasis on the current understanding of potential angiogenic agents and underlying genetic factors contributing to MMD presentation.

Abbreviations used in this paper: bFGF = basic fibroblast growth factor; G-CSF = granulocyte colony-stimulating factor; HGF = hepatocyte growth factor; MLS = maximum $\log_{10}$ odds (LOD) score; MMD = moyamoya disease; MMP = matrix metalloproteinase; TGF = transforming growth factor; VEGF = vascular endothelial growth factor.

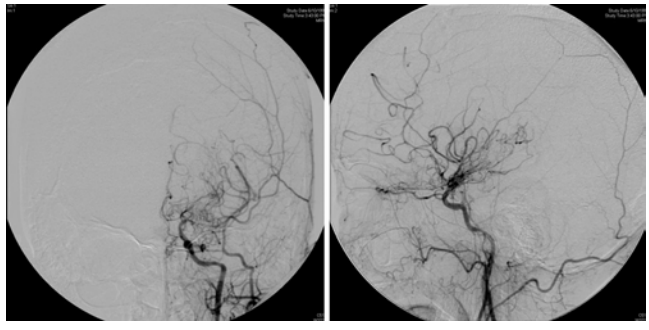

Fig. 1. Anteroposterior **(left)** and lateral **(right)** digital subtraction angiograms of the left internal carotid artery demonstrating the characteristic collateral vessels of MMD.

Methods

For this review, a systematic search of the English-language literature was performed with the PubMed/Medline database using the key words and various combinations of the key words: "moyamoya disease," "pathology," "genetics," and "angiogenic proteins." This search initially retrieved 112 articles, the abstracts of which were independently reviewed by 2 authors (D.G.W. and O.M.A.) for relevance to the topics of moyamoya pathophysiology or genetics. Reference lists of the relevant articles were reviewed for additional sources, and 43 articles were included in the final review.

Results and Discussion

Although the exact pathophysiology of MMD is yet to be fully elucidated, there have been several recent strides toward that goal. We reviewed the histopathology of the disease, and follow this by a discussion of suspect contributory angiogenic factors and their genetic underpinnings.

Histopathology

The large vessels of the circle of Willis, in the setting of MMD, typically display fibrocellular thickening of the tunica intima with excessive proliferation of the vascular smooth-muscle cells, marked tortuousness of the internal elastic lamina, and attenuation of the tunica media (Fig. 2).[34]

The distal collateral vascular networks that are characteristic of MMD, however, commonly demonstrate an irregular-shaped lumen with either intimal wall thickening or thinning consistent with the angiographic appearance of abnormal angioarchitecture (Fig. 3).[34]

Biochemistry and Angiogenic Factors

As a response to both hypoxia and decreased blood flow, angiogenic agents are generated in supraphysiological concentrations (Table 1).[12,20,25,27,42] These proteins induce the revascularization of the distal hypoperfused regions by forming the fragile collateral moyamoya vessels, which are implicated in the hemorrhagic presentations of MMD.

The potential impact of intraarterial microthrombi in the stenotic vasculature of MMD has been a point of contention. In their series, Yamashita et al.[40] noted the presence of thrombi in 16 of 22 patients with MMD and concluded that the thrombi were closely related to the development of a thickened intima in the intracranial arteries. They attributed this pathological development to the thrombotic components, such as platelets and plasma constituents. Furthermore, Bonduel and colleagues[2] presented evidence relating pediatric MMD to prothrombotic disorders including inherited protein S deficiency, lupus anticoagulant, and anticardiolipin antibodies in MMD. Masuda et al.,[22] however, found microthrombi to be absent in 5 of 6 patients. Furthermore, they noted the infiltration of macrophages and T cells in nonstenosed areas of the vessels, and they suggested that the microthrombi may be a result of the chronic inflammation rather than

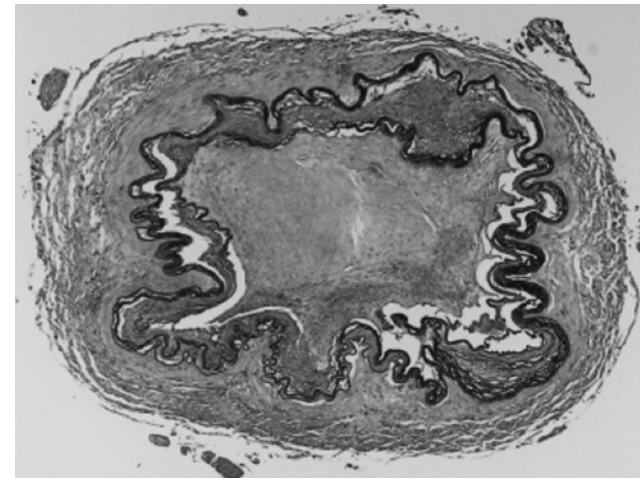

Fig. 2. Microscopic findings in the left middle cerebral artery showing obstruction of the lumen, fibrocellular intimal thickening, marked tortuousness of the internal elastic lamina, and attenuation of media. Elastica H & E, original magnification × 40. Reprinted from Takekawa et al: Pathological and immunohistochemical findings of an autopsy case of adult moyamoya disease. **Neuropathology 24:**236–242, 2004, with permission from John Wiley and Sons.

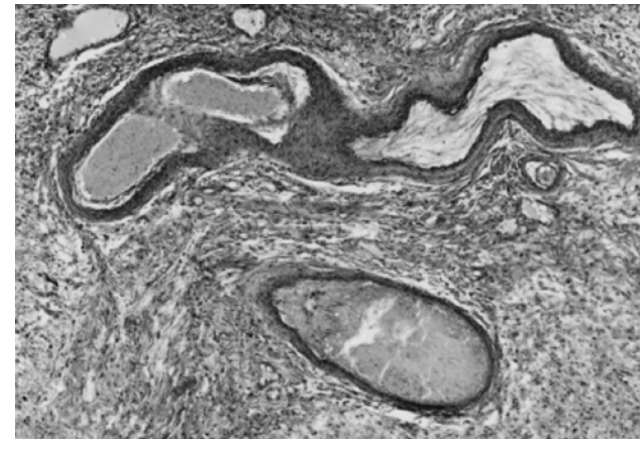

Fig. 3. Microscopic findings of peripheral portion of arteries in the left temporal lobe demonstrating dilated or irregular-shaped lumen and occasionally thickened intima. Elastica H & E, original magnification × 40. Reprinted from Takekawa et al: Pathological and immunohistochemical findings of an autopsy case of adult moyamoya disease. **Neuropathology 24:**236–242, 2004, with permission from John Wiley and Sons.

TABLE 1: Proteins implicated in the pathophysiology of MMD and resulting concentrations of their overexpression in MMD*

Protein	Mature Protein Weight (kDa)	Amino Acid Residues	Mean Overexpressed Concentration in MMD	Mean Control Concentration
VEGF	45.0[24]	121[24]	51.1%[18]†	13.8%[18]†
bFGF	18.0[25]	146[25]	64.0 pg/ml[19]	6.5 pg/ml[19]
HGF	103.0[26]	728[26]‡	820.3 pg/ml[17]	a) 408.2 pg/ml[17]; b) 443.2 pg/ml[17]
TGFβ_1	25.0[27]	112[27]	31.0 ng/ml[15]	11.0 ng/ml[15]
G-CSF	19.6[28]	174[28]	35.7 pg/ml[16]	19.6 pg/ml[16]

* Superscripted numbers refer to citations in the *References* section.
† Percentage of meningeal cellularity.
‡ HGF is transcribed as a 728 amino acid peptide and cleaved to fewer residues in its active form.

a cause. In either case, the observation of microthrombi is not specific to MMD and therefore is unlikely to provide a complete explanation for its pathophysiology.[3] It is also worth noting that although an infectious etiology has been postulated, there has been no significant confirmatory evidence to date.[38]

Specific proteins known to be expressed in abnormal quantities in MMD have been investigated in an attempt to better understand the molecular pathophysiology of the disease (Table 1).

Vascular Endothelial Growth Factor. Vascular endothelial growth factor is a 45-kD homodimeric, basic glycoprotein that binds heparin to function.[29] It plays a central role in pathological vasculogenesis and vascular permeability in intracranial lesions. Similarly, upregulated expression of VEGF-A_{165} in the β cells of pancreatic islets of Langerhans cells in mice has been shown to accelerate the onset of angiogenesis and tumor progression.[8] Additionally, VEGF has been shown to promote angiogenesis in the setting of cerebral ischemia.[27]

In the setting of MMD, supraphysiological expression of VEGF is seen around the affected vasculature. In a study of 11 patients, Sakamoto et al.[27] noted that the mean VEGF expression, or "meningeal cellularity," was 51.1% ± 4.9% in MMD compared with 13.8% ± 5.9% in control patients. Whereas Takekawa et al.[34] had previously identified VEGF in glial cells in autopsy studies of an adult MMD patient, Sakamoto et al. additionally localized VEGF to the dura mater in such cases. The presence of VEGF in the dura is an interesting finding that hints at extension of the pathological mechanisms of MMD beyond the cerebral vasculature. Although its excess concentration in MMD has been demonstrated, the specific role of VEGF in the pathophysiological mechanism of MMD remains unclear.

Basic Fibroblast Growth Factor. Basic fibroblast growth factor is an 18-kD protein generally made up of 146 amino acids.[26] It normally stimulates the proliferation of mesodermal and neuroectodermal cells,[36] and it has also been shown to induce growth of vascular smooth muscle and, when combined with VEGF, can play a leading role in angiogenesis.

Basic fibroblast growth factor has been shown to be abnormally elevated in the CSF of MMD.[33,42] Takahashi et al.[33] measured bFGF in the CSF of 15 patients with MMD (101 pg/ml) relative to patients with atherosclerotic and disc disease (8 pg/ml and 0 pg/ml, respectively). Yoshimoto et al.[42] similarly demonstrated elevated bFGF concentration in the CSF of MMD patients compared with the control group; with the mean bFGF in the CSF of MMD patient of 64.0 pg/ml compared with 6.5 pg/ml in controls. Furthermore, the presence of bFGF has been noted in the abnormally thickened tunica media, leading Yoshimoto et al. to indicate that the high levels of bFGF in MMD contribute significantly to both the stenosis and angiogenesis.

Hepatocyte Growth Factor. Hepatocyte growth factor is one of the largest disulfide-linked cytokines, and in humans the protein is synthesized as a single-stranded 728 amino acid protein. The 95-kD peptide consists of a 60-kD heavy chain and 35-kD light chain. Proteolytic activation of HGF involves the release of a 31 amino acid N-terminal signal peptide. The active protein has been found to stimulate proliferation of rat hepatocytes and stimulate the growth of various epithelial, endothelial, and mesenchymal cells.[10]

Nanba et al.[25] found a significant increase in both HGF and its receptor c-Met in the tunica media and intima of patients with MMD relative to 2 control groups: while the mean HGF in the CSF was 820.3 pg/ml in patients with MMD, it was 408.2 pg/ml in patients with cervical spondylosis and 443.2 pg/ml in those with unilateral internal carotid artery occlusion. The authors hypothesized that HGF overexpression leads to intimal thickening and vascular smooth-muscle cell migration.

Transforming Growth Factor–β_1. Transforming growth factor–β_1 is transcribed as a 390 amino acid peptide that is proteolytically activated to form the active 112 amino acid monomeric form of the active TGFβ_1 homodimer. It is a cytokine that is implicated in various cellular processes including cell growth, proliferation, and differentiation.[4] In normal concentrations, TGFβ_1 is involved in the expression cascade of various connective-tissue genes, whereas in supraphysiological concentrations it may contribute to pathological angiogenesis.[12]

Transforming growth factor–β_1 has also been implicated in the pathogenesis of MMD. Upregulation of TGFβ_1 has been demonstrated by Hojo et al.[12] who re-

ported serum TGFβ_1 levels in MMD patients of 31 ng/ml compared with 11 ng/ml in the control group.[12] Furthermore, no significant difference in serum levels of TGFβ_1 has been shown between patients with atherosclerosis and normal controls.[11] Therefore, a specific correlation has been speculated between TGFβ_1 and neovascularization in MMD.[12] Additionally, TGFβ_1 has been linked to the excessive production of elastin synthase, which is involved in intimal cell proliferation, a hallmark of MMD.[39]

Granulocyte Colony-Stimulating Factor. Granulocyte colony-stimulating factor predominates as a 174 amino acid mature protein weighing 19.6 kD.[43] It is a glycoprotein, growth factor, and cytokine, the main function of which is the stimulation of proliferation, survival, and maturation of neutrophil precursors and mature neutrophils.

An elevated concentration of G-CSF in the setting of MMD has been demonstrated by Ma et al.[20] with mean serum G-CSF concentration of 35.7 pg/ml and 23.5 pg/ml in patients with MMD and controls, respectively. The role which G-CSF plays in the pathogenesis of MMD has yet to be elucidated.

Other Proteins. In addition to the aforementioned major proteins, other proteins have been found, with limited evidence, to be elevated in MMD. Specifically, prostaglandin E_2,[39] interleukin-1β,[39] and cellular retinoic acid binding protein 1[18] have been shown to be increased in concentration. Furthermore, Soriano and associates[30] have demonstrated that several soluble endothelial adhesion molecules were elevated in the CSF of patients with MMD, suggesting chronic CNS inflammation. These included vascular cell adhesion molecule Type 1, intercellular adhesion molecule Type 1, and E-selectin. Additionally, hypoxia inducible factor–1α, which promotes smooth-muscle cell proliferation in the presence of bFGF and HGF, is present in elevated levels in MMD.[32]

Recently, Fujimura et al.[5] examined the serum levels of MMP-2 and -9 in 16 patients with MMD. Both MMP-2 and -9 (gelatinase A and B, respectively) diminish the impenetrability of the blood-brain barrier by interrupting the endothelial basal lamina. Both MMP-2 and -9 are involved in the pathophysiology of cerebral ischemia, formation, and rupture of cerebral aneurysms, as well as other CNS pathologies. Fujimura et al. found the serum level of MMP-9 to be significantly higher in patients with MMD than in healthy controls ($p = 0.0372$). No significant difference was seen in serum MMP-2 levels between the groups. This first study of MMPs in MMD may indicate a contribution to the pathological vascular instability, although further study is necessary before conclusions can be drawn.

Genetics

It has been suggested that in some Japanese families MMD may be transmitted through a polygenic or autosomal dominant mode with low penetrance.[41] Although familial occurrence accounts for approximately 9% of MMD cases, the majority of cases are sporadic.[3,21] Linkage analyses have shown associations with loci 3p24.2–p26,[15] 6q25,[16] 8q23,[28] 12p12,[28] and 17q25[24] (Table 2).

TABLE 2: Genetic loci associated with familial MMD and subsequent candidate genes at surrounding loci

Gene Loci	MLS	Suggested Candidate MMD Genes
3p24.2–p26[39]	1.5	genes encoding Marfan syndrome & von Hippel–Lindau disease
6q25[40]	1.6	*HLA*
8q23[41]	3.6	*TIEG, ANGPT1, TIE2, EBAG9, DD5*
12p12[41]	2.3	none
17q25[42]	3.1,* 4.6†	*BAIAP2*

* Two-point MLS.
† Multipoint MLS.

In a linkage study of 16 Japanese families with familial MMD, Ikeda et al.[15] reported that chromosome 3 was associated with MMD. They found that the patients' microsatellite polymorphism mapped to chromosome 3p24.2–p26 with an MLS of 1.5. Other genes mapping to the 3p chromosome are those responsible for Marfan syndrome and the *von Hippel–Lindau disease* gene responsible for hemangioblastoma, and the authors suggest that the proposed locus on chromosome 3p may encode a gene product that is principally important for the formation and maintenance of vascular wall homeostasis.[15]

A similar approach was taken by Inoue et al.[16] with the analysis of chromosome 6. The authors performed a linkage study to confirm their hypothesis that familial MMD is associated with human leukocyte antigens (HLAs). The *HLA* gene is located on chromosome 6, and a marker in chromosome 6q25 was shared by 16 of 19 Japanese families with MMD that were studied. Human leukocyte antigens tend to be associated with virus-related tumors, autoimmune, and infectious diseases.[14] Such associations are found in Takayasu arteritis and systemic lupus erythematosus. However, pathophysiological links between familial MMD and these other disease processes require further study.[16]

A 2004 study by Sakurai et al.[28] screened 12 nuclear families with MMD and found significant evidence for linkage to chromosome 8q23 (MLS 3.6) and suggestive evidence for linkage to 12p12 (MLS 2.3). The gene encoding *TIEG* (TGFβ_1–inducible early growth response) is located in chromosome 8q22.3. Because *TIEG* plays an active role in TGFβ_1 expression, it may be a candidate gene for MMD. Another candidate gene located in the 8q linkage is *ANGPT1*, a secreted ligand for *TIE2*, which is a receptor-like tyrosine kinase necessary for the normal development of vascular structures during embryogenesis. Furthermore, the authors proposed that *EBAG9* and *DD5*, a progestin-induced protein, may regulate angiogenesis through VEGF expression.

The study of chromosome 17 in relation to MMD began with Yamauchi et al.[41] in their microsatellite linkage analysis. The characteristic lesions associated with MMD are occasionally seen in neurofibromatosis Type 1. The causative gene for neurofibromatosis Type 1 has been localized to 17q11.2. The research team members extracted leukocyte DNA from members of 24 families with MMD, and they subjected the DNA to polymerase chain reaction for 22 microsatellite markers on chromo-

some 17. They used both 2-point and multipoint linkage analyses and localized a gene for familial MMD on chromosome 17q25 (2-point MLS 3.1; multipoint MLS = 4.6).

Recently, Mineharu and coworkers[24] further investigated the involvement of chromosome 17 in MMD. The authors found that penetrance was partly age dependent and involved genomic imprinting, making it difficult to distinguish family members yet to be affected on a pedigree analysis. Furthermore, the group continued the sequence analysis work of Nanba et al.,[25] who isolated a 9cM region on chromosome 17q25, identifying candidate genes for MMD. One of the candidate genes, *BAIAP2*, interacts with brain-species angiogenesis inhibitor–1 to inhibit bFGF, thereby inducing angiogenesis. Of the candidate genes selected, no mutations were identified, and therefore further study is needed to link MMD to chromosome 17q25.

Similar familial linkage studies conducted in the US have produced no clear results for the pathogenesis of MMD.[35] Further research of genes susceptible to familial MMD presentation will help lead to a more complete understanding of the etiology and pathophysiology of the disease.

Conclusions

The pathophysiology of MMD remains unclear although several angiogenic and cellular proliferative proteins have been associated with the disease and correlated with the histopathological appearance of the diseased vessels. Similarly, studies have shown a familial linkage with a low-penetrance autosomal dominant or polygenic mode of transmittance at loci on chromosomes 3, 6, 8, 12, and 17. While our understanding of the pathophysiology at the molecular and genetic levels continues to expand, it is hoped that this novel knowledge will help guide innovative approaches and treatment modalities for this disease, including targeted intracranial bypass and biologically adapted stents.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bendok. Acquisition of data: Weinberg, Arnaout. Analysis and interpretation of data: Bendok, Weinberg, Arnaout, Rahme, Aoun. Drafting the article: Weinberg, Arnaout. Critically revising the article: Bendok, Arnaout, Rahme, Aoun, Batjer.

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Moyamoya disease: functional and neurocognitive outcomes in the pediatric and adult populations

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Object. Moyamoya disease is an occlusive cerebrovascular disorder commonly resulting in neurocognitive impairment. The cognitive outcome parameters commonly affected are intelligence, memory, executive function, and quality of life. In this paper, the authors review the existing literature on cognitive and clinical outcomes in adult and pediatric moyamoya populations separately.

Methods. A systematic review of the cognitive and clinical outcome literature was performed using the PubMed/MEDLINE database. Outcomes data were contrasted between adult and pediatric populations.

Results. Intelligence is the main cognitive outcome parameter affected in pediatric patients with moyamoya disease, whereas adults most commonly suffer from executive function impairment. Memory has not been studied sufficiently in pediatric patients, and its dysfunction in the adult population remains controversial. Quality of life has not been studied appropriately in either population. Surgical revascularization is the only beneficial treatment option, and a combination of direct and indirect bypass techniques has shown benefit, but the impact on the above-mentioned parameters has not been sufficiently elucidated.

Conclusions. Moyamoya disease affects the cognition and daily function in pediatric patients to a greater extent than in adult patients. Due to the rarity of the disease, there is a distinct lack of high-level evidence regarding cognitive and clinical outcomes. *(DOI: 10.3171/2011.3.FOCUS1150)*

Key Words • **moyamoya disease** • **cognitive outcome** • **functional outcome** • **clinical outcome** • **pediatric** • **adult**

Moyamoya disease is a chronic cerebrovascular condition characterized by progressive stenosis of the arteries of the circle of Willis. This progressive occlusion leads to the recruitment of a large number of collateral vessels, giving moyamoya its characteristic "puff of smoke" appearance on angiographic studies.[2,14,26,29] The Ministry of Health and Welfare of Japan has subdivided moyamoya presentation into 4 categories: ischemic (63.4%), hemorrhagic (21.6%), epileptic (7.6%), and "other" (7.5%).[11] However, these categories are not mutually exclusive; patients with moyamoya disease can have hemorrhagic transformation of an ischemic stroke.[29]

Moyamoya disease is most prevalent in Asian populations and demonstrates unique epidemiological features in these populations compared with North American patients.[47] In the Asian population, moyamoya disease has a bimodal age of onset, with one peak in the 1st decade and another peak in the 3rd and 4th decades.[26] In addition, the disease process in children mainly causes ischemic symptoms due to inadequate perfusion, whereas in adults hemorrhage related to the fragility of the neovessels is more common.[2,29,47] In contrast, in the US, the most common mode of presentation is ischemia in both children and adults, whereas a hemorrhagic presentation is relatively rare (12%–17%).[4,47] Furthermore, the bimodal age distribution is not as clear in studies based on patients of North American descent.[2,4] It is important to note, though, the racial diversity of North American cohorts with patients of various ethnic backgrounds as compared with Asian cohorts composed primarily of patients of Asian descent.[49] It has been observed that an ischemic presentation in North American patients may possibly carry a more benign course of the disease.[4] However, this has not yet been validated, and conclusive evidence that cognitive and clinical outcomes differ between Asian and North American patients is not yet present in the literature.

In patients with moyamoya disease, cognitive and

Abbreviations used in this paper: CBF = cerebral blood flow; CVRS-II = California Visual Reproduction Subtest–Second Edition; DCS = dysexecutive cognitive syndrome; D-KEFS = Delis-Kaplan Executive Function System; EDAS = encephaloduroarteriosynangiosis; FSIQ = full-scale IQ; mRS = modified Rankin Scale; OEF = oxygen extraction fraction; PIQ = performance IQ; QOL = quality of life; rCBV = regional cerebral blood volume; rTTP = regional time to peak; SF-36 = 36-Item Short Form Health Survey; TIA = transient ischemic attack; VIQ = verbal IQ; WMT-RVRS = Wechsler Memory Test–Revised Visual Reproduction Subtest.

intellectual functioning is often affected.[21,30,36] The majority of outcome literature has focused on the neuropsychological aspect of children with the disease, whereas few studies have analyzed this outcome in adults. Vessel stenosis has been shown to progress at a faster rate in pediatric patients than in adults.[2,14,26] This progression has been associated with lower intelligence levels in pediatric patients.[26] The parameter that has been most commonly used to assess the mental status of moyamoya patients is the FSIQ. Other parameters include memory, executive functioning, and QOL. Clinical outcome has also been studied, with a specific focus on recurrent TIAs, cerebral infarction, and hemorrhage.

Moyamoya treatment aims at improving cerebral perfusion and decreasing neovessel formation, thus preventing future hemorrhagic and/or ischemic events.[14] No medical treatment has been proven efficacious. Surgical treatment can be broken down into 3 categories: direct, indirect, and combined revascularization. The direct bypass procedure involves the anastomosis of a branch of the external carotid artery, typically the superficial temporal artery with the middle cerebral artery.[2,13] Indirect revascularization involves the transposition of a biological vascularized graft onto the ischemic region of the brain, therefore inducing growth of new vessels. Various indirect techniques exist. Encephalomyosynangiosis involves use of the temporalis muscle, and is one of the most commonly applied techniques.[33] Another common indirect procedure is EDAS, in which an external carotid artery branch, typically the superficial temporal artery, is transposed to the ischemic tissue.[47] The dural layer may also be folded into the subdural space to induce more neovessel formation.[28] The combination of these techniques, encephaloduroarteriomyosynangiosis, is used to provide further revascularization.[22] Grafts that are used less commonly include the pericranial flap, omental tissue, and gracilis muscle.[31,41]

Methods

For this review, a systematic search of the English-language literature was performed with the PubMed/MEDLINE database by searching for the following keywords and various combinations thereof: "Moyamoya Disease," "Surgery," "Treatment," and "Outcome." This search initially retrieved 29 articles, which were reviewed and separated into pediatric and adult categories. The reference lists of the relevant articles were reviewed for additional sources, and 55 articles were included in the final review.

Pediatric Outcomes

Cognitive Outcomes

Intelligence. Intelligence is the most studied cognitive parameter in pediatric patients with moyamoya disease. The most commonly used intelligence tests are the Wechsler Intelligence Scale and its variations, including the Wechsler Intelligence Scale for Children–Revised (WISC-R), the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and the Wechsler Intelligence Scale for Children–Third Edition (WISC-III).[21,30,36] The FSIQ has 2 components: the VIQ and the PIQ. The VIQ is a measure of verbal comprehension and working memory, whereas the PIQ is a measure of perceptual organization and processing speed.[36] The extent of cognitive impairment has been correlated with the degree of vascular occlusion. Hence, the effect of revascularization surgery, direct and/or indirect, on cognitive functioning has been the focus of multiple studies.[32,34,35]

In patients with moyamoya disease, intelligence is commonly diminished relative to the general population.[19,30,32] In one study, Kuroda et al.[30] measured the FSIQ scores of 52 pediatric Japanese patients and compared these with scores from the general Japanese population. A significantly higher proportion of moyamoya patients were mentally impaired (as defined by an FSIQ score < 70) than were controls (15.4% and 2.2%, respectively). There were no significant differences between moyamoya patients and controls in all other intelligence score ranges.

One point of controversy is whether the diminished intelligence is due to a secondary condition accompanying moyamoya disease or is directly a product of the disease process. Hogan et al.[16] provided evidence for the latter in their analysis of intellectual function in non-Japanese children with moyamoya who also had sickle cell anemia. The prevalence of sickle cell anemia in moyamoya patients is higher than in the general population. Participants were grouped into patients with both moyamoya disease and sickle cell anemia, and a control group of patients with sickle cell anemia alone. Intelligence scores in children in the group with moyamoya disease and sickle cell anemia were significantly lower than those in the control group (VIQ, $p = 0.003$; PIQ, $p = 0.002$).[16] Additionally, a statistically significant reduction in PIQ independent of sickle cell anemia was seen in patients with moyamoya disease relative to those without moyamoya disease ($p = 0.004$), indicating a probable direct link between the moyamoya disease process and intelligence regression.[16]

Moyamoya disease has been postulated to cause progressive cognitive decline. Serial intelligence testing has been used to analyze this deterioration throughout the course of the disease.[1,19,24] Suzuki and Takaku[48] defined angiographic stages in relation to the degree of occlusion. The stenoses have been shown to progress until adolescence and stabilize by the age of 20 years.[8] Furthermore, older children tend to have worse cognitive impairment than younger children.[1,17,19,24] Imaizumi et al.[19] stratified patients by disease period and measured serial IQ scores. Patients with the disease for < 5 years showed significantly higher IQs than those afflicted for 5–10 years or for > 10 years ($p = 0.004$ and $p = 0.001$, respectively). However, no significant difference in intelligence existed between patients whose disease had been diagnosed > 5 years earlier and those who received their diagnosis > 10 years earlier. These results mimic the trend of disease progression. In another study, Ishii et al.[21] stratified preoperative patients by age and found that the mean FSIQ of older pediatric patients was lower than that of younger pediatric patients (patients between 13 and 16 years old: FSIQ = 82.6 ± 16.4; patients between 5 and 8 years old: FSIQ = 108.0 ± 12.9 [mean ± SD]).

Surgical revascularization has been proven beneficial in slowing cognitive decline in pediatric moyamoya patients.[20,32,34,35,50] The cognitive effects of EDAS were studied by Matsushima et al.[34] in 65 pediatric moyamoya patients. The authors measured intelligence by using IQ scores for children > 5 years of age and development quotient scores for children < 5 years. Although there was no improvement postoperatively, the surgery halted the cognitive decline, with intelligence scores stabilizing postoperatively. In another study, the same group of authors found that patients had normal intelligence levels 9.5 years postoperatively, given a preoperative FSIQ of > 70 (FSIQ = 100.0 ± 15.5; VIQ = 100.0 ± 15.7; PIQ = 100.2 ± 16.3).[36] However, when disease onset occurs before the 3rd year of life, cognitive function has been shown not to improve.[35]

Decreased CBF has been correlated with diminished intelligence.[44] Ishii et al.[21] correlated pre- and postoperative CBF levels with IQ scores in moyamoya patients. Preoperatively, patients with lower FSIQ scores generally had lower CBF values. Postoperatively, FSIQ improved or remained unchanged in 14, and PIQ improved or remained unchanged in 13 of the 15 tested patients. The patients with improved intelligence showed corresponding CBF improvement.

Although intelligence scores generally stabilize after surgical revascularization, this is not always the case.[21,30,34,35,50] Kuroda et al.[30] attributed poor cognitive outcome to 2 independent factors: 1) completed stroke as opposed to TIA (OR 33.4, 95% CI 2.4–474), and 2) "small craniotomy" surgery (OR 19.6, 95% CI 1.8–215). Revascularization by indirect bypass can only occur within the surgical window, because vascularized grafts can only be as large as this window. Furthermore, frontal lobe CBF has been correlated with intellectual development.[10] Because "small craniotomy" moyamoya surgeries are generally confined to the temporoparietal region, intelligence may not fully recover. Therefore, Kuroda et al. concluded that a "large craniotomy" is necessary to provide maximal revascularization and therefore obtain the best cognitive outcome.[23,44] This issue needs further study and must be measured against the risk incurred to collateral dural-to-pial anastomoses, which could be threatened by a larger craniotomy.

Memory. The vast majority of studies regarding cognitive outcome of pediatric moyamoya patients have focused on intelligence as a measure of higher functioning. Although there have not been many studies concerning memory, the present literature implies that memory is not impaired relative to other cognitive parameters. One study reported the neuropsychological testing of 2 pediatric moyamoya patients, in which memory was one of the parameters analyzed.[1] The authors used sections of the Wide Range Assessment of Memory and Learning test, including picture memory, story memory, design memory, and sentence memory to assess memory pre- and postoperatively. Although these measures were generally not impaired preoperatively, they still showed a notable gain in function postoperatively.

Executive Function. Executive function is the ability to plan and perform a series of actions in an effort to accomplish a specific motor goal. The integrity of the dorsolateral prefrontal cortices of the frontal lobes is required for this function.[10] This function has not been examined in pediatric moyamoya patients.

Quality of Life. There are very few papers exploring the QOL of children with moyamoya disease. The potential improvement in QOL postoperatively is a major consideration in the decision for surgical intervention. Guzman et al.[14] prospectively reported on the QOL in both adult and pediatric moyamoya patients treated at Stanford University Medical Center. The series involved 450 revascularization procedures performed in 329 patients, 96 of whom were children. The mRS was used as a QOL assessment tool. The authors found that 71.2% of patients had significantly improved postoperative mRS scores. Improvement by 1–2 points on the mRS was seen in 67.8% of patients. The best predictor of a good postoperative mRS score (0–2) was a preoperative mRS score of ≤ 2 (OR 26, $p < 0.0001$). Whereas the mRS score is a measure of disability, QOL is a much broader parameter that takes into account multiple dimensions, including physical, psychological, and social health. Quality of life measures such as the SF-36 have been used successfully to examine long-term QOL in stroke patients.[42] A multiple-domain test such as the SF-36 would give a more complete understanding of QOL in moyamoya patients, as it has in stroke patients. However, as a first measure, Guzman et al. provided an interesting insight into the postoperative improvement in QOL of moyamoya patients.

Clinical Outcome

Clinical outcome studies have focused on TIA, cerebral infarction, and hemorrhage. In one study of conservatively treated pediatric patients, TIA occurred most frequently during the first 4 years after disease onset, with the incidence declining thereafter.[32] Surgical revascularization has been shown to decrease the incidence of stroke and TIA.[13,22,25,38,45] Matsushima et al.[34] quantified the regression in TIA incidence by studying 65 pediatric moyamoya patients pre- and post-EDAS. Patients continued to have ischemic events until a mean of 239 days postoperatively, after which no ischemic events were recorded. Symptoms including headache, seizure, and involuntary movements disappeared after the last ischemic event. The authors concluded that EDAS effectively eliminates long-term ischemic episodes.

The major predictors of clinical outcome in the pediatric population remain controversial. Darwish and Besser[5] hypothesized that postoperative clinical outcome primarily correlated with clinical status at presentation. These authors studied 16 children with moyamoya disease and examined trends in mRS scores pre- and postoperatively. These mRS scores and the number of postoperative ischemic events only correlated with the clinical presentation and were not related to the type of revascularization procedure or patient age.

Other studies have analyzed predictors of clinical outcome from the perspective of hemodynamic parameters. Kim et al.[28] retrospectively analyzed 67 pediatric moya-

moya patients, and found the main predictors of long-term clinical outcome to be age at onset, type of surgical revascularization procedure, and postoperative cerebral hemodynamics. Furthermore, after analyzing 77 pediatric moyamoya patients by using postoperative basal/acetazolamide stress brain perfusion SPECT at 6 and 12 months postoperatively, So et al.[46] found that clinical outcome correlated best with cerebrovascular reserve. In addition, these authors measured a cerebrovascular reserve index and quantitatively showed a correlation between vascular reserve and clinical outcome. They concluded that postoperative SPECT results and cerebrovascular reserve index values predict clinical outcome in pediatric moyamoya patients.

Cerebral blood volume might also be used as a predictor of clinical outcome.[53] Quantitative MR perfusion imaging can be used to study hemodynamic parameters, including rTTP and rCBV. Using this imaging technique, Yun et al.[53] found that the rTTP was significantly shorter postoperatively than preoperatively ($p < 0.001$) and that the rCBV was significantly lower postoperatively than preoperatively ($p = 0.014$). Large rTTP delays and high rCBV levels preoperatively are due to dispersion of contrast material throughout the extensive network of collateral vessels. These values are both decreased postoperatively. Also, change in the rTTP was a significant predictor of clinical outcome, whereas change in the rCBV showed no such correlation.

Adult Outcomes

Cognitive Outcomes

Intelligence. In the few reports regarding intelligence in adult moyamoya patients, cognition has been shown to be less affected in adults than in children.[9,14,26] Karzmark et al.[26] confirmed this finding by measuring IQ scores with the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) in 36 adult patients. The mean FSIQ score was 95. The normal intelligence levels seen in adult patients contrast with the generally diminished intelligence seen in the pediatric moyamoya population. Further evidence was provided with the neuropsychological testing of 29 adults in which various forms of the adult Wechsler scales for intelligence were used.[9] The adult patients had a mean IQ score of 98.7 ± 17.2, which is comparable to that of the general population.

Memory. Memory has been studied more extensively in adult patients than in children. However, there is still controversy regarding the effects of moyamoya disease on memory in the adult population. The 2 main tests that have been used to examine adult memory function are the CVRS-II and the WMT-RVRS. Festa et al.[9] used neuropsychological testing to assess memory function in 29 adult patients. At initial presentation, 31% of patients showed verbal memory dysfunction on the delayed list recall test. The overall memory domain score was 1.1 SDs below the mean. The memory domain score is defined as the mean of z scores for immediate recall, delayed recall, and list recognition tests. The authors also studied working memory, which is a reflection of attention span, with 21% of patients falling lower than 1.5 SDs below the mean. The authors localized the impaired cognitive functions, including memory, to subcortical and frontal systems. The fact that these regions do not correspond with the regions of ischemia implies that the neurocognitive impairment may also be due to chronic hypoperfusion, in addition to acute localized ischemic events. Based on this finding, the authors concluded that overall cognitive dysfunction might be an indication for surgical intervention.[9]

Other studies have found memory to be unaffected in adult patients. Using subsets of the CVRS-II and WMT-RVRS, Karzmark et al.[26] analyzed memory in 36 adult moyamoya patients. Of all cognitive parameters tested, memory showed the lowest rates of impairment. Therefore, the authors concluded that medial temporal function is relatively spared in patients with moyamoya disease.

Executive Function. Executive function has also been studied more extensively in adults than in children. The major dimensions of executive function include flexibility of thinking, problem solving, motor planning, impulse control, and concept formation. The main tests that have been used to measure these dimensions are the D-KEFS Design Fluency Test, the Letter and Category Fluency Tests, and the Trail-Making Test Part B. The D-KEFS test assesses flexibility of thinking, impulse control, and planning.[6] The Letter and Category Fluency Tests examine semantic knowledge.[12] The Trail-Making Test Part B analyzes frontal lobe function in terms of problem solving and motor planning.[54]

Analysis of existing literature revealed executive function to be considerably impaired in adult moyamoya patients.[9,26] Festa et al.[9] found the executive function of 29 adult patients to be significantly diminished, with a mean Trail-Making Test Part B score that was 1.3 SDs below the mean. Karzmark et al.[26] found executive function to be the most impaired cognitive parameter in moyamoya patients. Of 36 adult patients, 11% showed impairment on the D-KEFS test, and 42% showed impairment on the Trail-Making Test Part B. Furthermore, 47% of patients showed Letter Fluency impairment and 44% showed Category Fluency impairment. Due to its role in executive function, the frontal lobe is thought to be directly affected in adult moyamoya patients.

Quality of Life. An extensive look at QOL in this population has not yet been performed. Some elements of QOL, including mRS and depression, have been studied to some degree. As previously mentioned, Guzman et al.[14] found that mRS scores improved postoperatively in adults and in children. In another study, Festa et al.[9] measured depression with the Centers for Epidemiological Studies Depression scale. The authors found that 8 (28%) of 29 patients showed evidence of depression. However, depression did not correlate with other neurocognitive findings, nor did it mirror the extent of cognitive impairment. In another study, only 2 (5.6%) of 36 adults reported a moderate level of depression, defined as a Beck Depression Inventory–II score between 20 and 28.[26] Depression prevalence has been found to be between 20% and 40% after acute neurological events such as stroke.[37] Karzmark et al.[26] rationalized the low prevalence of depression found

in moyamoya patients by the progressive nature of the disease. They argued that moyamoya patients do not realize the severity of their condition in terms of its impact on their ability to perform daily activities. Self-reported depression may underestimate the true detriment to QOL; therefore, QOL assessment is a fertile ground for future studies.

Perfusion. Hypoperfusion has been hypothesized as a principal cause of the cognitive decline seen in adult moyamoya patients.[9] In turn, improved perfusion postoperatively has been hypothesized to correlate with improved cognitive functioning. This relationship, though, has yet to be fully comprehended. To our knowledge only 1 series and 2 case reports have ever been published on the subject. All 3 studies revealed a correlation between cerebral perfusion as measured by perfusion-weighted MR imaging and neurological function pre- and postoperatively.[3,24,51] Wityk et al.[51] reported the improved cognitive function of a 24-year-old patient with moyamoya disease at a single follow-up evaluation 1 year postoperatively. The improved cognitive function was associated with a markedly increased perfusion of the involved hemisphere. Jefferson et al.[24] reported serial neurocognitive testing of a 48-year-old moyamoya patient preoperatively and at 5 weeks postoperatively. They found a dramatic improvement in cognitive domains, specifically verbal learning and delayed recall, which correlated with a drastic increase in perfusion. Calviere et al.[3] compared perfusion between 6 moyamoya patients with DCS and 4 moyamoya patients without DCS. Perfusion was significantly lower in those with DCS ($p = 0.019$) than in those without. Although these reports clearly revealed a correlation between increased perfusion and improved cognitive outcome, more data are needed and a prospective registry with serial cognitive and imaging follow-ups is warranted for further enhancement of our understanding of this observed phenomenon.

Clinical Outcome

Clinical outcome in adult moyamoya patients has been analyzed in terms of recurrent TIA, cerebral infarction, and hemorrhage. The postoperative risk of TIA and ischemic stroke decreases dramatically after revascularization.[29,47] This decreased risk was quantified in a study of 43 post-EDAS adult moyamoya patients in North America.[47] The primary outcomes studied were TIA, infarction, graft collateralization, mRS score, and perfusion changes. Postoperatively, 82% of the hemispheres showed increased perfusion, and 96% showed some collateral formation within the surgical region. The 5-year infarction-free survival rate was significantly increased, from 36% to 94% in hemispheres treated surgically ($p = 0.007$). Surgical intervention reduced the risk of infarction by 89%. Furthermore, the postoperative incidence of TIA was reduced from 58% on presentation to 7% during a median 41-month follow-up period (range 4–126 months). From these results, the authors concluded that indirect bypass procedures such as EDAS promote sufficient development of collateral vasculature, preventing future TIA and infarction.

Increased OEF can identify hemodynamic impairment, potentially predicting future ischemic events.[39] An ongoing study by Zipfel et al.[55] is prospectively analyzing the strength of OEF as a predictor of ipsilateral stroke and clinical outcome in moyamoya patients. These authors measure OEF levels with PET imaging on admission and at 1 and 3 years postoperatively. The interim results revealed that an elevation in cerebral OEF is frequently seen in moyamoya patients as a compensatory response to decreased perfusion. Hemodynamic impairment and increased OEF are predictors of stroke in carotid artery occlusion disorder,[7] and Zipfel et al. are attempting to correlate these factors in moyamoya patients.

Surgical Techniques and Outcomes

In relation to the clinical and cognitive outcomes of both pediatric and adult patients, the efficacy of surgical procedures used to treat moyamoya disease has undergone much investigation. Although neither indirect nor direct bypass techniques have been proven superior to one another, surgical intervention is the only successful treatment for moyamoya disease.[19,20,29,32,50] One study found that the 5-year risk of ipsilateral stroke was reduced from 82% in conservatively treated patients to 17% in surgically treated patients.[15] In a subsequent study, 25 pediatric moyamoya patients were followed, of whom 10 underwent surgical treatment, whereas 15 were treated conservatively.[20] Surgical intervention was found to be more effective than conservative treatment in preventing poor cognitive outcome, especially if done early in the clinical course.[20,32]

There is currently no clear consensus on the ideal timing for revascularization surgery.[9,14,29,40] A national Japanese survey found 1.5% of patients with moyamoya disease to be asymptomatic; 21.2% of these patients became symptomatic within a mean of 3.7 years.[52] Narisawa et al.[40] followed up on adult moyamoya patients who underwent direct bypass in 63 hemispheres and were treated conservatively in 47 asymptomatic hemispheres. Six (12.8%) of the 47 conservatively treated patients showed stenosis progression, whereas no cerebrovascular events were reported among surgically treated patients. The authors consequently drew the conclusion that asymptomatic moyamoya patients are at risk for disease progression and should undergo revascularization if they have ischemic symptoms or signs of stenotic progression.

The majority of the literature comparing direct and indirect bypass has found no significant difference in long-term outcome between the 2 procedures. However, in one study the 2 techniques were compared by retrospectively reviewing 368 moyamoya revascularization cases, and the investigators found that immediate postoperative ischemic events were more common after indirect revascularization (OR 5.8, 95% CI 1.96–17.2).[43] This could be due to the fact that indirect revascularization initiates a chronic sequence of chemical and biological events involving various growth factors that promote vessel formation only after 3–4 months postoperatively.[31] On the other hand, direct bypass immediately improves perfusion to the affected area. The literature suggests that a

combination of direct and indirect bypass is preferable, and in the long term no significant difference in outcome exists between the 2 procedures.[2,18,27]

Conclusions

Moyamoya disease is an important cause of ischemic and hemorrhagic stroke. The combination of indirect and direct revascularization techniques is the recommended surgical approach and is beneficial to both clinical and cognitive outcomes. Neurocognitive impairment differs between adult and pediatric populations. Intelligence is the most affected cognitive parameter in children, whereas executive function is the most impaired parameter in adults. Very few studies have analyzed QOL in either population. Advancements in perfusion imaging will allow for a clearer understanding of the disease progression and long-term outcome of moyamoya patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bendok, Rahme. Acquisition of data: Weinberg, Rahme. Analysis and interpretation of data: Bendok, Rahme. Drafting the article: Weinberg, Rahme, Aoun. Critically revising the article: Bendok, Batjer. Reviewed submitted version of manuscript: all authors. Approved the final version of the paper on behalf of all authors: Bendok.

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State of the art in managing nontraumatic intracerebral hemorrhage

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Nontraumatic intracerebral hemorrhage constitutes a major public health problem worldwide. Intracerebral hemorrhage leads to a high rate of morbidity and mortality. To date, no medical or surgical trials have clearly attested to the benefit of a particular therapy. The aim of this review was to summarize the best evidence for management decision-making in intracerebral hemorrhage. *(DOI: 10.3171/2011.3.FOCUS1145)*

Key Words • nontraumatic intracerebral hemorrhage • surgical management • hematoma

Nontraumatic intracerebral hemorrhage constitutes a major public health problem worldwide, accounting for 2 million (10%–15%)[81] of about 15 million strokes worldwide each year.[60] In the US, on average, someone has a stroke every 40 seconds.[60] Its direct cost is around US$12.7 billion of the US$73.7 billion related to stroke care annually.[60] Despite active research, it is still the least treatable cause of stroke and a leading cause of morbidity, disability, and death worldwide.[75] During the first month after ICH onset, the proportion of patients that die has varied from 22% to 62%.[17,24,39] Only 20% of persons who survive achieve functional independence at 6 months post-ICH.[39]

Incidence varies on the basis of age, race, and demographics. The incidence of ICH increases exponentially with advancing age, with rates doubling every 10 years after the age of 35 years.[19] Intracerebral hemorrhage is more common in Asian, African, and Hispanic American populations.[57,67] These differences are mostly predominant in hemorrhages in deep cerebral locations and in young and middle-aged people. Differences might be explained by the decreasing incidence in some populations that can easily access medical care and blood pressure control.[55,77]

Intracerebral hemorrhage commonly affects both supratentorial and infratentorial structures. In one study of 1014 ICHs, 50% were in a deep location (periventricular white matter, caudate nucleus, globus pallidus, putamen, internal capsule, or thalamus), 35% were lobar (gray matter or subcortical white matter), 10% were cerebellar, and 6% were in the brainstem (midbrain, pons, or medulla).[37]

In this review, we discuss the major risk factors and clinical and radiological features of ICH, as well as the clinical trials on managing this condition.

Risk Factors and Etiologies

Age increases the incidence of ICH, and men and postmenopausal women appear to have a greater risk.[6] Alcohol consumption doubles the risk of ICH when consuming more than 2 standards units of alcohol per day.[34] Sympathomimetics, such as amphetamines, increase the risk of ICH,[34] and smoking produces only a small increase in the risk of ICH.[6]

Hypertension is the most significant modifiable risk factor[70] and is estimated to be the cause of 50%–70% of all ICHs.[6,19,83] Hypertension is nearly as common in primary lobar hemorrhage as in deep, cerebellar, and pontine hemorrhages.[15] The more the stage of hypertension increases, the more the risk of ICH is important.[79] Regardless, hypertension is a very prevalent condition, and its existence should not exclude other causes of ICH, especially among young people.

Cerebral amyloid angiopathy is a risk factor for spo-

Abbreviations used in this paper: AVM = arteriovenous malformation; CAA = cerebral amyloid angiopathy; DAF = dural arteriovenous fistula; DS = digital subtraction; ICH = intracerebral hemorrhage; INR = International Normalized Ratio; rFVIIa = recombinant activated factor VII.

radic ICH. It is characterized by the deposition of congophilic material, usually amyloid-beta protein, in the walls of cortical and leptomeningeal bloods vessels. The incidence of CAA increases with age so that nearly 50% of all individuals older than 80 years have affected cortical and leptomeningeal blood vessels.[87] The major clinical manifestation of CAA is lobar hemorrhage, commonly associated with variations in the gene encoding apolipoprotein E.[64] Cerebral amyloid angiopathy is estimated to be the cause of 50% of lobar hemorrhages in elderly people.[91]

Anticoagulant therapy is a significant cause of secondary ICH. The incidence of anticoagulant-associated ICH quintupled during the 1990s probably due to the increasing use of this therapy.[36] Anticoagulant-associated ICH is estimated to be the cause of nearly 20% of all ICHs.[36] This condition is related to a higher risk of hematoma expansion and a higher mortality rate.[36] Patients on anticoagulant therapy often suffer from chronic hypertension or CAA, and thus these anticoagulant agents might exacerbate an existing risk.[45]

The other well-known causes of ICH are hemorrhagic transformation of ischemic stroke, vascular abnormalities (aneurysm, AVM, DAF, and cavernous malformation), venous thrombosis, vasculitis, arteritis, coagulopathy, and neoplasia.

Clinical and Radiological Features

Both ICH and ischemic stroke cause focal neurological deficits such as hemiparesis, hemisensory loss, aphasia, ophthalmoplegia, and visual fields cuts. Intracerebral hemorrhage produces blood leakage into the brain, causing compression, increasing intracranial pressure, and scattering in ventricles and subarachnoid spaces. Thus, ICH can cause additional symptoms such as headache, nausea, vomiting, progressive deterioration, and coma. Clinically, however, it is not always easy to distinguish an ischemic process from a hemorrhagic process. Intracerebral hemorrhage should be most suspected in patients presenting with a sudden focal deficit, including several vascular territories, that gradually increases over the time.

The immediate recommended imaging procedure to establish whether a process is ischemic or hemorrhagic is CT of the head.[16] In cases of ICH, CT provides information on the location of the hematoma, its size, the existence of accompanying blood in ventricles or subarachnoid space, and the presence of perihematoma edema. The existence of accompanying bleeding in the subarachnoid space points to AVM or aneurysm, perihematoma edema points to intracranial tumor, ICH located in the basal ganglion points to chronic hypertension, and lobar ICH points to CAA.

Although CT is the first-line diagnostic approach, MR imaging with gradient echo sequences can detect hyperacute ICH with equal sensitivity and overall accuracy. Furthermore, MR imaging is more accurate for the detection of microhemorrhages.[35]

Surgically treatable causes of ICH should be considered. These causes include vascular abnormalities such as aneurysm, AVM, DAF, cavernous malformation, and tumor. When a vascular abnormality is suspected, DS angiography is considered the standard imaging protocol. However, this technique is invasive and painful and requires a high level of skill. Neurological complications occur in 1.3% of cases,[90] and the mortality rate is about 0.1%.[44] There is also a high frequency of silent embolism in up to 23% of cases.[13] Compared with DS angiography, both CT angiography and MR angiography are noninvasive techniques. Moreover, CT angiography can be performed immediately after the initial noncontrast CT with a single bolus of intravenous contrast medium to allow rapid diagnosis and treatment. The procedure allows one to acquire images from the aortic arch to the vertex in a single acquisition within 11–16 seconds. Furthermore, CT angiography is becoming part of the standard protocol in patients presenting with ICH at many institutions.[12,48,93]

Authors of many studies have been evaluating the diagnostic accuracy of CT angiography in terms of its ability to detect cerebral aneurysms and have reported good results.[12] In 2003, in a meta-analysis of 21 studies published between 1995 and 2002, Chappell et al.[21] documented a 93% rate of sensitivity and 87.8% rate of specificity. More recently, with the current-generation, high-speed, multislice, dual-source CT scanners, authors have reported sensitivities between 95.1% and 98%[1,22,31,53] and specificities between 94.1% and 100%.[1,22,31,53] However, based on an aneurysm size < 3 mm, diagnostic accuracy decreases (sensitivity: 86.1%; specificity: 94.1%).[31] Computed tomography angiography is also highly accurate in displaying the vascular anatomy and characterizing the aneurysm for choosing the most appropriate treatment.[1,48,86] Magnetic resonance angiography is less accurate than CT angiography in detecting aneurysms, with a sensitivity between 55% and 93%.[5,49,51,78] Although MR angiography shows promise in acute ICH, its accessibility, availability, and scan time remain major disadvantages. As regards AVMs, few studies have evaluated the diagnostic accuracy of CT angiography in detecting these lesions. In a prospective study of 45 patients, Eshwar Chandra et al.[33] showed that CT angiography correctly predicted 83% of AVMs. Computed tomography angiography and MR angiography seem to have good accuracy. Magnetic resonance imaging is superior in demonstrating the exact anatomical relationships of AVMs.[69] However, MR angiography tends to underestimate AVM size.[68] The reason for this difference between MR angiography and CT angiography is the ability of MR to separate out the draining veins.[68] Furthermore, a small lesion in the presence of a hematoma can be missed.[10] Regarding DAFs, CT angiography and MR angiography have not been shown to be sensitive enough on their own to identify these lesions.[26,28,56] Indeed, the lack of temporal resolution and the peripheral location of dural feeders makes CT angiographic identification difficult.[93] As regards cavernous malformations, MR imaging is currently the best technique to make the diagnosis, with the T2* gradient recalled echo sequences being described as the reference standard.[20,58] If the first MR image is negative, it would be wise to wait 3 or 4 weeks before doing another MR imaging study.

In the event of a negative CT angiography or negative MR angiography and a considerable suspicion of vascu-

lar abnormalities, the patient should be examined further with DS angiography, especially young patients.

Intracerebral hemorrhage is a dynamic process, and early clinical deterioration might occur due to hematoma expansion.[18] Hematoma growth is an independent predictor of death and outcome.[27] Intraventricular hemorrhage is also an independent predictor of death and poor outcomes.[14,30,42,84] It is estimated to be present in 45% of patients with ICH and is related to ICH volume and location.[43]

Medical Management Trials

In emergency departments, treatment commonly includes airway support, blood pressure control, intracranial pressure monitoring and management, and, if necessary, anticoagulation reversal. To date, no trials have completely assessed the definitive benefits of tested therapies.

Blood Pressure Management

Early elevation of blood pressure is common after ICH,[76] and there is a strong correlation between increasing blood pressure and poor outcomes.[38,59,71,85] Several nonrandomized studies[72,74] have suggested that an early reduction in blood pressure is associated with better outcomes.

To date, the largest trial concerning blood pressure reduction management in ICH is INTERACT (intensive blood pressure reduction in acute cerebral haemorrhage trial).[3] In that study, adults were enrolled if they had an ICH confirmed by CT within 6 hours of onset and an elevated systolic blood pressure (150–220 mm Hg). Eligible patients were randomized in 2 groups: guideline-based treatment to lower blood pressure (201 patients) and intensive treatment to lower blood pressure (203 patients).[3] From 1 to 24 hours after treatment, the mean systolic blood pressure was significantly different between the 2 groups. The risk of severe adverse events was not altered by an intensive reduction in blood pressure. At 90 days after treatment, there was no significant difference in outcomes between the 2 groups.[3] The mean hematoma expansion was significantly greater in the guideline treatment group at 24 hours after treatment. However, after adjusting for the initial hematoma volume and the time from ICH onset to CT, the median hematoma growth differed between the groups ($p = 0.06$).[3] Anderson et al.[2] provided more information about hematoma growth in the INTERACT. The adjusted mean absolute increases in hematoma growth were significantly different between the 2 groups over 72 hours.[2]

At present, INTERACT2[29] is an ongoing trial aimed to confirm these results and to establish whether early intensive treatment to lower blood pressure is associated with better outcomes.

The ATACH (Antihypertensive Treatment of Acute Cerebral Hemorrhage) trial[4] was a phase I multicenter prospective study assessing the feasibility and safety of a reduction in blood pressure by intravenous nicardipine in patients with a systolic blood pressure superior or equal to 170 mm Hg (target blood pressure level of 170–200 mm Hg in the first group, 140–170 mm Hg in the second group, and 110–140 mm Hg in the third group).[4]

Hemostatic Therapy

More than 33% of ICHs enlarge from 3 to 24 hours after onset, and there is a strong correlation between volume hematoma and outcomes.[18,27] Thus, therapies to avoid hematoma expansion might improve outcomes.

Two large trials have been focused on the rFVIIa,[62,63] an agent aimed to promote hemostasis to limit hematoma enlargement.

A phase IIb, international, multicenter, randomized placebo-controlled trial has evaluated escalating doses of rFVIIa administered within 4 hours of ICH onset.[63] Adults with ICH confirmed by CT within 3 hours after onset were randomized in 4 groups to receive placebo (96 patients), 40 μg of rFVIIa per kilogram of body weight (108 patients), 80 μg of rFVIIa per kilogram of body weight (92 patients), or 160 μg of rFVIIa per kilogram of body weight (103 patients) within 1 hour after the baseline CT. Hematoma volume increased significantly more in the placebo group than in the 3 treatment groups. The mortality rate at 90 days after treatment was significantly higher in the placebo group. The authors concluded that treatment with rFVIIa within 4 hours after ICH onset limits hematoma growth, reduces the mortality rate, and improves functional outcomes at 90 days after treatment.

The FAST (Factor Seven for Acute Hemorrhagic Stroke) trial[62] is a phase III clinical trial on the safety and efficacy of rFVIIa in ICH. Adults with ICH were randomized in 3 groups to receive placebo (268 patients), 20 μg of rFVIIa per kilogram of body weight (276 patients), or 80 μg of rFVIIa per kilogram of body weight (297 patients) within 4 hours after ICH onset. Treatment with 80 μg of rFVIIa per kilogram of body weight significantly reduced hematoma growth. The authors of this study concluded that hemostatic therapy with rFVIIa reduced hematoma growth but did not improve survival or functional outcomes after ICH.

The results of these 2 large trials[62,63] are concordant in terms of the reduction of hematoma growth thanks to rFVIIa. However, the results are discordant regarding outcomes, perhaps because of the more elevated frequency of arterial events in the group treated with 80 μg of rFVIIa per kilogram of body weight.

Anticoagulant-Associated ICH

Anticoagulant-associated ICH is linked to a higher risk of hematoma expansion and a higher mortality rate.[36] Patients with this ICH subtype should receive anticoagulation reversal such as fresh-frozen plasma or prothrombin-complex concentrate[61,92] and vitamin K.[47] If rapid normalization of the INR to below 1.4 is not achieved, the risk of death increases.[40] However, these protocols often require a long time before obtaining a normalized INR. The use of rFVIIa to correct the INR has been described in healthy volunteers,[32] and its administration can normalize INR within minutes. Recombinant FVIIa has been used in patients with ICH before their needed neurosurgical procedures with good clinical results.[41,80]

Protamine sulfate should be used in patients treated with unfractionated or low-molecular-weight heparin.[88]

Surgical Management Trials

The surgical management of ICH is one of the most controversial issues in neurosurgery. The management method is different based on the hematoma location. Although surgical treatment is still under debate, it is well codified regarding an infratentorial hematoma location.

Supratentorial Hematoma

Different surgical options have been evaluated and considered as safe: open craniotomy,[54] frameless stereotactic aspiration,[9] or endoscopic evacuation[8] with or without thrombolysis. A randomized study[25] compared these 3 techniques for basal ganglia hemorrhage. Ninety patients were randomly assessed in 3 groups: 30 patients underwent endoscopic surgery, 30 underwent stereotactic aspiration, and 30 underwent craniotomy. Stereotactic aspiration needed a significantly greater time delay before surgery than the other techniques ($p < 0.001$). The craniotomy group had the longest operation time ($p < 0.001$) and more blood loss ($p < 0.001$). Endoscopic surgery had the highest hematoma evacuation rate ($p < 0.01$). The mortality rate at 3 months after treatment among the techniques was not significantly different; it was 0% in the endoscopic surgery group, 6.7% in the stereotactic aspiration group, and 13.3% in the craniotomy group. However, the functional independence mean and the Barthel Index scores were significantly better in the endoscopic surgery group than in the craniotomy group.

Prasad et al.[73] performed a meta-analysis to assess whether surgical treatment (craniotomy, stereotactic aspiration, and endoscopic evacuation) plus routine medical management was effective as compared with routine medical treatment alone. They included 10 clinical trials[7,11,23,46,50,52,65,66,82,94] in the meta-analysis. The primary outcome was death or dependence at the end of the follow-up. This meta-analysis was the first to demonstrate that surgery is more effective in reducing the odds of death than is medical management. Indeed, the odds ratio for death at the end of the follow-up was 0.74 (95% CI 0.61–0.90). However, in a subgroup analysis, a difference was found among the surgeries. Stereotactic aspiration or endoscopic evacuation significantly reduced the odds of death (OR 0.66 [95% CI 0.46–0.95]), whereas craniotomy did not reduce the odds of death (OR 0.82 [95% CI 0.59–1.15]).

The largest study comparing surgery versus medical treatment for ICH is STICH (Surgical Trial in Intracerebral Haemorrhage).[65] This trial did not show an overall benefit from surgery as compared with medical management.

An ongoing controlled trial, STICH II is focused on spontaneous lobar ICH of ≤ 1 cm from the cortex surface of the brain. Its authors aim to assess whether early surgery plus appropriate medical treatment is effective as compared with the best medical treatment combined with delayed surgery only if it becomes necessary.

Another large Chinese study[89] has investigated the benefits of surgery as compared with medical treatment. Three hundred seventy-seven patients with basal ganglia ICH were randomly assessed in a minimally invasive craniopuncture group (195 patients) and in a conservative control treatment group (182 patients). There was no difference in cumulative fatality rates at 3 months after treatment between the 2 groups. However, the proportion of dependent survival patients in the craniopuncture group (40.9%) was significantly lower than in the conservative treatment group (63%).

The MISTIE (Minimally Invasive Surgery plus Tissue Plasminogen Activator for Intracerebral Hemorrhage Evacuation) trial is an ongoing trial designed to find the best dose of thrombolytic agent to reduce hematoma volume via stereotactic aspiration.

Many questions persist. Actually, despite the existence of several trials, there are no guidelines on the best management for supratentorial ICH. Subgroup analyses (ICH location, Glasgow Coma Scale score, clinical evolution, and so forth) are necessary to know for whom a surgical treatment is beneficial. It also seems interesting to differentiate the subtypes of surgery in terms of each subtype of hematoma location or population characteristic.

Cerebellar Hemorrhage

There are guidelines for the treatment of these subtypes of ICH, which comprise around 10% of all ICH cases.[16] Surgery is a Class I recommendation in patients with a cerebellar hemorrhage larger than 3 cm who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from a ventricular obstruction.[16] In these conditions, hematoma evacuation should be performed as soon as possible.

Conclusions

Some surgical trials on ICH tend to show a benefit from surgery in reducing the mortality rate and the proportion of dependent patients. However, larger trials focusing on subgroup analyses are required to know who surgery could really benefit. The ongoing STICH II should be able to reveal whether craniotomy for lobar ICH is beneficial. Further multidisciplinary and multicenter studies are required to establish clear guidelines on the management of ICH.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Acquisition of data: Dubourg. Analysis and interpretation of data: Dubourg. Drafting the article: Dubourg. Study supervision: Messerer.

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The relationships between endothelial nitric oxide synthase polymorphisms and the formation of intracranial aneurysms in the Korean population

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Object. Some genetic factors are known to be associated with the formation of cerebral aneurysms in the Caucasian population. One of these factors is endothelial nitric oxide synthase (eNOS) gene polymorphisms. Endothelial nitric oxide synthase genes encode eNOS, which synthesizes NO from L-arginine. There continues to be controversy about the relationships between eNOS gene polymorphisms and the formation of intracranial aneurysms. In this study, the authors evaluated these relationships in the Korean population.

Methods. Three eNOS polymorphisms (eNOS 27VNTR, T786C, and G894T) were genotyped in 96 patients with ruptured aneurysms, 53 patients with unruptured aneurysms, and in 121 volunteers via polymerase chain reaction–restriction fragment length polymorphism analysis.

Results. The mean ages of the patients and healthy volunteers were 52.9 ± 12.3 years and 55.2 ± 9.1 years, respectively. The patient group was composed of 56 men and 93 women, and the healthy volunteer group was composed of 46 men and 75 women. Only the incidence of smoking history was significantly higher in the patient group than in the control group ($p = 0.001$). The genotypic frequencies for the 3 eNOS gene polymorphisms were in agreement with those predicted by Hardy-Weinberg equilibrium. There were no significant associations between the eNOS recessive models and the formation of an aneurysm. The authors found no genotypic differences between similar races among patients with aneurysms.

Conclusions. The present study shows that eNOS 27VNTR, T786C, and G894T polymorphisms cannot be used as indicators of the formation of intracranial aneurysms in Korean patients. To confirm these findings an additional analyses might need to be performed using a larger sample size. There were no differences in the genotypic distributions and allelic frequencies between similar races among patients with aneurysms, which were the same in previously reported normal populations. *(DOI: 10.3171/2011.2.FOCUS10227)*

Key Words • cerebral aneurysm • 27VNTR polymorphism • T786C polymorphism • G894T polymorphism • endothelial nitric oxide synthase

The incidence of subarachnoid hemorrhages due to ruptured cerebral aneurysms is 10 to 11 per 100,000 people per year. The prevalence of unruptured cerebral aneurysms has increased due to the development of diagnostic imaging techniques such as MR angiography, and it has been reported to be more than 2% of the population.[32] The hemodynamic mechanisms of aneurysmal formation are well known, and aneurysms located in the posterior circulation as well as larger aneurysms are known to be more prone to rupture than others.[32] In addition, there are some reports about environmental and genetic factors associated with the formation, growth, and rupture of cerebral aneurysms. Endothelial nitric oxide synthase gene polymorphisms are among the genetic factors known to be associated with aneurysms.

Nitric oxide is synthesized by the catalyzing action of the NOS family enzymes via the conversion of L-arginine, nicotinamide adenine dinucleotide phosphate, and O_2 to NO and citrulline.[29] Nitric oxide was originally known as "endothelial-derived relaxing factor," which is responsible for the potent vasodilating properties of stimulated endothelia.[30] Since then, NO has been widely implicated as a biological mediator of activities ranging from neuronal function to immune system regulation, including relaxation of the vascular smooth muscle, vasodilation, maintenance of the vessel wall geometry,[34] inhibition of vascular smooth muscle cell proliferation and platelet and monocyte adhesion,[41] and protection from vascular dis-

Abbreviations used in this paper: eNOS = endothelial nitric oxide synthase; PCR = polymerase chain reaction; RA = ruptured aneurysm; URA = unruptured aneurysm.

ease.[9] Therefore, altered NO levels have been reported to be related to many conditions and activities such as sepsis,[26] reproduction,[33] infection,[8] hypertension,[20] exercise,[21] diabetes,[44] hypoxia,[23] and cancer.[37] In particular, reduced NO levels can result in cardiovascular disease, carotid atherosclerosis, hypertension, and aortic aneurysm.[27]

There are 3 types of NOS: neuronal (nNOS/NOS1), endothelial (eNOS/NOS3), and inducible (iNOS/NOS2).[2] Neuronal NOS is mainly expressed in neurons of the central[31] and peripheral nervous systems, but can also be found in other cells such as skeletal muscle myocytes,[10] lung epithelial cells,[3] and skin mast cells.[36] Endothelial NOS is mainly expressed by endothelial cells and can be found in neurons,[7] dermal fibroblasts,[40] epidermal keratinocytes,[36] thyroid follicular cells,[5] hepatocytes, and smooth muscle cells.[6] Inducible NOS is expressed in many cell types, including chondrocytes,[22] epithelial cells,[3] hepatocytes,[11] glial cells, and some types of immune cells.[4] Endothelial NOS and nNOS are normally expressed and regulated by Ca^{2+}/calmodulin, whereas iNOS is relatively insensitive to Ca^{2+} and is usually expressed by endotoxin and inflammatory cytokines.[2]

Endothelial NOS is encoded by eNOS genes on chromosome 7q35–36. Polymorphisms of the eNOS genes may alter the structure and stability of the eNOS enzyme[42] or modify the interactions of eNOS genes with other components.[42] These alterations can result in decreased expression or activities of the eNOS enzyme and eventually decrease NO production.[39] Polymorphisms of eNOS genes might be related to the formation or rupture of intracranial aneurysms because decreased NO production can result in cardiovascular disease and carotid atherosclerosis. However, there is still some controversy about the relationships between eNOS gene polymorphisms and plasma NO levels. Veldman et al.[39] reported that the G894T eNOS gene polymorphism, a transversion of guanine (G) to thymine (T) at a locus 894 base pairs in exon 7 of the eNOS gene, is associated with reduced basal NO production and might have functional implications in the development of atherosclerosis or hypertension. Tsukada et al.[38] reported that the 27VNTR eNOS gene polymorphism, a 27-base pair variable-number-tandem-repeat polymorphism in intron-4 of the eNOS gene, had a strong association with plasma NO metabolites. On the other hand, Moon et al.[24] indicated that there was no substantial effect of the G894T eNOS gene polymorphism on the variance of plasma NO metabolites in a healthy Korean population. Schneider et al.[35] reported no biological effect of the G894T eNOS gene polymorphism on the cardiovascular system through its influence on endothelium-dependent vasodilation.

Three types of eNOS genes were recently studied: 1) eNOS 27VNTR;[41] 2) eNOS T786C, a substitution of thymine (T) to cytosine (C) at a locus 786 base pairs upstream of the eNOS gene;[25] and 3) eNOS G894T.[43] The relationship between the formation of an intracranial aneurysm and eNOS gene polymorphisms is controversial. This study examined 3 eNOS gene polymorphisms in patients with cerebral aneurysms (including both RAs and URAs), and volunteers. The aim of this study was to evaluate the relationships between the formation of an aneurysm and eNOS gene polymorphisms in the Korean population.

Methods

Study Participants

The study population consisted of 96 patients with ruptured subarachnoid hemorrhages, 53 patients with URAs, and 121 healthy volunteers. The patients were enrolled in the neurosurgery department at Bundang CHA Hospital between May 2008 and April 2010. The diagnosis of an RA was based on each patient's history and radiological findings, such as brain CT and conventional angiography. A diagnosis of a URA was based on the radiological findings, such as MR angiography or conventional angiography. The 121 volunteers were healthy individuals who visited the Bundang CHA General Hospital for a health examination and had no history of cerebrovascular disease. The volunteers all underwent MR angiography, which revealed no cerebrovascular disease in any of the volunteers. The institutional review board of Bundang CHA General Hospital approved this study. All study participants were Korean, and each participant provided informed consent before being enrolled (Table 1).

Genetic Analysis

A single blood sample was collected from patients with RAs, patients with URAs, and healthy controls. Genomic DNA was extracted from peripheral blood leukocytes using the G-DEX blood extraction kit (Intron). The nucleotide changes were determined by PCR-restriction fragment length polymorphism analysis using the isolated genomic DNA as a template.

Endothelial NOS 27VNTR Polymorphism. The primer sequences used to detect the eNOS intron 4 polymorphism were 5'-AGGCCCTATGGTAGTGCCTTT-3' (sense) and 5'-TCTCTTTAGTGCTGTGGTCAC-3' (antisense). The PCR reaction was performed in a 20-μl reaction volume including 100 ng of genomic DNA, 10 pmol of each primer, and 10 μl of HotStarTaq master mix (Qiagen). The PCR reaction began with an initial denaturation step for 15 minutes at 95°C. This step was followed by 35 cycles at 94°C for 1 minute, 49°C for 40 seconds, and 72°C for 40 seconds, with a final extension at 72°C for 7 minutes. The PCR products were separated by electrophoresis (Mupid-2Plus) on a 3% agarose gel stained with ethidium bromide. Fragments of 393 bp and 420 bp corresponded to the eNOS alleles 4a and 4b, respectively.

Endothelial NOS T786C Polymorphism. The PCR was performed using primers 5'-ATGCTCCCACCAGG GCATCA-3' (sense) and 5'-GTCCTTGAATCTGACATT AGGG-3' (antisense). A 236-bp fragment was amplified by PCR in a final volume of 20 μl containing 100 ng of genomic DNA, 10 pmol of each primer, and AccuPower HotStart PCR Premix (Bioneer). Amplification was performed in 35 cycles consisting of denaturation (94°C, 30 seconds), annealing (51°C, 40 seconds), and extension (72°C, 40 seconds). The 236-bp PCR products were digested with 5 units of the restriction enzyme NgoMIV (New England Biolabs Inc.) at 37°C for 16 hours, producing fragments of

TABLE 1: Demographic and clinical characteristics of the patients with aneurysms and healthy controls

Variable	RA & URA	RA	URA	Controls	p Value
no. of patients	149	96	53	121	
mean age ± SD	52.9 ± 12.3	51.2 ± 12.7	55.8 ± 10.9	55.2 ± 9.1	0.07
male (%)	56 (37.6)	39 (40.6)	17 (32.1)	46 (38.0)	
female (%)	93 (62.4)	57 (59.4)	36 (67.9)	75 (62.0)	0.942
smoking (%)	40 (26.8)	30 (31.2)	10 (18.9)	13 (10.7)	0.001*
hypertension (%)	76 (51.0)	44 (45.8)	32 (60.4)	60 (49.6)	0.816
diabetes (%)	11 (7.4)	7 (7.3)	4 (7.5)	20 (16.5)	0.019*

* Statistically significant (patients vs controls).

236 bp for the T allele or fragments of 203 bp and 33 bp for the C allele. The restriction digest products were analyzed by electrophoresis on a 3% agarose gel containing ethidium bromide and visualized using the Molecular Imager Gel Doc XR System (BIO-RAD).

Endothelial NOS G894T Polymorphism. For the detection of the eNOS G894T polymorphism, the primers 5'-CATGAGGCTCAGCCCCAGAAC-3' (sense) and 5'-AG TCAATCCCTTTGGTGCTCAC-3' (antisense) were used in a PCR reaction. The volume for each PCR reaction was 20 μl containing 100 ng of genomic DNA, 10 pmol of each primer, and AccuPower HotStart PCR Premix (Bioneer). The PCR reaction was run for 35 cycles, and each cycle consisted of denaturing at 94°C for 45 seconds, annealing at 63°C for 45 seconds, and extension at 72°C for 45 seconds. The resulting 206-bp fragment was digested with 10 units of the restriction enzyme BanII (Fermentas GmbH) for 16 hours at 37°C. The DNA fragments were separated by electrophoresis on 3% agarose gel. The 206-bp PCR product was cleaved into 119-bp and 87-bp fragments in the presence of a G nucleotide at 894 but not in its absence.

Statistical Analysis

The demographics are reported as the mean ± SD for continuous variables and as percentages of the totals for the categorical variables. The univariate relationships between the demographic variables and conditions were assessed using an independent samples t-test for the continuous variables and Pearson chi-square test for the categorical variables. The genotypic distribution and allelic frequencies were assessed using the Pearson chi-square test. The allelic frequency distribution at each polymorphism locus was tested against Hardy-Weinberg equilibrium under the Mendelian biallelic expectation by performing the Pearson chi-square test. Multivariate associations were assessed using logistic regression analysis for the categorical variables. All data were analyzed using SPSS for Windows, version 11.0 (SPSS). A probability value < 0.05 was considered significant.

Results

Table 1 describes the demographic and clinical characteristics of the 149 patients with aneurysms (96 with RAs, 53 with URAs) and 121 healthy controls. The mean ages of the patients and controls were 52.9 ± 12.3 years and 55.2 ± 9.1 years, respectively. The patient group was composed of 56 men and 93 women, and the control group was composed of 46 men and 75 women. Comparisons of age, sex, and hypertension revealed no significant differences between the patient and control groups. The incidence of smoking history was significantly higher in the patient group than the control group ($p = 0.001$), and the incidence of diabetes was significantly higher in the control group than in the patient group ($p = 0.019$)

Table 2 lists the genotypic distributions and allelic frequencies of the patient and control groups. Among the patients, the genotypic frequencies for eNOS T786C ($p = 0.998$), eNOS 27VNTR ($p = 0.998$), and eNOS G894T ($p = 0.996$) were in agreement with those predicted by Hardy-Weinberg equilibrium. Among the controls, the genotypic frequencies were also compatible with Hardy-Weinberg equilibrium (eNOS T786C, $p = 0.908$; eNOS 27VNTR, p

TABLE 2: Genotypic distributions and allelic frequencies of the 149 patients and 121 healthy controls

Genotype	No. of Patients (%)	No. of Controls (%)	OR (95% CI)*	p Value
786TT	122 (81.9)	99 (81.8)	1.000	
786TC	24 (16.1)	22 (18.2)	0.885 (0.471–1.662)	0.707
786CC	3 (2.0)	0		0.121
TC+CC	27 (18.1)	22 (18.2)	0.996 (0.537–1.845)	0.99†
T allele‡	0.9	0.91		0.996
4b4b	122 (81.9)	96 (79.3)	1.000	
4a4b	24 (16.1)	25 (20.7)	0.755 (0.408–1.398)	0.428
4a4a	3 (2.0)	0		0.126
ab+aa	27 (18.1)	25 (20.7)		0.643§
b allele‡	0.9	0.9		1
894GG	125 (83.9)	98 (81.0)	1.000	
894GT	24 (16.1)	23 (19.0)	0.818 (0.438–1.527)	0.532¶
894TT	0	0		1
G allele‡	0.92	0.91		0.996

* Differences in frequencies between the patient group and the control group.
† eNOS T786C recessive model (TT vs TC+CC).
‡ Values indicate allelic frequency.
§ eNOS 27VNTR recessive model (4b4b vs 4a4b+4a4a).
¶ eNOS G894T recessive model (GG vs GT+TT).

TABLE 3: Adjusted ORs for vascular risk factors and eNOS gene polymorphisms in relation to aneurysm formation

Variable	OR (95% CI)	p Value
age	0.659 (0.388–1.121)	0.124
sex	1.409 (0.788–2.519)	0.248
smoking	3.464 (1.622–7.396)	0.001*
hypertension	1.41 (0.829–2.398)	0.205
diabetes	0.393 (0.173–0.892)	0.025*
eNOS 27VNTR recessive model (4b4b vs 4a4b+4a4a)	no frequency difference	0.999
eNOS T786C recessive model (TT vs TC+CC)	no frequency difference	0.999
eNOS G894T recessive model (GG vs GT+TT)	0.832 (0.429–1.611)	0.585

* Statistically significant.

= 0.994; eNOS G894T, p = 0.987). There were no significant associations between the eNOS recessive models and the formation of an aneurysm. This was the same for all 3 genes (eNOS T786C, p = 0.99; eNOS 27VNTR, p = 0.643; eNOS G894T, p = 0.532) and for all 3 alleles (T allele, p = 0.996; b allele, p = 1.000; G allele, p = 0.996).

The adjusted ORs for vascular risk factors (age, sex, smoking, hypertension, diabetes) and eNOS gene polymorphisms with regard to aneurysm formation were obtained (Table 3). Smoking history (OR 3.464, p = 0.001) and no history of diabetes (OR 0.393, p = 0.025) were significantly associated with the formation of an aneurysm. The other factors, including eNOS gene polymorphisms, were not associated with the formation of an aneurysm (Table 3).

In normal populations, genotypic and allelic differences between races have been examined.[1,16] This study compared the genotypic and allelic differences between Asian and Caucasian patients with aneurysms (Table 4). The American (a) group was composed of patients from the Mayo Stroke Center, Mayo Clinic, in Rochester, Minnesota, and the American (b) group was composed of patients from the University of California, San Francisco. There were no significant differences in the distribution of the eNOS T786C, 27VNTR, and G894T genes between Korean and Japanese patients (p = 0.882, 0.895, and 0.18, respectively), but there were significant differences between these 3 distributions in Korean and American (a) patients (p = 0, 0.002, and 0, respectively), Koreans and American (b) patients (p = 0, 0, 0.027, respectively), and Koreans and Germans (p = 0, 0.032, and 0, respectively). There were even some differences between American (a) and German patients (p = 0.065, 0.439, and 0.017, respectively) and American (b) and German patients (p = 0.001, 0.001, and 0, respectively).

Discussion

Despite recent medical developments, approximately 50% of patients with a ruptured cerebral aneurysm die or become severely disabled, and the cost of treatment is very high. If a URA can be detected before rupture, the patient can be treated more safely with a better prognosis and at a lower cost. Recently, diagnostic imaging techniques, such as CT angiography or MR angiography, have been developed, and a URA can be detected more easily. However, these imaging studies are relatively difficult and expensive.

There is some controversy about the relationships between the formation of an intracranial aneurysm and

TABLE 4: Genotypic and allelic differences of eNOS gene polymorphisms in patients with aneurysms according to race

Genotype	Korean (149 patients)	Japanese* (405 patients)	American (a)† (107 patients)	American (b)‡ (319 patients)	German§ (142 patients)
786TT (%)	122 (81.9)	326 (80.5)	50 (46.7)	167 (52.4)	48/135 (35.6)
786TC (%)	24 (16.1)	72 (17.8)	46 (43.0)	119 (37.3)	60/135 (44.4)
786CC (%)	3 (2.0)	7 (1.7)	11 (10.3)	33 (10.3)	27/135 (20)
T allele frequency	0.9	0.89	0.68	0.71	0.58
4b4b (%)	122 (81.9)	325 (80.2)	68 (63.6)	141/236 (59.7)	98 (69.0)
4a4b (%)	24 (16.1)	70 (17.3)	38 (35.5)	63/236 (26.7)	41 (28.9)
4a4a (%)	3 (2.0)	10 (2.5)	1 (0.9)	32/236 (13.6)	3 (2.1)
b allele frequency	0.9	0.89	0.81	0.73	0.84
894GG (%)	125 (83.9)	349 (86.2)	67 (62.6)	184/245 (75.1)	64 (45.1)
894GT (%)	24 (16.1)	50 (12.3)	32 (29.9)	53/245 (21.6)	67 (47.2)
894TT (%)	0	6 (1.5)	8 (7.5)	8/245 (3.3)	11 (7.7)
G allele frequency	0.92	0.92	0.78	0.86	0.69

* From data by Krischek et al., 2006.

† From data by Khurana et al., 2005. American (a) group composed of patients from the Mayo Stroke Center, Mayo Clinic, Rochester, Minnesota.

‡ From data by Ko et al., 2008. American (b) group composed of patients from the University of San Francisco, California.

§ From data by Krex et al., 2006.

eNOS gene polymorphisms. In a recent study, Khurana et al.[13–15] found the following positive correlations: between the eNOS 27VNTR polymorphism and the formation of a cerebral aneurysm, between the eNOS T786C polymorphism and cerebral vasospasm after an aneurysmal subarachnoid hemorrhage in Caucasian patients, and between eNOS polymorphisms and a tendency for aneurysmal rupture. Ozum et al.[28] suggested that the G894T polymorphism of the eNOS gene has a positive relationship with the formation of an intracranial aneurysm. On the other hand, Krischek et al.[19] reported no relationship between eNOS polymorphisms and rupture of a cerebral aneurysm in Japanese patients. Moreover, Akagawa et al.[1] reported the same findings of negative association between the T786C polymorphism of the eNOS gene and the formation of an intracranial aneurysm.

In this study, we could not find any evidence of a positive relationship between 3 eNOS gene polymorphisms and the formation of an intracranial aneurysm. The same results were obtained in the relationships between the allelic frequencies and the formation of an intracranial aneurysm. Our study group was relatively small (149 patients with aneurysms and 121 healthy controls). Therefore, additional studies with a larger study group will be needed to confirm the relationship between the genotypic distribution of eNOS gene polymorphisms and sex in the patient group. Univariate and multivariate logistic regression analyses revealed a relationship between smoking history and the formation of an intracranial aneurysm. This is consistent with previous reports showing that smoking is related to the formation of an aneurysm.[12] In our study, diabetes history had a negative relationship with the formation of an intracranial aneurysm, which is not consistent with previous reports showing that diabetes is not related to the formation of an aneurysm. We cannot explain the reason of a negative relationship between diabetes history and the formation of aneurysm. One possible cause is the small number of patients and controls with diabetes history. In a larger study, a positive relationship might be revealed.

This study compared the genotypic and allelic differences in aneurysmal patients of different races. The outcome was similar to the previously reported findings in control populations.[1,16] There were no racial differences in the eNOS gene polymorphism distributions in similar races, such as Korean and Japanese patients. However, there were racial differences in different races, such as Korean and American or Korean and German patients. There were even some racial differences between American (b) and German patients. This is because the American (b) group included a variety of races such as Latinos, Asians, and African Americans.[17] These racial differences with regard to the distribution of eNOS gene polymorphisms might be related to differences in the incidence and prevalence of intracranial aneurysms. Therefore, if the genotypic distribution and allelic frequencies are studied relative to the prevalence and incidence of intracranial aneurysms, it might be possible to identify relationships between polymorphisms of the eNOS gene and the formation of an intracranial aneurysm.

Conclusions

Endothelial NOS 27VNTR, T786C, and G894T polymorphisms cannot be used as indicators of the formation of intracranial aneurysms in Korean patients. However, our study group was relatively small. Therefore, further analysis with a larger group will be needed to confirm the relationship between the genotypic distribution of the eNOS gene polymorphisms and aneurysmal formation. There were no differences in the genotypic distributions and allelic frequencies between similar races in aneurysmal patients, whereas there were some differences between different races, which were demonstrated previously in normal populations.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: TG Kim, Baek. Acquisition of data: TG Kim, NK Kim, Huh. Analysis and interpretation of data: TG Kim. Drafting the article: TG Kim. Statistical analysis: TG Kim. Administrative/technical/material support: Huh, Chung, Choi. Study supervision: Yu.

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The natural history of intracranial cavernous malformations

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Literature reports on the natural history of cerebral cavernous malformations (CMs) are numerous, with considerable variability in lesion epidemiology, hemorrhage rates, and risk factors for hemorrhage. In this review, the authors performed a meta-analysis of 11 natural history studies. The overall male-to-female ratio was 1:1, and the mean age at presentation was 30.6 years. Overall, 37% of patients presented with seizures, 36% with hemorrhage, 23% with headaches, 22% with focal neurological deficits, and 10% were asymptomatic. Some patients had more than one symptom. Seizure presentation was most prevalent among supratentorial CMs, while focal neurological deficits were common in patients with infratentorial CMs. By location, CMs were in the cerebral hemispheres (66%), brainstem (18%), basal ganglia or thalamus (8%), cerebellum (6%), and other (2.5% [combined supra- and infratentorial, callosal or insular]). Overall, 19% of patients harbored multiple intracranial CMs, and 9% had radiographically apparent associated developmental venous anomalies. An overall annual hemorrhage rate of 2.4% per patient-year (range 1.6%–3.1%) was identified across 3 studies. Prior hemorrhage and female sex were risk factors for bleeding, while CM size and multiplicity did not affect hemorrhage rates. Although not impacting the hemorrhage rate itself, deep location was a risk factor for increased clinical aggressiveness. *(DOI: 10.3171/2011.3.FOCUS1165)*

Key Words • cavernous malformation • cavernoma • hemorrhage • natural history

Cavernous malformations are clusters of dilated sinusoidal channels lined by a single layer of endothelium.[3,8,19,20,26] In contradistinction to arteriovenous malformations, these lesions do not have smooth muscle or elastin in their lining, and they are angiographically occult. Their prevalence across several reports ranges from 0.4% to 0.6% of the population.[8,14,22,26,27] Since 1991, multiple natural history reports have surfaced in the literature, with significant dissension in regard to lesion epidemiology and particularly hemorrhage risk. Herein, we review 11 studies describing the epidemiology, clinical presentation, and natural history of these lesions in an attempt to elicit more cogent data so as to clarify hemorrhage rates and risk factors for bleeding.

Methods

A PubMed search using the terms "cavernoma," "cavernous malformation," "cavernous hemangioma," "natural history," "bleed," and "hemorrhage" was performed. To minimize bias and to more naturally reflect the clinical course of these lesions, surgical series were excluded, leaving a total of 11 retrospective and prospective natural history studies in the English-language literature for analysis. Accounting for de novo CM development after birth, 4 retrospective studies were excluded from our analysis of CM hemorrhage rates.

Abbreviations used in this paper: CM = cavernous malformation; DVA = developmental venous anomaly.

Results

Epidemiology and Clinical Presentation

Epidemiological data and information on patient presentation were extracted from 10 natural history studies with a total of 837 patients (Table 1). The male-to-female ratio was 1:1 (422 males and 415 females). The mean age at presentation was 30.6 years. Across 9 studies with 775 patients providing data on clinical presentation, 37% presented with seizures, 36% with hemorrhage, 23% with headaches, and 22% with focal neurological deficits (some patients had more than one).[2,7,8,15,17,20,23,26,31] Ten percent of patients were asymptomatic.

Across 9 series providing applicable data on cerebral CM location in 1055 patients, 803 (76%) were supratentorial, 243 (23%) were infratentorial, and 9 (1%) were both.[2,7,8,14,17,20,23,26,31] Across 7 studies with 747 cerebral CMs providing further detailed information on lesion location, 491 lesions (66%) were located in the cerebral hemisphere (lobar), 131 (18%) in the brainstem, 61 (8.2%)

TABLE 1: Review of natural history studies of cerebral CMs*

Authors & Year	No. of Pts	No. of CMs	Female/ Male	Mean Age (yrs)	Presentation	Location	No. w/ Multiple CMs	No. w/ DVAs	Study Design
Aiba et al., 1995†	110		52:58		62 hemorrhage; 25 seizures; 23 incidental	52 lobar; 8 BG/T; 2 callosal; 15 brainstem; 5 cerebellar			prospective
Cantu et al., 2005	133		66:67	34.3	78 hemorrhage; 64 seizure; 62 focal deficit; 57 headache; 3 incidental	73 lobar; 13 BG/T; 25 brainstem; 8 cerebellar; 9 supra-/infratentorial; 5 spinal	17	12	retrospective
Del Curling et al., 1991	32	76	15:17	37.6	3 hemorrhage; 16 seizure; 11 headache; 7 focal deficit; 6 incidental	65 supratentorial; 11 infratentorial	6		retrospective
Kim et al., 1997‡	62	108	24:38	32.2		31 lobar; 5 BG/T; 10 brainstem; 3 cerebellar	13		retrospective
Kondziolka et al., 1995	122		62:60	37.3	61 hemorrhage; 28 seizure; 18 headache	59 lobar/cerebellar; 43 brainstem; 20 BG/T	25	2	prospective
Labauge et al., 2000	40	232	19:21	33.3	19 hemorrhage; 12 seizure; 5 incidental; 4 focal deficit	176 supratentorial; 26 brainstem; 30 cerebellar			familial retrospective
Moriarity et al., 1999§	68	228	44:24	34.6	9 hemorrhage; 44 headache; 33 seizure; 31 focal deficit; 1 incidental	77 lobar; 13 BG/T; 16 brainstem; 5 cerebellar	25	13	prospective
Porter et al., 1997	173		85:88	37.5	44 hemorrhage; 62 seizure; 35 focal deficit; 11 headache; 21 incidental	96 lobar; 12 BG/T; 2 insular; 1 callosal; 52 brainstem; 10 cerebellar	31	22	prospective
Robinson et al., 1991	66	76	30:36	34.6	6 hemorrhage; 34 seizure; 30 focal deficit; 20 headache; 9 incidental	55 lobar; 4 BG/T; 8 brainstem; 9 cerebellar	7	3	prospective
Zabramski et al., 1994	31	128	18:13	25.0	16 headache; 12 seizure; 5 focal deficit; 12 incidental	107 lobar; 6 BG/T; 5 callosal; 5 brainstem; 5 cerebellar	26	2	familial retrospective

* BG/T = basal ganglia or thalamus; Pts = patients.
† Data on CM location were only provided for a subset of patients.
‡ Data on clinical presentation and hemorrhage on presentation were not provided for all patients. Data on CM location were provided for 49 lesions.
§ Data on CM location were provided for 111 lesions.

in the basal ganglia or thalamus, 45 (6.0%) in the cerebellum, 9 (1.2%) were combined supra- and infratentorial, 8 (1.1%) were in the corpus callosum, and 2 (0.27%) were in the insula.[2,7,14,20,23,26,31] Across 7 general distribution studies with 656 patients, 125 patients (19%) harbored multiple intracranial CMs.[7,8,14,15,20,23,26] Developmental venous anomalies were seen in 54 (9%) of 593 patients in 6 studies reporting associated vascular malformations.[7,15,20,23,26,31] Table 2 summarizes overall epidemiological, clinical presentation, and hemorrhage rate data.

Hemorrhage

Several retrospective analyses of CM hemorrhage rates assume lesion presence since birth (that is, congenital); hemorrhage rates then would be calculated from birth. Given the known phenomenon of de novo CM formation,[5,6,9,21,24,31] however, such studies are inaccurate and will underestimate the actual hemorrhage rates of these lesions once they are discovered. The "congenital" theory explains the extremely low annual hemorrhage in the often-cited early report by Del Curling et al.[8] of 0.25% per patient-year or 0.1% per lesion-year.

To avoid underestimation, we reviewed the prospective natural history data in Tables 3 and 4; the latter table presents data from familial studies. Using this basis, hemorrhage rates are calculated from the onset of initial discovery of the cavernoma, not from birth. Despite the exclusion of retrospective reports, however, the data remain quite heterogeneous. Robinson et al.[26] reported an annual hemorrhage rate of 0.7% per lesion-year. The studies of Kondziolka et al.,[15] Moriarity et al.,[20] and Porter et al.[23] reported annual hemorrhage rates ranging from 1.6% to 3.1% per patient-year. Across these 3 studies including a total of 363 patients followed up for 1121.5 patient-years, the overall hemorrhage rate was 2.4% per patient-year.[15,20,23] Rates are calculated per patient-year by taking the quotient of total number of hemorrhages experienced by an individual patient and the number of years the patient is followed up. Thus, patients with multiple lesions may have higher hemorrhage rates as calculated per patient-year as opposed to per lesion-year; the latter is the quotient of number of hemorrhages per lesion and years followed. Indeed, the greatest annual hemorrhage rate of 3.1% per patient-year from the study of Moriarity et al. was for 228 lesions in 68 patients.

In addition to a variable denominator used to report hemorrhage rates, the definition of a CM hemorrhage

TABLE 2: Summary of epidemiological, clinical presentation, and overall hemorrhage rate data*

Parameter	Value†
no. of studies reviewed	10
total no. of pts	837 (31–173)
male/female ratio	1:1 (0.5–1.6:1)
mean age at presentation (yrs)	30.6 (25–37.6)
overall clinical presentation (%)	
seizure	97
hemorrhage	36
headache	23
focal deficit	22
incidental	10
CM location (%)	
supratentorial	76
infratentorial	23
supra- & infratentorial	1
lobar	66
brainstem	18
BG/T	8
cerebellar	6
callosal	1
insular	0.2
% pts w/ multiple CMs	19 (11–37)‡
% pts w/ CM & DVA	9 (2–19)
overall annual hemorrhage rate (per pt-yr)	2.4% (1.6%–3.1%)
annual hemorrhage rate (per les-yr)	0.7%§
familial annual hemorrhage rate (per pt-yr)	5.1% (4.3%–13%)¶
familial annual hemorrhage rate (per les-yr)	0.8% (0.6%–2%)¶

* les-yr = lesion-year; pt-yr = patient-year.

† Data in parentheses represent ranges across reviewed studies.

‡ Excludes the familial study of Zabramski et al. in which 81% of patients harbored multiple CMs.

§ Only provided from the study of Robinson et al.

¶ Hemorrhage rate for patients with a family history of cerebral CM.

varied significantly across these studies. Moriarity et al.[20] and Robinson et al.[26] used a stringent definition of extralesional blood and accompanying symptoms. Aiba et al.[2] and Porter et al.[23] used more lax radiographic definitions of hemorrhage and generally relied on a clinical event. The definition of hemorrhage in the study of Kondziolka et al.[15] was based solely on radiographic evidence.

Rebleed rates across these natural history studies varied widely from 0% to 22.9% per patient-year.[2,15,20] While the study of Robinson et al.[26] was not adequately powered to detect the impact of prior hemorrhage on subsequent bleeding, the studies of Aiba et al.,[2] Kondziolka et al.,[15] and Porter et al.[23] demonstrated a significantly increased risk of rehemorrhage after an initial hemorrhage. In fact, the studies of Kondziolka et al. and Aiba et al. purported prior hemorrhage as the primary risk factor for a subsequent hemorrhage, citing annual rehemorrhage rates of 4.5% and 22.9% per patient-year, respectively. In contrast, Moriarity et al.[20] reported no cases of rehemorrhage in their study. Importantly, however, of 68 patients in this study, only 9 had hemorrhages, while 62 of 110 patients in the study of Aiba et al. and 61 of 122 patients in the study of Kondziolka et al. presented with hemorrhage. This intuitively demonstrates the greater power of these 2 studies to detect the clinical significance of a prior hemorrhage on subsequent bleeding, validating the maxim of prior hemorrhage increasing the risk of subsequent bleeding from a CM.

Consistent across our reviewed series, CM size and the presence of multiple lesions did not impact hemorrhage rates.[2,15,20,23,26] Age younger than 40 years old was seen as a risk factor for hemorrhage in only 1 study.[2] Three of 5 reviewed natural history studies reported female sex as a risk factor for hemorrhage.[2,20,26] This was in fact the most significant factor increasing hemorrhage rates in the study of Moriarity et al.,[20] with an annual bleed rate of 4.2% per patient-year for females as opposed to 0.9% per patient-year for males. This study, along with the study of Robinson et al.[26] that reported an increased hemorrhage risk among females, used a consistent, stringent definition of CM hemorrhage: new symptoms and new extralesional blood. Porter et al.[23] reported CM location as the primary factor influencing hemorrhage risk, citing a 4.1% per patient-year annual hemorrhage rate for deep lesions (deep hemispheric or brainstem). Although reported as a risk factor in some retrospective studies as well,[7,17] all other prospective studies we evaluated did not demonstrate lesion location as a significant risk factor for hemorrhage.[2,15,20,27] This can likely be explained in part by the definition of hemorrhage in each study. Moriarity et al. and Robinson et al. used a strict definition of extralesional blood and new symptoms. Kondziolka et al.[15] relied on radiographic evidence alone. Porter et al.[23] allowed for changes in lesion size with new symptoms to be considered hemorrhagic events. While it is not intuitive why changing the location of a CM would increase its risk of hemorrhage, it is logical to expect more subtle, morphological changes in a CM to present symptomatically in eloquent locations. Furthermore, asymptomatic overt hemorrhage in a superficial location that would be counted radiographically in the study of Kondziolka et al. would not be accounted for in the study of Porter et al. Thus, it is reasonable to consider deep CMs as clinically more aggressive lesions owing to the sensitivity of their location to more subtle lesional changes. This is further underscored by the annual clinical event rate of 10.6% reported in the study of Porter et al. for deep lesions.

Data across prospective familial studies were generally consistent, reporting annual hemorrhage rates of 4.3%–13% per patient-year and 0.6%–2% per lesion-year.[16,31] These ranges include asymptomatic, radiographic hemorrhage. Combining the data for 64 patients observed for 116 patient-years and 362 CMs observed for 750 lesion-years, the annual radiographic hemorrhage rate is 5.1% per patient-year and 0.8% per lesion-year.[16,31] Emphasis should be placed on rates per lesion-year in these patients given the vast multiplicity of these lesions, making their bleeding tendency ostensibly similar to nonfamilial cases. In addition, these studies consistently demonstrated a 0.4% new lesion rate per patient-year.[16,31]

TABLE 3: Hemorrhage rates from prospective nonfamilial natural history studies

Authors & Year	No. of Pts	No. of CMs	Hemorrhage Definition	Follow-Up (pt-yrs)*	Hemorrhage Rate (per pt-yr)*	Specific Hemorrhage Rate (per pt-yr)	Rehemorrhage Rate (per pt-yr)	Factors Impacting Hemorrhage Rate	
								Increased Risk	No Effect
Aiba et al., 1995	110		new symptoms & perilesional or intralesional hemorrhage	196.5 hemorrhage group; 254 seizure group	reported in subgroups only	0% incidental; 0.39% seizure group	22.9% overall; 19.4% males; 25.2% females; 25.2% <40 yrs; 14.1% >40 yrs; 34% female <40 yrs	prior hemorrhage, female sex, age <40 yrs	location
Kondziolka et al., 1995	122		hemorrhage on MRI	341.6 overall; 167 nonhemorrhage group; 178 hemorrhage group	2.6%	0.6% incidental	4.5% overall	prior hemorrhage	location, sex, many CMs
Moriarity et al., 1999	68	228	new symptoms & extralesional hemorrhage	352.9	3.1%	0.9% males; 4.2% females; 5.2% superficial; 3.1% deep	0%	female sex	prior hemorrhage, location, CM size
Porter et al., 1997	173		new symptoms & extralesional hemorrhage or increase in lesion size by 20%	427	1.6%	4.1 % deep; 0% superficial; 4.2% event rate: 4.2%; 10.6% deep; 0% superficial		deep location, prior hemorrhage†	sex, many CMs
Robinson et al., 1991	57	66	new symptoms & extralesional hemorrhage/ positive lumbar puncture	143 les-yrs	0.7%/les-yr			female sex	age, CM size

* Follow-up and hemorrhage rates in patient-years unless otherwise specified.
† Patients presenting with hemorrhage and a focal neurologic deficit had an increased risk of subsequent hemorrhage.

TABLE 4: Prospective familial natural history studies

Authors & Year	No. of Pts	No. of CMs	Hemorrhage Definition	Yrs of Follow-Up	Hemorrhage Rate	Specific Hemorrhage Rate	New Lesion Formation (per pt-yr)
Labauge et al., 2001	33	234	hemorrhage on MRI	70 pt-yrs; 468 les-yrs	4.3%/pt-yr; 0.6%/les-yr		0.4
Zabramski et al., 1994	31	128	new symptoms & hemorrhage on MRI (may be intralesional)	46 pt yrs; 282 les-yrs	6.5%/pt-yr; 1.1%/les-yr	13%/pt-yr; 2%/les-yr*	0.4

* Includes asymptomatic hemorrhages.

Discussion

Quite consistently across most natural history studies, patients presented at a relatively young age without a sex predilection. With similar consistency across these studies—and as we reinforce, lesion distribution is generally reflective of the distribution of CNS tissue without a further biased tendency of CM localization—76% of CMs were supratentorial and 23% were infratentorial. Importantly, location does impact patient presentation. Although seizure was the most common presentation seen in our review (37% of patients) and in other studies as well, it is even more common in the subgroup of supratentorial lesions. In the study of Moriarity et al.,[20] 53% of patients with supratentorial lesions presented with seizures. Small hemorrhages into noneloquent supratentorial parenchyma may be silent, and thus a large number of supratentorial CMs may go undiagnosed unless a patient presents with a seizure. Reflecting the sensitivity of eloquent surrounding tissue, patients with infratentorial lesions are more likely to present with focal deficits; 64% of patients with infratentorial lesions in the study by Moriarity et al. presented with focal deficits compared with 41% of patients with supratentorial lesions. Varyingly widely across our reviewed studies (9%–59% of patients), we found that overall, 36% of patients presented with hemorrhage. Intuitively, this rate, along with the number of incidental cases, will vary with the nature of the study and institutional referral pattern, underscoring the utility of meta-analytical review. Indeed, the true distribution of CM location and mode of presentation will depend on the percentage of patients presenting with incidental lesions as opposed to those presenting with symptoms referable to their CM.

Overall, approximately one-fifth of patients with cerebral CMs will harbor additional lesions. This rate increases significantly in familial cases to at least four-fifths of patients.[31] Seen in primarily sporadic cases, an associated DVA was noted in 9% of cases we reviewed overall. This contrasts somewhat with primarily surgical series that cite a greater association of approximately 15%–26% of cases,[1,4,28,30] with some citing the potential of increased CM aggressiveness when associated with these lesions.[1,3,25,30] Even a causal relationship has been proposed[1,3,24] and has been supported by multiple reports of de novo CM development in the presence of a DVA.[5,6,9,24] We have seen this phenomenon in multiple cases at our institution as well (Fig. 1). Mechanisms including hemorrhagic angiogenic proliferation following microhemorrhage due to venous hypertension[3] and venous outflow restriction opening preexisting arteriovenous connections[29] have been proposed.

In addition to de novo CM development in the presence of a DVA, this phenomenon has been extensively noted following radiation therapy[11,13,18,21] and in familial cases.[16,31] We believe that the continued accumulation of evidence of de novo CM formation, particularly in cases in which a prior DVA was seen, underscores the fact that these lesions are not congenital (Fig. 2). We think that they develop in the presence of a venous anomaly in the context of venous outflow restriction and resultant hemorrhage. This proposal is supported by the study of Porter et al.,[24] in which all 86 patients (including familial cases) had associated venous anomalies seen at the time of sur-

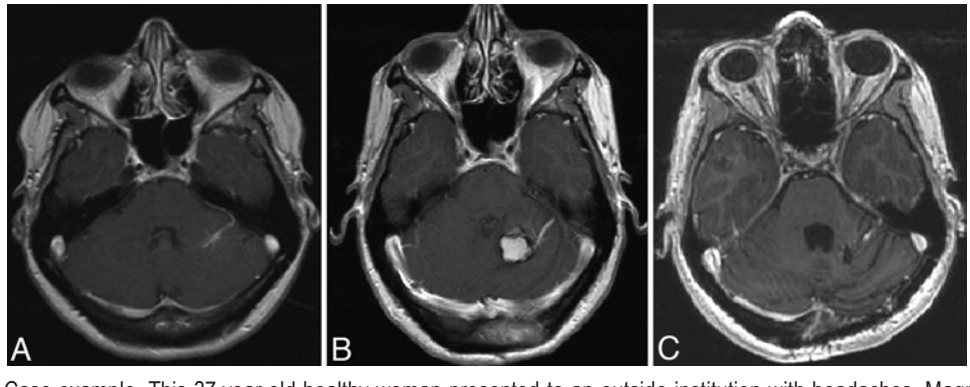

Fig. 1. Case example. This 37-year-old healthy woman presented to an outside institution with headaches. Magnetic resonance imaging only demonstrated a cerebellar developmental venous anomaly **(A)**. Four years later, the patient presented with acute severe headache and vertigo. She underwent suboccipital decompression at an outside hospital, and postoperative MR imaging demonstrated hemorrhage from a de novo cerebellar CM **(B)**. After transfer to our institution, the lesion was completely resected **(C)**.

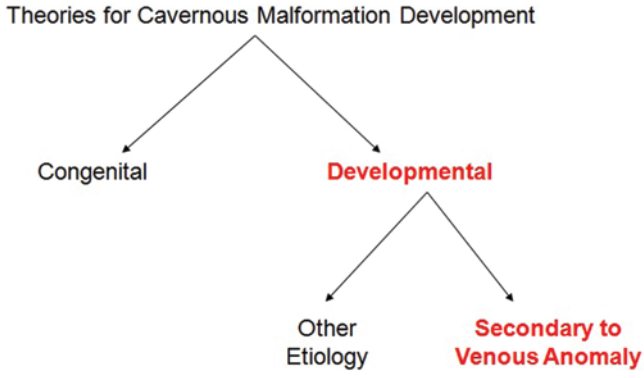

Fig. 2. Theories of CM development. Based on the senior author's extensive operative experience, the association of these lesions with a developmental venous anomaly is almost universal.

gery. Only 32% of those seen intraoperatively were seen on preoperative MR imaging, and only 14% were seen on preoperative angiographic studies, underscoring that these venous anomalies can be radiographically occult.

De novo CM development emphasizes the importance of prospective natural history data as we review in Tables 3 and 4. Frank hemorrhage from these lesions may be a result of venous congestion leading to turgor against the thin endothelial walls of the lesion and resultant rupture into the adjacent parenchyma. This mechanism is further supported by evidence that the radiographic presence of a DVA has been associated with a more aggressive clinical course.[1,3,25,30] Notably, subarachnoid hemorrhage from cavernous malformations is rare, possibly because most are parenchymal lesions that do not proliferate into the subarachnoid space.

An overall annual hemorrhage rate of 2.4% per patient-year was seen across 3 natural history studies,[15,20,23] with an expected, lower 0.7% annual hemorrhage rate per lesion-year reported in the study by Robinson et al.[26] Despite heterogeneity in defining CM hemorrhage, the 2 studies using the most stringent definition of hemorrhage (extralesional hemorrhage and new symptoms) reported the highest and lowest overall annual rates of hemorrhage (0.7% per lesion-year[26] and 3.1% per patient-year),[20] providing validity to this range and our mean hemorrhage rate. Most studies demonstrated increased hemorrhage rates after a prior hemorrhage[2,15,23] and in females.[2,20,27] The latter is reinforced by several reports purporting a hormonal responsiveness of CMs[2,24,26] and by the finding of estrogen receptors on CMs.[24] Gazzaz et al.[12] reported a case of a 26-year-old woman who suffered 4 hemorrhages from a thalamic CM, each occurring 3 weeks after starting hormonal therapy and never recurring once hormonal treatment ceased. The finding of a possibly increased rehemorrhage risk among younger patients in the study of Aiba et al.[2] may also be explained by hormonal influence. Finally, several reports have suggested increased CM aggressiveness in pregnant patients.[10,25,26] The increased venous pressure associated with pregnancy may accentuate an already compromised venous outflow in patients with CM.

Although not used in prospective studies to date, considering the first hemorrhage from a cavernoma as its genesis and considering hemorrhage rates thereafter is a consideration that would likely underscore a more aggressive natural history to these lesions. In addition, it would reveal a true mean age of symptomatic presentation and would provide greater internal validity for specific extrapolation to the patient population seen by neurosurgeons and neurologists, that is, patients with symptomatic CMs.

Other factors such as CM size and multiplicity did not affect hemorrhage rates.[2,15,20,23,26] The latter is reinforced by a mean annual hemorrhage rate of 0.8% per lesion-year (range 0.6%–2%) across familial studies in which most patients harbored multiple CMs.[16,31] Underscored by the 10.6% annual clinical event rate for deep CMs in the study by Porter et al.,[23] lesions in eloquent locations are likely to be clinically more aggressive, although actual annual hemorrhage rates are generally not affected by lesion location.[2,15,20,26] Importantly, there was no significant difference in the degree of recovery between hemorrhagic and nonhemorrhagic clinical events: approximately one-third of patients had resolution of symptoms, one-third improved, and one-third suffered permanent sequelae.[23]

Conclusions

Cavernous malformations generally present in the younger population without a sex predilection. Supratentorial lesions most commonly present with seizures, while other modes of presentation include hemorrhage, headache, and focal neurological deficits. Lesion distribution generally reflects the distribution of CNS tissue, with the majority in the supratentorial compartment. One-fifth of patients overall will harbor multiple intracranial CMs, increasing to at least four-fifths in familial cases. Developmental venous anomalies are present radiographically in approximately one-tenth of cases overall, although they are likely to be more prevalent in aggressive lesions and may play a role in CM development. An overall annual hemorrhage rate of 2.4% per patient year was seen, with prior hemorrhage and female sex increasing the risk of subsequent hemorrhage. Cavernous malformation size, multiplicity, and location did not affect hemorrhage rates, although deep lesions were more clinically aggressive.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Gross, Lin. Analysis and interpretation of data: Day, Gross, Du. Drafting the article: Day, Gross. Critically revising the article: all authors. Study supervision: Day.

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