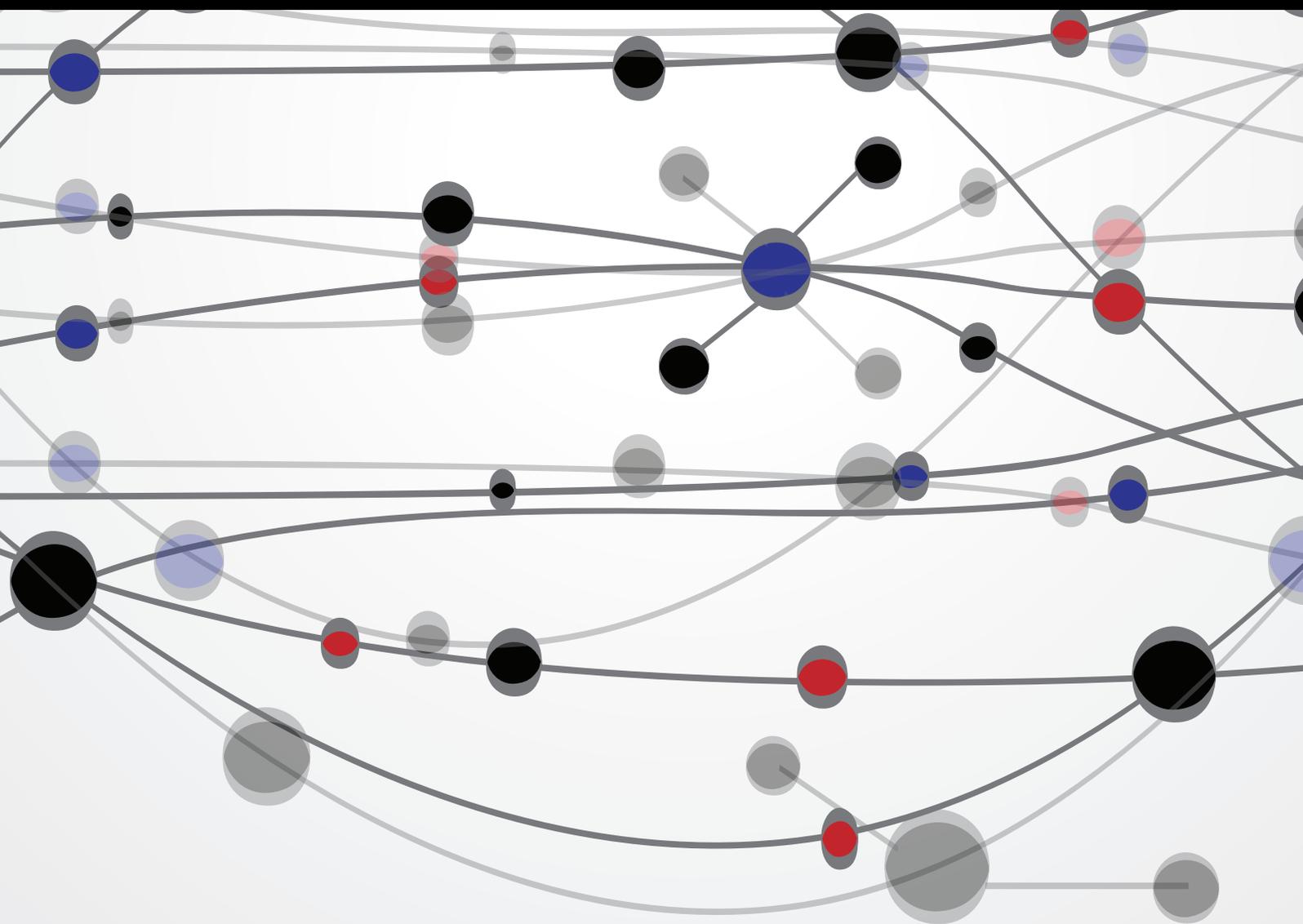


Developments in Neurovascular Diseases and Treatments

Guest Editors: Robert M. Starke, Aaron S. Dumont, Andrew Southerland, Steven J. Montieth, and Webster Crowley





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The Scientific World Journal

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Editorial

Developments in Neurovascular Diseases and Treatments

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Vascular diseases of the cerebral circulation represent a complex and diverse spectrum of pathology. Within the cerebrovascular field, there have been numerous recent advances in patient diagnosis, evaluation, imaging analysis, medical therapies, microsurgical treatments, and minimally invasive therapeutic modalities. These improvements have been driven by research developments from *in vitro*, *in vivo*, translational, and clinical studies. We review and add to the primary literature concerning this special issue.

Stroke is a major cause of morbidity and mortality. Although intravenous tissue plasminogen activator has been a validated medical therapy in patients with acute ischemic stroke, there are many patients who fail to meet the defined time window for treatment. Neuroprotective agents for acute stroke could provide a major therapeutic advantage for many patients. In this issue, H.-K. Liew et al. demonstrate that “Granulocyte-Colony Stimulating Factor Increases Cerebral Blood Flow via a NO Surge Mediated by Akt/eNOS Pathway to Reduce Ischemic Injury.” Further studies are indicated to better define potential alternative medical therapies in acute ischemic stroke patients. Although earlier randomized clinical trials (RCTs) challenged the use of endovascular therapy in acute cerebrovascular occlusion [1–3], refinements in patient selection and three recent RCTs have validated the benefit of endovascular mechanical thrombectomy,

preferably with retrievable stents (i.e., stentrievers), in patients with large vessel occlusion [4, 5]. Limitations of prior RCTs of endovascular stroke intervention included the use of earlier generation thrombectomy devices. In this issue, O. Ozdemir et al. provide us with “Predictors of a Good Outcome after Endovascular Stroke Treatment with Stent Retrievers”.

Long-term follow-up in the International Study of Unruptured Intracranial Aneurysms (ISUIA) [6] and the International Subarachnoid Hemorrhage Aneurysm Trial (ISAT) has validated both microsurgical clipping and endovascular coiling in the treatment of ruptured and unruptured aneurysms [7]. As these outcomes are based on patients who were primarily treated during the 1990s, they may be based on antiquated means of patient evaluation and treatment. Recently, there have been many advances in medical therapies, imaging, microsurgical treatment, and endovascular therapies for cerebral aneurysms [8]. In the current issue, N. Ajiboye et al. provide us with an update on “Unruptured Cerebral Aneurysms: Evaluation and Management.” Cerebral vasospasm continues to be a leading cause of morbidity and mortality following aneurysm rupture. Recent RCTs have not provided us with further therapeutic strategies [9]. Perhaps refinements in patient evaluation and selection will improve patient outcomes. S. H. Sheen et al. provide

a protocol on “Intravenous Flat-Detector Computed Tomography Angiography for Symptomatic Cerebral Vasospasm following Aneurysmal Subarachnoid Hemorrhage.” These new imaging modalities may yield a less invasive means for the evaluation and treatment of patients with aneurysmal subarachnoid hemorrhage.

Recent RCTs and prospective cohort studies have challenged current management strategies for unruptured cerebral arteriovenous malformations (AVMs), but these analyses have not been without limitations [10, 11]. When indicated, current AVM interventions include microsurgery, radiosurgery, and embolization. These therapeutic options are also often used individually or as part of a multimodality approach. In this issue N. Ajiboye et al. provide us with an update through “Cerebral Arteriovenous Malformations: Evaluation and Management.” Additionally, S. Peschillo et al. provide us with a review on treatment options in “Brain AVMs: An Endovascular, Surgical, and Radiosurgical Update.”

Neurovascular diseases are a heterogeneous group of disorders that are often associated with poor clinical outcomes. S. Tabuchi provides us with a review on “Auditory Dysfunction in Patients with Cerebrovascular Disease” and A. Y. Lu et al. provide us with an assessment of “Hemifacial Spasm and Neurovascular Compression.” Although the majority of neurovascular diseases are primarily arterial pathologies, cerebral venous diseases may also incur significant morbidity. To round out this issue, we provide an update and review of “Endovascular Treatment of Venous Sinus Stenosis in Idiopathic Intracranial Hypertension: Complications, Neurological Outcomes, and Radiographic Results.” Although cerebrospinal fluid diversion has been a mainstay of treatment in patients with idiopathic intracranial hypertension (IIH) refractory to medical therapy, recent advances in endovascular therapies have provided an effective alternative treatment option. Specifically, venous sinus stenting has been shown to provide durable neurological improvement in IIH patients with venous sinus stenosis and a significant physiologic pressure gradient. Further studies regarding associated complications, neurological outcomes, and radiographic results are necessary.

Improvements in clinical evaluation, imaging, and treatment will lead to better outcomes in patients with neurovascular disease. Although there continue to be many advances in neurovascular disease, these options must be carefully assessed and compared to existing modalities to ascertain the best practices for our patients. Within this compilation of studies, we hope to elucidate areas of uncertainty, recent developments, and clinical necessity.

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Clinical Study

Predictors of a Good Outcome after Endovascular Stroke Treatment with Stent Retrievers

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Background and Purpose. Successful recanalization after endovascular stroke therapy (EVT) did not translate into a good clinical outcome in randomized trials. The goal of the study was to identify the predictors of a good outcome after mechanical thrombectomy with stent retrievers. **Methods.** A retrospective analysis of a prospectively collected database included consecutive patients treated with stent retrievers. We evaluated the influence of risk factors for stroke, baseline NIHSS score, Alberta Stroke Program Early CT (ASPECT) score, recanalization rate, onset-to-recanalization and onset-to-groin puncture time, and glucose levels at admission on good outcomes. The number of stent passes during procedure and symptomatic hemorrhage rate were also recorded. A modified Rankin Scale (mRS) score of 0–2 at 90 days was considered as a good outcome. **Results.** From January 2011 to 2014, 70 consecutive patients with an acute ischemic stroke underwent EVT with stent retrievers. The absence of a medical history of diabetes was associated with good outcomes. Apart from diabetes, the baseline demographic and clinical characteristics of patients were similar between subjects with poor outcome versus those with good outcomes. Median time from onset to recanalization was significantly shorter in patients with good outcomes 245 (IQR: 216–313 min) compared with poor outcome patients (315 (IQR: 240–360 min); $P = 0.023$). Symptomatic intracranial hemorrhage was observed in eight (21.6%) of 37 patients with poor outcomes and no symptomatic hemorrhage was seen in patients with good outcomes ($P = 0.006$). In multivariate stepwise logistic regression analysis, a favorable ASPECT score (ASPECT > 7) and successful recanalization after EVT were predictors of good outcomes. Every 10-year increase was associated with a 3.60-fold decrease in the probability of a good outcome at 3 months. The probability of a good outcome decreases by 1.43-fold for each 20 mg/dL increase in the blood glucose at admission. **Conclusion.** To achieve a good outcome after EVT with stent retrievers, quick and complete recanalization and better strategies for patient selection are warranted. We need randomized trials to identify the significance of tight blood glucose control in clinical outcome during or after EVT.

1. Introduction

Early recanalization of occluded intracranial vessels is strongly associated with improved functional outcomes in patients with acute stroke treated with intravenous thrombolysis [1]. The overall recanalization rate was 46.2% with intravenous (IV) thrombolysis in a meta-analysis of 53 studies [2]. However, the recanalization rate is low in large vessel occlusions with IV thrombolysis. The complete recanalization rate is 10% in patients treated with IV thrombolysis

for terminal internal carotid artery (ICA) occlusion and 31% in tandem ICA and middle cerebral artery (MCA) occlusion [3, 4]. Endovascular treatment (EVT) aims to increase the recanalization rate in patients with large vessel occlusion. Although recently published randomized trials have demonstrated better recanalization rates with the endovascular stroke treatment (EVT) compared to intravenous (IV) thrombolysis, successful recanalization did not translate into a better outcome with EVT [5–7]. However, in IMS III, SYNTHESIS expansion, and MR RESCUE trials, only

a small proportion of patients were treated with new stent retrievers and this was criticized in these trials [5–7]. EVT with stent retrievers has achieved better recanalization and clinical outcomes when compared with MERCI device and intra-arterial thrombolysis [8, 9]. Nevertheless, even in the stent retriever studies, a good outcome was achieved, no more than 60% of the patients [8, 9]. Therefore, patient selection is mandatory to have a good clinical outcome and for the avoidance of futile recanalization no matter what endovascular approach is used. The aim of our study is to identify the predictors of good outcome after EVT with new stent retrievers. Identifying predictors of good outcome may help us to improve the outcome after acute stroke endovascular treatment.

2. Materials and Methods

We performed a retrospective study of consecutive patients with acute ischemic stroke who underwent EVT with new stent retrievers between January 1, 2011, and February 1, 2014, at Eskisehir Osmangazi University Stroke Center and at Adana Baskent University, Department of Neurology. From 2011 to 2014, 2500 acute stroke patients were admitted to two stroke centers. Two hundred of 2500 (8%) acute stroke patients were eligible for recanalization treatment including intravenous thrombolysis and endovascular treatment. Intravenous fibrinolysis was initiated in 110 of 200 patients. EVT was performed in 90 patients. Among 90 patients, 10 patients received intra-arterial thrombolysis alone and the penumbra mechanical thrombectomy system was performed in 10 patients. Seventy acute ischemic stroke patients who underwent new stent retrievers were included in the analysis. The local ethics committee approved the analysis and data collection.

3. Patient Selection

All patients were evaluated by a stroke neurologist and underwent cranial CT scanning without contrast. Endovascular treatment with new stent retrievers was initiated within 6 h of symptom onset for the anterior circulation stroke and 8 h of symptom onset for the basilar thrombosis. Patients aged 18–80 years presenting with moderate-to-large strokes (NIHSS ≥ 10) in the setting of an angiographically (digital subtraction angiography) proven occlusion of a proximal intracranial artery (e.g., internal carotid artery, middle cerebral artery M1 and/or M2 segments, and basilar or vertebral arteries) were potential candidates for EVT. In accordance with institutional stroke protocol, moderate-to-severe acute stroke patients presenting with 4.5 h after onset received IV rtPA (0.9 mg/kg over 40 minutes) and were examined by a stroke neurologist. In the presence of dramatic clinical improvement (NIHSS ≥ 8), a full dose of IV fibrinolysis was administered and EVT was not considered. If no dramatic clinical improvement was observed after IV rt-PA, patients transferred to neuroangiography suite for EVT. With this protocol, we detected major intracranial vessel occlusion in all of our patients on DSA (Figure 2). In patients with

TABLE 1: Patient selection criteria for endovascular stroke treatment with stent retrievers.

Inclusion and exclusion criteria
<i>Clinical inclusion criteria</i>
Age: 18–80 years
Patients who presented within 6 h of symptom onset for the anterior circulation stroke
Patients who presented within 8 h of symptom onset for the basilar thrombosis
An NIHSS ≥ 10 at the time that I.V rt-PA is begun and if no dramatic clinical improvement was observed after IV rt-PA
Patients who had contraindication to IV rt-PA and NIHSS ≥ 10 at the admission
<i>Clinical exclusion criteria</i>
Moderate to severe stroke patients who had dramatic clinical improvement (NIHSS ≥ 8) after IV rt-PA
History of severe allergy to contrast medium or nitinol
Patients with a preexisting neurological disease that cause moderate disability (mRS ≥ 2)
Advanced and terminal illness
Presumed septic embolus or suspicion of bacterial endocarditis
Clinical presentation suggests a subarachnoid hemorrhage even if the initial CT scan is normal
Baseline lab values: glucose <50 mg/dL or >400 mg/dL, platelets $<100\,000$
<i>Imaging exclusion criteria</i>
CT evidence of intraparenchymal tumor
CT evidence of intracranial hemorrhage
Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on baseline CT or having ASPECT score of <5
MRI or CT evidence of extensive brainstem lesions (e.g., bilateral pons or mesencephalic involvement)

anterior circulation stroke, the presence of early infarct signs within the MCA territory was assessed on baseline CT scans using the Alberta Stroke Program Early Computed Tomography (ASPECT) score [10]. Patients with an evidence of intracranial hemorrhage or major ischemic infarction (acute ischemic change in more than a third of the middle cerebral artery territory or having an Alberta Stroke Program Early CT score of <5) were excluded from EVT. For posterior circulation strokes, patients with extensive brainstem lesions (e.g., bilateral pons or mesencephalic involvement) were excluded from EVT. Patients who had contraindication to IV fibrinolysis or presenting between 4.5 and 6 h for anterior circulation strokes or 4.5 and 8 h for posterior circulation strokes were treated with stand-alone thrombectomy. Patients with known coagulopathy or systemic bleeding disorder and a prestroke score on the mRS ≥ 2 , which could affect the outcome, were excluded from the analysis. Details of the inclusion and exclusion criteria for EVT were given in Table 1.

4. Outcome Measures and Clinical Assessment

Clinical severity at baseline and 24 h after symptom onset was assessed prospectively by using the National Institutes of Health Stroke Scale (NIHSS) conducted by the stroke neurologist. A good outcome was defined as a score of 0 to 2 on the modified Rankin Scale (mRS) at 90 days. A poor

outcome was defined as a score of 3 to 6 on the mRS at 90 days. Subsequent NIHSS recordings were collected at 1 and 24 hours after the EVT. Dramatic recovery was defined as an NIHSS score of 0 to 3 at 24 hours or a decrease of ≥ 10 points in the NIHSS score at 24 hours [11]. Stroke type was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial criteria after a diagnostic work-up was completed [12]. The extent of hypodensity on baseline noncontrast CT (NCCT) was quantified as described in ASPECT score. ASPECT score was presented as dichotomized into ≤ 7 and > 7 [13]. We determined the cutoff point and dichotomization for ASPECT score based on clinical judgement and previous literature [13]. All patients had a CT or MRI scan 24 hours after the EVT.

5. Interventional Treatment

All procedures were performed on a monoplane flat detector angiography machine (Siemens Axiom Artis, Siemens Healthcare, Erlangen, Germany) under conscious sedation. Stent retrievers were used as first-line device. The Revive device (Codman endovascular) was used in 15 cases, the Solitaire FR device (Covidien, Irvine, California) was used in 14 cases, Trevo (Stryker, Kalamazoo, Michigan) was used in 10 cases, and pREset (Phenox GmbH, Bochum, Germany) was used in 31 cases. In the anterior circulation, a 6F guiding catheter or a long 6F sheath (Neuron MAX, Penumbra, Inc., Alameda) was placed in the internal carotid or common carotid artery. In some cases, a triple coaxial system consisting of a long sheath, a five-French intermediate catheter, and a 0.021-inch microcatheter was used. For the posterior circulation, a 6F Envoy guiding catheter (Codman endovascular) was placed through a sheath into the vertebral artery. Cervical access vessel occlusion or stenosis was initially treated with angioplasty. In case of persistent cervical vessel occlusion despite angioplasty, stenting was performed after giving 600 mg clopidogrel and 600 mg acetylsalicylic acid via a nasogastric tube. Except patients who underwent emergency carotid stenting, all patients received 100 mg ASA before EVT in the emergency department. During interventional stroke procedure, 2000 units of bolus heparin were given routinely. A 0.021-inch inner lumen microcatheter was navigated distal to the point of occlusion over a 0.014-inch guidewire. The stent retriever advanced through the microcatheter. After deployment, the stent retriever was maintained in place for approximately 5 minutes. The microcatheter and the fully deployed stent retriever pulled back together under continuous manual aspiration with 50 mL syringe into the guiding catheter or distal access catheter. The modified thrombolysis in cerebral infarction (TICI) score was used to evaluate recanalization results. Successful recanalization was defined as TICI 2b or 3. The treatment was considered a failure if the target vessel was not successfully recanalized with a maximum of 4 passes with stent retrievers. No antiplatelet or heparin was administered within 24 h of procedure. A CT or MRI was performed 24 hours after the procedure. If no hemorrhage was present, aspirin 300 mg/day was given. In the study, the time from symptom onset to groin puncture

(OTP) and from onset to recanalization (ORT) and the number of stent deployments were recorded.

6. Complication Definitions

Hemorrhagic transformations were classified according to radiological and clinical criteria [13, 14]. Hemorrhagic infarction 1 (HI1) was defined as small petechiae along the margins of the infarct and HI2 was defined as confluent petechiae within the infarcted area but no space occupying effect. Parenchymal hematoma 1 (PH1) was defined as blood clots in $\leq 30\%$ of the infarcted area with some slight space-occupying effect, and PH2 was defined as blood clots in $> 30\%$ of the infarcted area with a substantial space occupying effect. Symptomatic intracerebral hemorrhage was defined as local or remote PH2 or PH1 on the 24-hour postprocedural CT scan combined with an increase of ≥ 4 NIHSS points from baseline or leading death [13, 14]. We reported the rate of subarachnoid or intraventricular hemorrhage.

7. Statistical Analysis

The Kolmogorov-Smirnov test for normality and the equal variance test were performed before any statistical analysis was used. Bivariate comparisons were made using χ^2 exact tests for categorical, Student's *t*-test was used for continuous variables, and the Mann-Whitney *U*-test was used for ordinal variables and continuous variables that were not normally distributed. Univariate analysis was performed to compare the outcome, baseline characteristics, procedural parameters, and complications of patients with good outcome and patients with poor outcome after EVT. For multivariate analysis, logistic regression was used to assess the effect of clinical, neuroimaging, procedural parameters on good outcomes (mRS 0–2) with a backward inclusion model. The goodness-of-fit of the models was assessed using Hosmer and Lemeshow χ^2 test. The significance level was set at $P < 0.05$. Statistical analysis was performed using SPSS version 19 (IBM SPSS Statistics; SPSS Inc., Chicago, IL, USA).

8. Results

8.1. Patient Characteristics. During the study period, 70 consecutive (29 female and 41 male; mean age 57 ± 10.4) patients with acute occlusion of intracranial large vessels occlusions underwent EVT with stent retrievers. Detailed patient baseline characteristics, procedural parameters, and target vessels are summarized in Table 1.

8.2. Procedural Results. Thirty-three of 70 patients (47%) received IV thrombolysis before EVT. Fifteen patients (21.4%) received intra-arterial rt-PA and mechanical thrombectomy. After IV thrombolysis, combined intra-arterial rt-PA and mechanical thrombectomy was performed in 13 of 70 patients (18.6%). Stent retriever alone was performed in 21 of 70 patients (30%). Fifty-nine of 70 patients (84%) had anterior circulation stroke (M1, 34 (48.6%); M2, 5 (7.1%); Carotid T, 10 (14.3%); MCA/ICA tandem occlusion 10 (14.3%)). Eleven

out of 20 patients with concomitant cervical carotid occlusion were treated with only angioplasty and 8 patients underwent both stenting and angioplasty prior to an intracranial recanalization procedure. Manual aspiration was performed in one patient for the cervical carotid occlusion followed by stent retriever deployment for MCA occlusion. One patient with proximal MCA occlusion and one patient with carotid T occlusion were treated with angioplasty due to persistent intracranial stenosis after the deployment of stent retrievers. Apart from these patients who underwent angioplasty and stenting, no patients received adjuvant thrombectomy device including the penumbra aspiration system, angioplasty, or permanent stenting. Eleven patients (16%) had basilar thrombosis leading to posterior circulation stroke. Successful recanalization (TICI scores of 2b and TICI 3) was achieved in 47 (67%) of 70 patients. Successful recanalization rates did not differ significantly between anterior (69%) and posterior (64%) circulation vessel occlusions ($P > 0.05$). Recanalization rates were 76% (25 of 33) and 60% (22 of 37) in patients with or without concomitant IV thrombolysis, respectively ($P = 0.232$). Symptomatic hemorrhage was observed in 8 patients (11.8%). Posttreatment imaging revealed 6 (8.6%) PH1 cases and 4 (5.7%) PH2 cases. Two patients (2.85%) had both diffuse SAH and PH2. Five patients (7.1%) had asymptomatic focal SAH. Symptomatic hemorrhage rates were 12.1% (4 of 33) and 10.8 (4 of 37) in patients with or without concomitant IV thrombolysis, respectively ($P < 0.05$). Administration of intravenous or intra-arterial rt-PA in patients who underwent EVT did not affect the symptomatic hemorrhage rate. Symptomatic hemorrhage was observed in 2 patients in the stand-alone thrombectomy group and 1 in patients who received IV thrombolysis and EVT, 3 in patients who received IV thrombolysis, intra-arterial rt-PA, and EVT, and 2 in patients who received intra-arterial rt-PA and EVT ($P = 0.425$).

8.3. Predictors of Good Outcome. Overall, thirty-seven patients (53%) had poor outcomes (mRS 3–6) and 33 patients (47%) had good outcomes (mRS 0–2) at 3 months. Tables 2 and 3 give the detailed results on the univariate and multivariate analysis of potential factors predicting good clinical outcomes at three months. Univariate analysis was done to compare the baseline characteristics and procedural parameters of patients with good outcomes and poor outcomes at three months. No differences were found in sex, medical history of smoking, hypertension, dyslipidemia, atrial fibrillation, and baseline NIHSS score between patients with good outcomes and those with poor outcomes (Table 2). The absence of a medical history of diabetes was associated with good outcome ($P = 0.022$). The mean age was significantly lower in patients with good outcomes compared with poor outcome patients (60 ± 8.8 versus 54 ± 11.2 ; $P = 0.012$). Patients with good outcomes had significantly lower baseline glucose levels than those with poor outcomes (127 ± 38.5 versus 187 ± 11.2 ; $P < 0.001$). Among patients with anterior circulation stroke, twenty-six of the 42 patients (62%) with ASPECT > 7 and 4 of 13 patients (23.5%) with ASPECT ≤ 7 had a good outcome after EVT ($P = 0.017$). Administration

TABLE 2: Baseline characteristics and procedural parameters of all patients.

Characteristics	
Age, y	57.4 (10.4)
Female sex, <i>n</i> (%)	29 (41.4)
NIHSS score on admission, median (IQR)	20 (18–22)
Vascular risk factors, <i>n</i> (%)	
Hypertension	42 (60)
Diabetes mellitus	21 (30)
Atrial fibrillation	24 (34)
Dyslipidemia	41 (59)
Current smoking	32 (46)
Stroke etiology, <i>n</i> (%)	
Cardioembolism	34 (49)
Large artery disease	27 (38)
Other determined etiology	2 (3)
Unknown etiology	7 (10)
ASPECT > 7 , <i>n</i> (%)	42 (71)
Occlusion site, <i>n</i> (%)	
Carotid T occlusion	10 (14)
MCA/ICA tandem occlusion	10 (14)
M1 middle cerebral artery	34 (49)
M2 middle cerebral artery	5 (7)
Basilar thrombosis	11 (16)
Time issues	
Onset to groin puncture, min	205 (180–251)
Onset to recanalization, min	270 (240–340)
Successful recanalization, <i>n</i> (%)	
(TICI 2b, 3)	47 (67)
Outcome, <i>n</i> (%)	
Modified Rankin Scale: 0–2	33 (47)
Modified Rankin Scale: 3–6	37 (53)
Mortality	19 (27)
Dramatic recovery	29 (41)
Symptomatic ICH, <i>n</i> (%)	8 (11.4)

Values are mean (SD), median (IQR), or *n* (%) as appropriate.

NIHSS: National Institutes of Health Stroke Scale, mRS; Modified Rankin Score, ASPECT; Alberta Stroke Program Early CT Score for MCA territory stroke, and ICH; intracerebral hemorrhage.

A two-sided P value < 0.05 was considered statistically significant. NS: not significant.

of IV thrombolysis prior to EVT did not have influence on the outcome in the analysis ($P = 0.158$). Twenty-five of 29 patients (86.2%) who had a dramatic recovery at 24 hours achieved good clinical long-term outcome and only eight of 41 patients (19.5%) who did not have dramatic recovery achieved good clinical long-term outcome ($P < 0.001$). Twenty-eight of 33 patients (85%) patients with good outcome achieved successful recanalization as compared to 19 of 37 patients (51.4%) with poor outcome ($P = 0.006$). The median OTP time was non-statistically significantly shorter

in patients with good outcomes 187 (IQR: 150–240) compared with those with poor outcomes (240 (IQR: 180–300); $P = 0.088$). Median time from onset to the achievement of recanalization was significantly shorter in patients with good outcomes 245 (IQR: 216–313) compared with poor outcome patients (315 (IQR: 240–360); $P = 0.023$). Twenty-five of 32 patients (78%) had good clinical outcome if symptom onset-to-recanalization time was ≤ 5 hours. However, in the presence of symptom-to-recanalization time beyond 5 hours, only nine of 23 patients (39%) had a good outcome despite successful recanalization after EVT. The median number of passes with stent retrievers was significantly lower, 1 (IQR: 1–2), in patients with good outcome than in those with poor outcome (2 (IQR: 2–3); $P = 0.008$). Only 11 of 24 patients (46%) achieved complete recanalization if more than two passes with stent retrievers were required compared with patients who required ≤ 2 attempts (78%; $P = 0.013$). Nine of 11 basilar thrombosis patients (81%) and 15 of 59 patients (25%) with anterior circulation vessel occlusions required more than >2 passes with stent retrievers ($P = 0.001$). Symptomatic intracranial hemorrhage occurred in eight (21.6%) of 37 patients with poor outcome and no symptomatic hemorrhage was observed in patients with good outcome ($P = 0.006$). Patients with symptomatic intracranial hemorrhage had higher admission glucose levels compared with those without hemorrhage (202 ± 85 versus 153 ± 58 ; $P = 0.038$).

In multivariable logistic regression analysis, including the admission NIHSS score, OTP time, age, serum glucose levels, and recanalization, dichotomized ASPECT was performed. As shown in Table 3, age, serum glucose levels, presence of successful recanalization, and ASPECT > 7 on CT were predictors of good clinical outcomes. Every 10-year age increase was associated with a 3.60-fold decrease in the probability of a good functional outcome at 3 months. The probability of a good outcome decreases by 1.43-fold for each 20 mg/dL increase in the admission blood glucose. Recanalization was the strongest independent predictor of a good outcome (OR: 48.6; 95% CI: 4.2–559; $P = 0.002$).

9. Discussion

This study including analysis from two centers assessed the predictors of good clinical outcomes of patients being treated with stent retrievers. We have identified that a favorable baseline CT (ASPECT score > 7), and successful recanalization (TICI 2b-3) are independent predictors of good clinical outcomes (Table 4). Older age and higher glucose levels have a negative impact on clinical outcome. In addition, shorter symptom-onset-to-recanalization time and reduced numbers of stent deployment during the procedure are associated with good clinical outcome.

There is compelling evidence that a good clinical outcome is strongly correlated with successful recanalization [2]. In the present study, we found that complete recanalization is the most powerful independent predictor of good clinical outcomes after EVT with stent retrievers. The IMS III study showed no benefit of endovascular procedures over

TABLE 3: Predictors of good clinical outcome.

Variable	Good outcome <i>n</i> = 33	Poor outcome <i>n</i> = 37	<i>P</i>
Age, y	53.8 \pm 2.0	60.7 \pm 2.0	0.012
Female sex, <i>n</i> (%)	13.8 (39.4)	16 (43.2)	0.934
NIHSS score on admission, median (IQR)	20 (18–22)	21 (20–22.5)	0.064
Vascular risk factors, <i>n</i> (%)			
Hypertension	17 (51.5)	25 (67.6)	0.261
Diabetes mellitus	5 (15.2)	16 (43.2)	0.022
Atrial fibrillation	10 (30.3)	14 (37.8)	0.681
Dyslipidemia	18 (54.5)	23 (62.2)	0.687
Current smoking	17 (51.5)	15 (40.5)	0.497
Cardioembolic stroke etiology, <i>n</i> (%)	13 (39.3)	20 (54)	0.324
Large artery disease, <i>n</i> (%)	14 (51.8)	19 (44.1)	0.704
ASPECT >7 , <i>n</i> (%)	26 (87)	16 (55.2)	0.017
Admission glucose, mg/dL	126 \pm 38.5	187 \pm 67.6	0.002
Occlusion site, <i>n</i> (%)			
Carotid T occlusion	2 (21.6)	8 (6.1)	0.09
MCA/ICA tandem occlusion	5 (13.2)	5 (15.2)	1.00
Basilar thrombosis	3 (9.1)	8 (21.6)	0.267
Time issues			
Onset to groin puncture, min	187.5 (150–240)	240 (180–300)	0.088
Onset to recanalization, min	245 (216–314)	315 (240–360)	0.023
Onset to recanalization >5 h*	7 (22)	14 (61)	0.008
Successful recanalization, <i>n</i> (%)			
(TICI 2b, 3)	28 (85)	19 (51.4)	0.006
Number of stent deployment	1 (1-2)	2 (2-3)	0.008
IV thrombolysis, <i>n</i> (%)	19 (57.6)	14 (37.8)	0.158
Symptomatic ICH, <i>n</i> (%)	0 (0)	8 (21.6)	0.006

Values are mean (SD), median (IQR), or *n* (%) as appropriate. NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Score, ASPECT; Alberta Stroke Program Early CT Score for MCA territory stroke, and ICH: intracerebral hemorrhage. A two-sided *P* value <0.05 was considered statistically significant. NS: not significant. *Patients who achieved successful recanalization were included in the analysis.

standard IV thrombolysis; however, the rate of successful recanalization (TICI 2b-3) was $<45\%$ [6]. The lower rate of successful recanalization in IMS III may be related to less use of newer technologies such as stent retriever. The Solitaire With the Intention for Thrombectomy (SWIFT) trial and the TREVO II trial compared new technology stent retrievers with a first-generation MERCI retriever and have shown the superiority of stent retrievers over MERCI retriever in

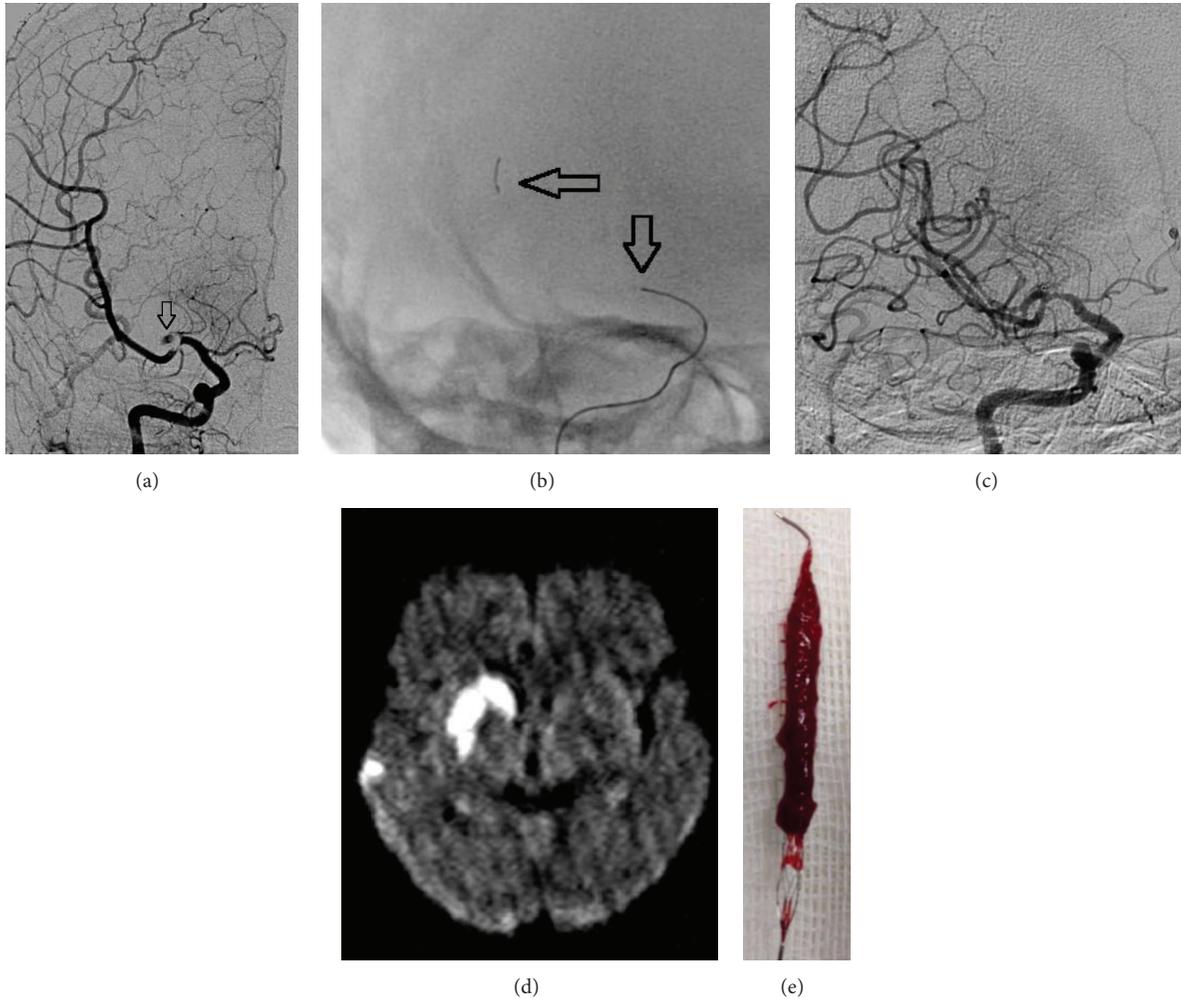


FIGURE 1: (a) Angiogram shows a thrombus on proximal MCA and an occlusion of superior division of MCA. (b) Deployed REVIVE device (distal and proximal markers = black arrow). (c) After retrieval of the stent, the vessel is recanalized to a TICI-3 state. (d) Control MRI scan shows right hemispheric striatocapsular infarction and multiple parietal small embolic infarctions. At 3 months, patients had a good outcome. (e) Large thrombus is adherent to the stent struts.

TABLE 4: Results of logistic regression to find independent predictors of good clinical outcome.

	OR	95% CI	P
Age, years	0.893	0.805–0.990	0.032
Glucose, mg/dL	0.98	0.962–0.996	0.017
ASPECT >7, <i>n</i>	9.63	1.34–69	0.024
Successful recanalization, <i>n</i>	43.8	3.314–580	0.004

NIHSS: National Institutes of Health Stroke Scale and ASPECT: Alberta Stroke Program Early CT Score for MCA territory stroke. Onset-to-groin puncture time and NIHSS score were included in the analysis and did not predict good outcome.

achieving successful revascularization [8, 15]. Since TICI and modified TICI are superior to TIMI for evaluating tissue reperfusion and predicting clinical outcome, TICI scale was used in our study [16, 17]. Unlike the SWIFT trial, which has

used the TIMI grading scale, recanalization was assessed with the TICI scale in the TREVO II trial [8]. In the TREVO II trial, 68% of the patients achieved successful recanalization (core laboratory, TICI ≥ 2b). In line with TREVO II trial, successful recanalization rate was 67% in our study [15].

In present the study, time to recanalization was associated with good outcomes. Moreover, good clinical outcomes were observed in 78% of patients after EVT if symptom-onset-to-recanalization time was ≤5 hours. A recent analysis of pooled data from the MERCI, TREVO, and TREVO II trials showed an 11% increase in the odds of functional dependence in every 30-minute delay from stroke onset to endovascular treatment [18]. Furthermore, previous studies have shown that onset-to-reperfusion time has a great impact on mortality, functional outcomes, and intracerebral hemorrhage rates [18–21]. A prospective multicenter registry of patients with basilar artery occlusion showed an association between early recanalization and a more favorable outcome and all patients with severe stroke treated >9 hours after symptom onset did not benefit

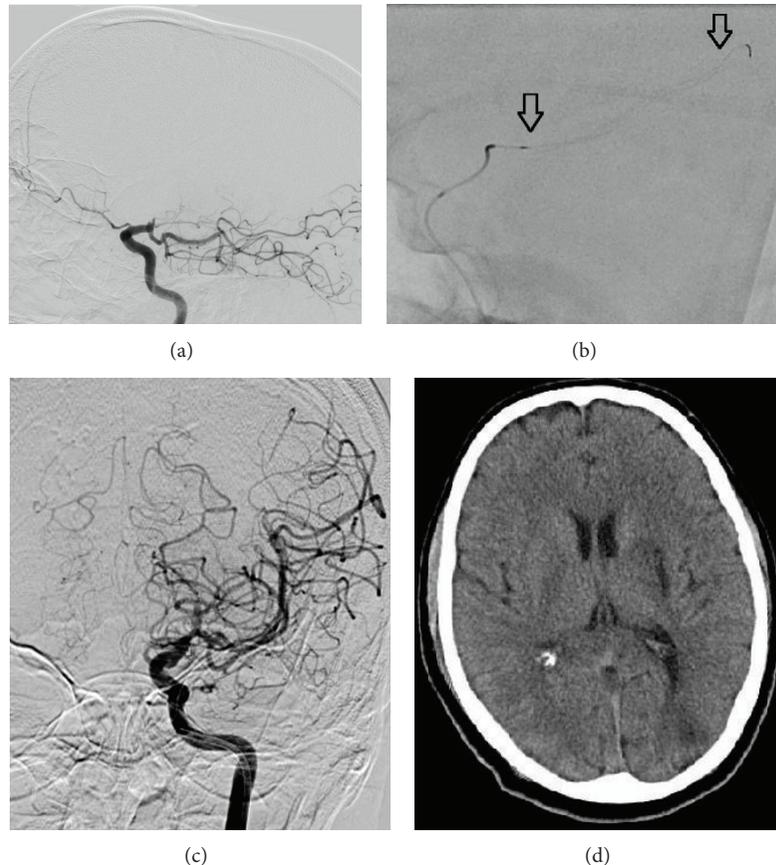


FIGURE 2: (a) DSA reveals persistent carotid T occlusion and fresh thrombus on the occluded segment. Fetal PCA is observed on the lateral projection (black arrow). (b) Deployed Trevo-ProVue device (distal and proximal markers = black arrow). (c) After two passes with Trevo device, successful recanalization was achieved (TICI 2b). Both anterior cerebral arteries are filled from right hemisphere. (d) Control CT scan shows small infarction on basal ganglia.

from recanalization therapy [22]. In the endovascular arm of the IMS III trial, important delays were demonstrated prior to reperfusion.

Several studies have shown that baseline core infarct size is an important predictor of endovascular treatment outcomes [23, 24]. MR diffusion-weighted imaging is the most accurate method to identify infarct core; however, NCCT remains the most commonly used neuroimaging modality [24]. Using ASPECT score to rate ischemic change on NCCT may provide a systematic method to quantify early ischemic changes in the brain due to acute ischemic stroke in the anterior circulation [25, 26]. In the present study, a favorable baseline CT scan (ASPECT > 7) was independent predictor of a 90-day good clinical outcome after EVT with stent retrievers. Moreover, 62% of anterior circulation stroke patients with baseline favorable CT scans achieved good clinical outcomes. In a large study of patients with anterior circulation stroke treated with the Penumbra system supports the importance of pretreatment NCCT ASPECT score in predicting clinical outcomes after EVT. Higher ASPECT score was associated with reduced mortality and better functional outcomes [10]. Moreover, patients with favorable baseline CT scans (ASPECT > 7) were almost twice

as likely to achieve a favorable outcome in the IMS III trial [27].

In this study, younger age was an independent predictor of good clinical outcomes. In addition, every 10-year age increase was associated with a 3.6-fold decrease in the probability of good outcome. In a multicenter study of endovascular treatment of anterior circulation stroke, outcome was highly dependent on patients' age. Good clinical outcomes were observed in 60% of the patients within the lowest age quartile (range: 18–56 years). In contrast, only 37% of patients within the range between 69 and 76 years had good clinical outcomes. Furthermore, even in the absence of any hemorrhagic complications and after the exclusion of patients with prestroke disability, older age exists as a predictor of poor outcomes despite successful recanalization [28]. A recent analysis of pooled data confirms the dramatic impact of age on outcomes after EVT. Every 10-year age increase was associated with a 92% relative increase in the odds of functional dependence after EVT with a TREVO thrombectomy device. The proportion of functional dependence was 82% in those aged >80 years and only 28% in people who aged ≤60 years [18]. Reduced plasticity, impaired collateral circulation, higher frequency

of prestroke comorbid conditions and poststroke medical complications, and difficult vessel anatomy may contribute to reduced functional outcomes in older age [28]. Although advanced age has some negative effect on EVT outcome, it is important to consider all predictors of good clinical outcomes globally, rather than excluding patients from EVT only because of advanced age.

Our analysis demonstrated a 1.43-fold decrease in the probability of a good outcome for each 20 mg/dL increase in blood glucose at admission. Furthermore, admission glucose level was significantly associated with increased risk of symptomatic ICH after EVT with stent retrievers. In a registry and systematic review, admission blood glucose and history of diabetes mellitus were associated with poor clinical outcomes and increased risk of ICH in patients treated by IV and/or intra-arterial therapy [29]. Moreover, a multicenter trial evaluated the prognostic significance of blood glucose at admission and change in blood glucose at 48 hours from the baseline value in diabetic and nondiabetic patients before and after EVT. The failure of blood glucose decrease in the first 48 hours (glucose level drop > 30 mg/dL) and higher blood glucose levels (glucose \geq 116 mg/dL) were both significant predictors of poor outcome and death. Only higher glucose levels at admission were associated with poor outcomes in diabetic patients [30]. There are several explanations regarding the contribution of higher glucose levels to poor outcomes and ICH. Hyperglycemia is associated with larger infarct volumes and reduced salvage of perfusion-diffusion mismatch tissue [31]. On the other hand, hyperglycemia may cause a larger increase of the infarct volume leading to a worse clinical outcome despite recanalization [32]. Increased risk of ICH in patients with hyperglycemia after EVT may be due to the blood-brain barrier disruption and microvasculature impairments [33, 34].

In the study, the median number of stent deployment was lower in good outcome patients. On the other hand, patients who required more passes (number of stent deployment > 2) with stent retrievers were less likely to achieve successful recanalization. A larger clot extent and proximal clot location causing resistant clots may explain the association between lower recanalization rates and the need for more passes with stent retrievers. The majority of patients with basilar thrombosis required more than 2 passes with stent retrievers during EVT. Thus, additional endovascular strategies such as the Penumbra aspiration system may be used in these patients.

Our study has several limitations. The retrospective nature of the study is a limitation. Data were extracted from a prospectively collected database, but the angiograms were retrospectively analyzed (Figure 1). The overall number of patients analyzed is small and thus may reduce the significance of our statistical analysis. We did not consider EVT in patients with advanced age (\geq 80 years); therefore, our results may not be fully representative of the entire stroke population. Posterior circulation stroke patients were included in the analysis and the bias may be introduced since NIHSS score provides limited information. Furthermore, the associations of collateral flow and thrombus length with good

outcomes have not been investigated systematically in this analysis.

10. Conclusion

There are multiple factors that determine the predictors of good clinical outcome in patients who underwent endovascular treatment with stent retrievers. It is important to achieve quick and higher rates of recanalization to improve good outcome. Hence, reducing the delays before or during endovascular stroke procedure is recommended. History of diabetes and higher admission glucose levels are inversely related to good outcome. Randomized trials are warranted to delineate the significance of tight blood glucose control on clinical outcome in the setting of endovascular stroke treatment. Clearly, in a time period, a large number of RCTs are underway; the only sensible course of action for a self-respecting intervention center is joining a multicenter trials. If not possible, the second best one would be to meticulously register all patients and adhere to protocols, until either trials have convincingly proven the absence of the presence of a clinically relevant treatment effect.

Conflict of Interests

Ozcan Ozdemir, Semih Giray, Zulfikar Arlier, Demet Funda Baş, Yusuf Inanc, and Ertugrul Colak declare that they do not have any conflict of interests disclosure.

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Research Article

Granulocyte-Colony Stimulating Factor Increases Cerebral Blood Flow via a NO Surge Mediated by Akt/eNOS Pathway to Reduce Ischemic Injury

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Granulocyte-colony stimulating factor (G-CSF) protects brain from ischemic/reperfusion (I/R) injury, and inhibition of nitric oxide (NO) synthases partially reduces G-CSF protection. We thus further investigated the effects of G-CSF on ischemia-induced NO production and its consequence on regional cerebral blood flow (rCBF) and neurological deficit. Endothelin-1 (ET-1) microinfused above middle cerebral artery caused a rapid reduction of rCBF (ischemia) which lasted for 30 minutes and was followed by a gradual recovery of blood flow (reperfusion) within the striatal region. Regional NO concentration increased rapidly (NO surge) during ischemia and recovered soon to the baseline. G-CSF increased rCBF resulting in shorter ischemic duration and an earlier onset of reperfusion. The enhancement of the ischemia-induced NO by G-CSF accompanied by elevation of phospho-Akt and phospho-eNOS was noted, suggesting an activation of Akt/eNOS. I/R-induced infarct volume and neurological deficits were also reduced by G-CSF treatment. Inhibition of NO synthesis by L-N^G-Nitroarginine Methyl Ester (L-NAME) significantly reduced the effects of G-CSF on rCBF, NO surge, infarct volume, and neurological deficits. We conclude that G-CSF increases rCBF through a NO surge mediated by Akt/eNOS, which partially contributes to the beneficial effect of G-CSF on brain I/R injury.

1. Introduction

Cerebral stroke is a medical emergency which has been one of the leading causes of death and disability worldwide. Cerebral ischemia/reperfusion (I/R) injury is most frequently observed in the vascular territory of the middle cerebral artery (MCA). Therapeutic intervention by reestablishing blood flow is an essential strategy. Therapeutic benefit of thrombolytics such as recombinant tissue-plasminogen activator (rt-PA) remains limited by hemorrhagic side effects and narrow therapeutic time window [1]. A neuroprotective drug that can reestablish cerebral blood flow (CBF) without side effects is thus needed.

Granulocyte-colony stimulating factor (G-CSF) is a cytokine that can penetrate the blood brain barrier [2, 3]

to exert neuroprotective effects against cerebral I/R injury [4–7]. The neuroprotective effects of G-CSF are mediated via various mechanisms, including antiapoptosis, anti-inflammation, angiogenesis, neuronal differentiation, and stem cell mobilization [5–9]. A long-term neurological recovery promoted by G-CSF from ischemic brain injury has been attributed to the enhancement of angiogenesis through endothelial proliferation to increase vascular surface area, branch points, and length [4]. Despite the long-term vasculature promoting mechanism of G-CSF, the direct effect of G-CSF on regional cerebral blood flow (rCBF) remains unclear.

Nitric oxide (NO) is a key regulator of vascular tone [10]. It is known that NO is produced by NO synthase (NOS). Several growth factors activate protein kinase Akt/PKB which

can phosphorylate endothelial NOS to promote NO synthesis [11, 12]. G-CSF also exerts cardioprotective effect on myocardium during I/R injury via Akt/eNOS pathway [13]. Therefore, we tested the hypothesis that G-CSF may exert neuroprotection through activation of Akt/eNOS pathway, leading to beneficial NO release and the consequent improvement of blood flow in the ischemic brain.

2. Materials and Methods

2.1. General Procedures. All experimental protocols were approved by the Animal Care and Use Committee of the Tzu Chi University, Taiwan, in accordance with guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Animals were housed under a 12-hour light/dark cycle with free access to food and water. Utmost efforts were made to minimize the suffering and the number of animals used.

Male Sprague-Dawley rats (250 g to 350 g) were anesthetized by intraperitoneal pentobarbital (50 mg/kg, i.p., Sigma-Aldrich, St. Louis, MO, USA) or urethane (0.75 g/kg, Sigma-Aldrich). Under anesthesia, a femoral cannula (PE-50 polyethylene tube) was inserted for the monitoring of arterial pressure. The arterial pressure was recorded with MP35 amplifier (BIOPAC system, CA, USA). Body temperature was maintained automatically with a heating pad (CMA-150, CMA Microdialysis, Sweden) at $37.5 \pm 0.5^\circ\text{C}$. Animal was placed in a Stoelting stereotaxic apparatus (Stoelting Co., USA) during the induction of ischemia and real-time measurement of NO level or rCBF, respectively. A midline incision of the scalp was made to expose the skull, and two burr holes were drilled for insertions of microinjection tube for ischemic induction and insertions of laser Doppler Flowmeter probe or NO-selective electrode, respectively. For evaluation of the neurological deficit, animals went through the same procedures but without the femoral cannulation.

2.2. Cerebral Ischemia/Reperfusion (I/R) Injury. Endothelin-1 (ET-1; Sigma-Aldrich, St. Louis, MO, USA) was used to induce transient vasoconstriction of the MCA to achieve I/R as described previously [14–16] with some modification. Briefly, 400 pmol of ET-1 in 10 μL of saline was microinfused (1 $\mu\text{L}/\text{min}$ for 10 minutes) via a 30-gauge needle positioned in proximity to the root of MCA (stereotaxic coordinates: anteroposterior (AP) 0.0 mm, mediolateral (ML) 5.2 mm, and dorsoventral (DV) 8.0 mm relative to bregma). A >75% reduction of rCBF resulting from the ET-1 infusion served as the criterion of successful induction of ischemia.

2.3. Groupings. Rats were randomly assigned as groups 1 to 5: Group 1: sham control ($n = 7$), in which 10 μL of saline was microinfused (1 $\mu\text{L}/\text{min}$) proximate to the root of MCA at 0 min; Group 2: G-CSF ($n = 11$), in which 200 $\mu\text{g}/\text{kg}$ of G-CSF (Kirin Pharma. Co., Ltd, Japan), dissolved in 0.5 mL normal saline, was subcutaneously injected at 0 min without I/R induction; Group 3: I/R ($n = 22$), in which ET-1, 400 pmol in 10 μL saline, was microinjected (1 $\mu\text{L}/\text{min}$) proximate to

the root of MCA; Group 4: I/R + G-CSF, in which G-CSF 50 $\mu\text{g}/\text{kg}$ ($n = 4$ for measurement of blood flow) or 200 $\mu\text{g}/\text{kg}$ ($n = 28$ for measurement of blood flow, NO level, neurological functions, total infarct volume, and western blot analyses), dissolved in 0.5 mL, was subcutaneously injected immediately followed by the ET-1 infusion; Group 5: NOS inhibitor + I/R + G-CSF ($n = 17$), in which NOS inhibitor L-N^G-Nitroarginine Methyl Ester (L-NAME; Sigma-Aldrich, St. Louis, MO, USA) 30 mg/kg, dissolved in 0.5 mL saline, was intraperitoneally administered 30 minutes prior to I/R + G-CSF administration. Rats had free access to food and water before the experiments.

2.4. Real-Time Measurement of Regional Cerebral Blood Flow (rCBF). The rCBF was monitored with MNP 110XP probe (Oxford Optronix, UK) inserted during surgery and connected to a Laser Doppler Blood Flow Perfusion Monitor 403A (OxyFlo 2000, Oxford Optronix, UK). The probe was placed in the striatum at AP 0.0 mm, LM 3.0 mm, and DV 5.0 mm. The rCBF data of the baseline control period were normalized by averaging rCBF values over a 10-minute time period before drug administration by using the following formula: percentage change = $[(df/dF) * 100]$, where df is the flow after injection and dF is the mean flow during the 10-minute baseline control period.

2.5. Real-Time Measurement of Regional NO Concentration. Regional NO levels were monitored with a NO-selective sensor probe that consisted of porphyrin-electroplated, Nafion-coated, and carbon fiber electrodes (INC-020, Inter Medical, Japan) connected to a NO detector (IMN-101, Inter Medical, Japan) as described previously [17]. The electrodes, immersed in a small chamber filled with 0.1M phosphate-buffered saline (PBS, pH 7.4), had been calibrated for sensitivity and selectivity by being exposed to a graded series of various concentrations (10^{-3} , 10^{-4} , 10^{-5} , and 10^{-6} M) of the stable NO donor standard, S-nitroso-N-acetyl-DL-penicillamine (SNAP; Doujin, Kumamoto, Japan) [18]. The calibrated NO-selective electrodes were stereotaxically placed in the striatum at AP 0.0 mm, ML 3.0 mm, and DV 5.0 mm. The relative regional NO values of the baseline control period were normalized by averaging striatal NO voltage values over a 10-minute period before drug administrations.

2.6. Western Blot Analysis. Rats were decapitated under deep anesthesia at 0, 15, and 30 minutes and 1 hour after various treatments. The brains were rapidly removed and the ipsilateral striatum was separated and rapidly frozen in liquid nitrogen and stored at -80°C until further analysis. Protein samples ($n = 4$ for each group) for Western blot were performed as described previously with some modifications [2]. Briefly, equal amounts of protein (80 μg) were loaded onto 8%-sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gel and electrophoresed, followed by blotting of the protein onto a polyvinylidene difluoride (PVDF) membrane (Millipore, Bedford, MA, USA), which were then blocked with 5% nonfat milk in 0.05% Tween-Tris-buffered saline. The membrane was then probed with

primary antibodies overnight at 4°C with gentle rotation. The primary antibodies and concentrations used were as follows: phospho-eNOS (Ser 1177) (Cell Signaling, USA, 1:500), eNOS (Upstate, USA, 1:1000), phospho-nNOS (Ser 1416) (Upstate, USA, 1:500), nNOS (Upstate, USA, 1:2000), phospho-Akt (Ser 472/473) (BD, USA, 1:1000), Akt (BD, USA, 1:2000), and β -actin (BD, USA, 1:10000). Following washing and incubation with the respective secondary antibodies (Chemicon, USA, 1:2000;) for 1 hour at room temperature, the membranes then reacted with chemiluminescent ECL Plus Western blotting detection system (Amersham Biosciences, UK). The bands were visualized by exposure to X-ray films (Kodak, USA) and developed later. Intensities of bands were quantified with a densitometric analysis system (GS-800 Calibrated Densitometer, Bio-Rad, Hercules, CA) and calculated as the optical density \times area of band.

2.7. Measurement of Infarct Volume. Rats were decapitated under deep anesthesia at 24 hours after I/R. Brains were removed and the forebrain was sliced into 1 mm thick coronal sections and stained with 2% 2,3,5-triphenyltetrazolium (TTC; Sigma, MO, USA) for 20 minutes at 37°C in the dark. The sections were photographed and the unstained area (i.e., the infarct area) was quantitated using Image J (NIH, USA). These sections were also used for verification of correct positioning of the ET-1 infusion tube, laser Doppler probe, or NO selective sensor probe.

2.8. Neurological Deficit Testing. Modified Neurological Severity Score (mNSS) was evaluated before (0) and on 1, 2, 3, 7, and 14 days after I/R in I/R, I/R + G-CSF and L-NAME + I/R + G-CSF, respectively. Neurological function is graded on a scale of 0–18 (normal score, 0; maximal deficit score, 18). The mNSS is a composite of motor, sensory, reflex, and balance tests [19].

2.9. Statistical Analysis. All values (regional blood flow, NO expression, and total infarct volume) are presented as means S.E.M. and analyzed by Prism software for Student's *t*-test. The statistical comparisons among multiple groups were made using one way ANOVA followed by Bonferroni correction. In all instances, *n* refers to the number of animals in a particular group. A *P* value of less than 0.05 was considered statistically significant.

3. Results and Discussion

3.1. G-CSF Accelerated Recovery of rCBF following Ischemia. Intracerebral infusion of ET-1 to the proximity of MCA reduced rCBF immediately by 75% of the basal within 5 minutes (resulting ischemia) and maximally by 86.7% within 8.1 \pm 0.6 minutes (I/R, *n* = 8, Figure 1(b)). The blood flow recovered gradually (reperfusion): the time for flow recovery to 50% of the baseline (TFR₅₀) was 39.9 \pm 1.2 minutes (I/R, *n* = 8, Figure 1(c)). G-CSF (50 μ g/kg or 200 μ g/kg) subcutaneously given at the onset of ischemia shortened the TFR₅₀ resulting in an earlier reperfusion (Figures 1(a) and 1(c)). Since 200 μ g/kg G-CSF was more effective in reducing

the TFR₅₀ as compared to the lower dose (50 μ g/kg), it was adopted for subsequent experiments (Figures 1(a) and 1(c)). G-CSF treatment significantly accelerated the recovery of the rCBF during the ischemic period (7 minutes to 43 minutes after the onset of ischemia, Figure 1(b), *P* < 0.05) and induced an early reperfusion as evidenced by the shorter TFR₅₀ (Figure 1(c); I/R + G-CSF (24.0 \pm 2.2 minutes) versus I/R (39.9 \pm 1.2 minutes), *P* < 0.001). The basal systemic blood pressure was 101.6 \pm 3.0 mmHg (*n* = 34), and no significant differences existed between the I/R and I/R + G-CSF rats (data not shown). These results indicated an accelerated recovery of blood flow by G-CSF.

3.2. L-NAME Abolished the Flow Recovery by G-CSF during I/R. Ample evidence suggests that NO production from eNOS is neuroprotective [20–22], especially in maintaining rCBF [20]. Pretreatment with L-NAME, a NOS inhibitor, significantly abolished the effect of G-CSF in shortening of the rCBF during the ischemic period (at 26 to 38 minutes after the onset of ischemia, Figure 1(b), *P* < 0.05) and reversed the TFR₅₀ from 24.0 \pm 2.2 minutes (I/R + G-CSF 200 μ g/kg) to 44.8 \pm 6.1 minutes (L-NAME + I/R + G-CSF) (Figure 1(c), *P* < 0.01). Control animals with saline, G-CSF, or L-NAME alone had no significant effect on rCBF (data not shown). These results indicated that NO produced by NOS might participate in the effect of G-CSF on rCBF during I/R.

3.3. The G-CSF Enhancement of Ischemia-Induced NO Surge Was Attenuated by L-NAME. We further measured the changes of NO by real-time NO detection in the striatal tissue via a NO-selective sensor probe coupled with an *in vivo* voltammetry [17]. Regional NO increased sharply (NO surge) as soon as ischemia occurred, lasted for 35 minutes, and decreased rapidly to the baseline (Figure 2(a)). I/R + G-CSF treatment enhanced the ischemia-induced NO surge within the 5- to 20-minute period (Figure 2(a), *P* < 0.05). G-CSF also significantly increased cumulative regional NO concentration during the 0–15- and 16–30-minute periods (*P* < 0.05), but not 31–45- and 46–60-minute periods (Figure 2(b)). As compared with I/R + G-CSF group, pretreatment with L-NAME abolished NO surge induced by G-CSF within 5 to 38 minutes (Figure 2(a), *P* < 0.05).

These findings might indicate a new mechanism by which G-CSF reduces ischemic damage by promoting early recovery of rCBF through a fast production of NO, the NO surge. NO in turn will dilate cerebral blood vessels and improve collateral blood flow (striatal blood flow).

3.4. The G-CSF Enhancement of Ischemia-Induced NO Surge Was Mediated by Activation of Akt/eNOS Pathway. To elucidate the mechanism of G-CSF-induced NO surge in ischemic brain tissue, we delineated the Akt/eNOS signalling pathway by western blotting (Figures 3 and 4). The I/R significantly increased the levels of phosphorylated eNOS to 4.15 \pm 2.54-fold at 15 minutes (Figure 3(b), *P* < 0.05). As compared with I/R group, G-CSF treatment (I/R + G-CSF) significantly

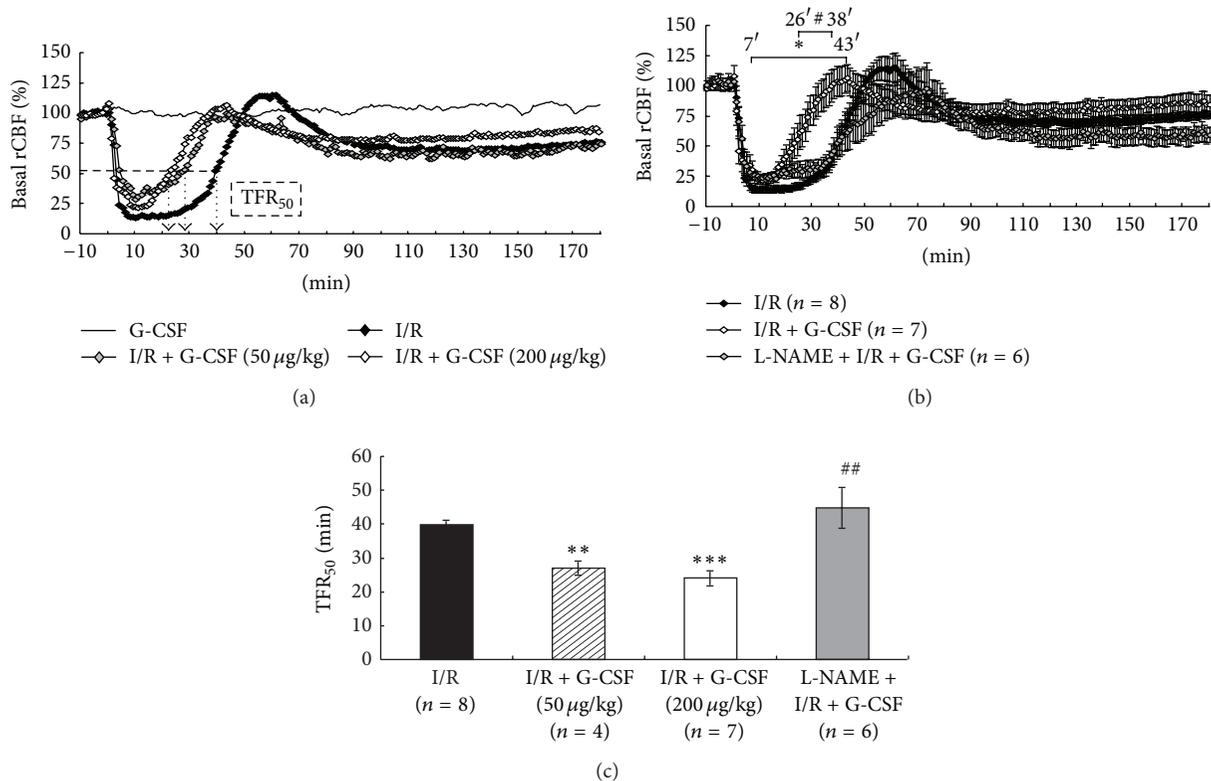


FIGURE 1: Time course of real-time rCBF in rat striata. Representative tracing of rCBF in (a) shows that administration of 50 or 200 µg/kg G-CSF (I/R + G-CSF) significantly accelerated the recovery of striatal rCBF. Further real-time analysis of rCBF in rats with I/R, I/R + G-CSF, and L-NAME + I/R + G-CSF within 3 hours (b) shows that 200 µg/kg G-CSF shortened the recovery time from 43 minutes to as early as 7 minutes (* $P < 0.05$) as compared with I/R. L-NAME pretreatment (L-NAME + I/R + G-CSF) significantly blunted the effect of G-CSF in early recovery of rCBF (from 26 minutes to 38 minutes, # $P < 0.05$) as compared with I/R + G-CSF. (c) Statistical results of TFR₅₀ showing that administration of G-CSF (both 50 µg/kg and 200 µg/kg) significantly accelerated TFR₅₀. 200 µg/kg G-CSF treatment promoted faster TFR₅₀ (24.0 ± 2.2 minutes, *** $P < 0.001$) than 50 µg/kg G-CSF treated rats. 50 µg/kg G-CSF treated rats showed faster TFR₅₀ (27.0 ± 2.0 minutes, ** $P < 0.01$) as compared with the I/R rats (39.9 ± 1.2 minutes). L-NAME-pretreatment (L-NAME + I/R + G-CSF) blunted the shortening of TFR₅₀ (44.8 ± 6.1 minutes, ## $P < 0.01$) as compared with I/R + G-CSF (200 µg/kg) animals. Data are presented as mean percentage changes of basal rCBF \pm S.E.M.

increased the levels of phosphorylated eNOS to 15.66 ± 4.82 -fold at 15 minutes (Figure 3(b), $P < 0.05$), and the elevation diminished at the 30- and 60-minute period in both I/R and I/R + G-CSF groups.

The I/R increased the levels of phosphorylated nNOS to 5.52 ± 0.67 -, 6.46 ± 1.03 -, and 5.25 ± 0.42 -fold, respectively, at 15, 30, and 60 minutes (Figure 3(b), $P < 0.01$). As compared with I/R group, G-CSF treatment (I/R + G-CSF) had no significant effects on phosphorylated nNOS expression at 15 minutes but reduced the phosphorylated nNOS expression at 30 ($P < 0.01$) and 60 minutes ($P < 0.05$) (Figure 3(c)).

The I/R increased the levels of phosphorylated Akt to 3.97 ± 1.24 -, 7.23 ± 1.99 -, and 2.57 ± 0.39 -fold, respectively, at 15, 30, and 60 minutes (Figure 4(b), $P < 0.01$). As compared with I/R group, G-CSF treatment (I/R + G-CSF) significantly increased the expression of phosphorylated Akt to 9.46 ± 2.34 -fold at 15 minutes, but there were no differences at 30 and 60 minutes, respectively (Figure 4(b), $P < 0.01$). The G-CSF treatment (I/R + G-CSF) group had no significant effects on

total eNOS, nNOS, and Akt expression as compared with I/R group (data not shown).

In this study, only the contributions by the constitutive NOSs (eNOS and nNOS) were considered in the G-CSF-induced enhancement of NO production, because the G-CSF effects on NO production were immediate (Figure 3). The catalytic activity of iNOS is only detectable at 12 hours after cerebral ischemia and peak after 48 hours [23]. Several studies have also shown that NO mediates neurotoxicity in primary brain cultures [24–26]; however, NO that is generated from eNOS is considered to be neuroprotective [20–22]. This tissue NO surge is probably due to the activation of eNOS rather than nNOS at initial 15 minutes (Figure 3). It is noteworthy that the timing of the NO production is very important. Early enhancement of NO concentration within 1 hour of ischemic onset is equally effective in both transient and permanent strokes, whereas later treatment is ineffective [27]. In agreement with finding by others [28–30], our results showed that early activation of both eNOS and

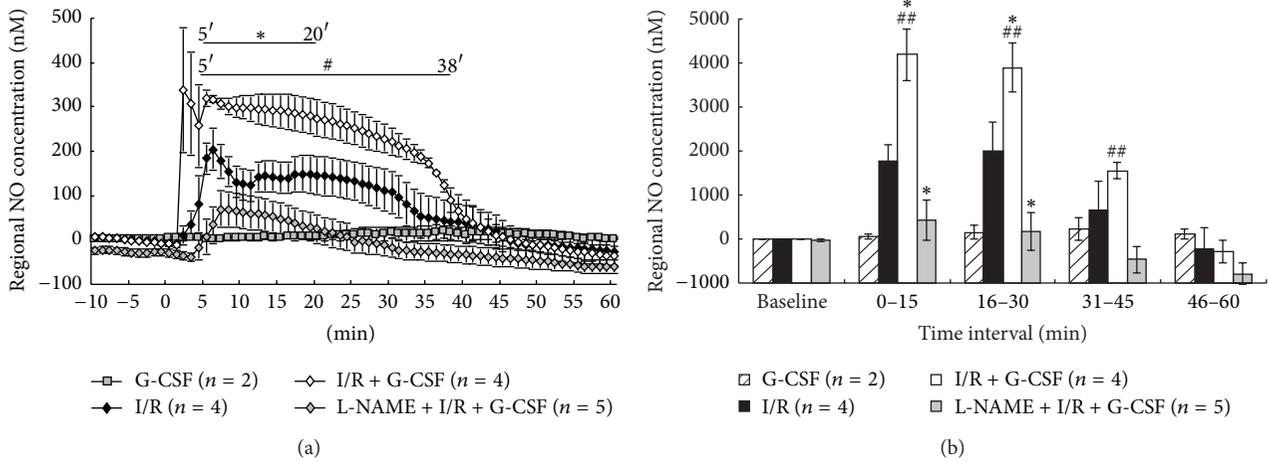


FIGURE 2: Real-time regional nitric oxide (NO) in striatal tissue of rats. (a) I/R induced rapid and sharp NO release (I/R). G-CSF treatment (I/R + G-CSF (200 μ g/kg)) enhanced a marked NO increase (from 5 to 20 minutes, * P < 0.05) as compared to the I/R group. L-NAME pretreatment (L-NAME + I/R + G-CSF) significantly reduced the striatal NO release (from 5 to 38 minutes, # P < 0.05) as compared to the I/R + G-CSF group. (b) Cumulative real-time regional NO concentration (nM) per 15-minute interval shows that the regional NO of I/R + G-CSF increased markedly at both the 0–15- and 16–30-minute intervals (* P < 0.05) as compared to the I/R group. The L-NAME pretreatment (L-NAME + I/R + G-CSF) significantly reduced the regional NO concentration at both the 0–15- and 16–30-minute intervals as compared with I/R (* P < 0.05) or I/R + G-CSF (** P < 0.01). Data are presented as mean of regional NO concentration \pm S.E.M. (nM).

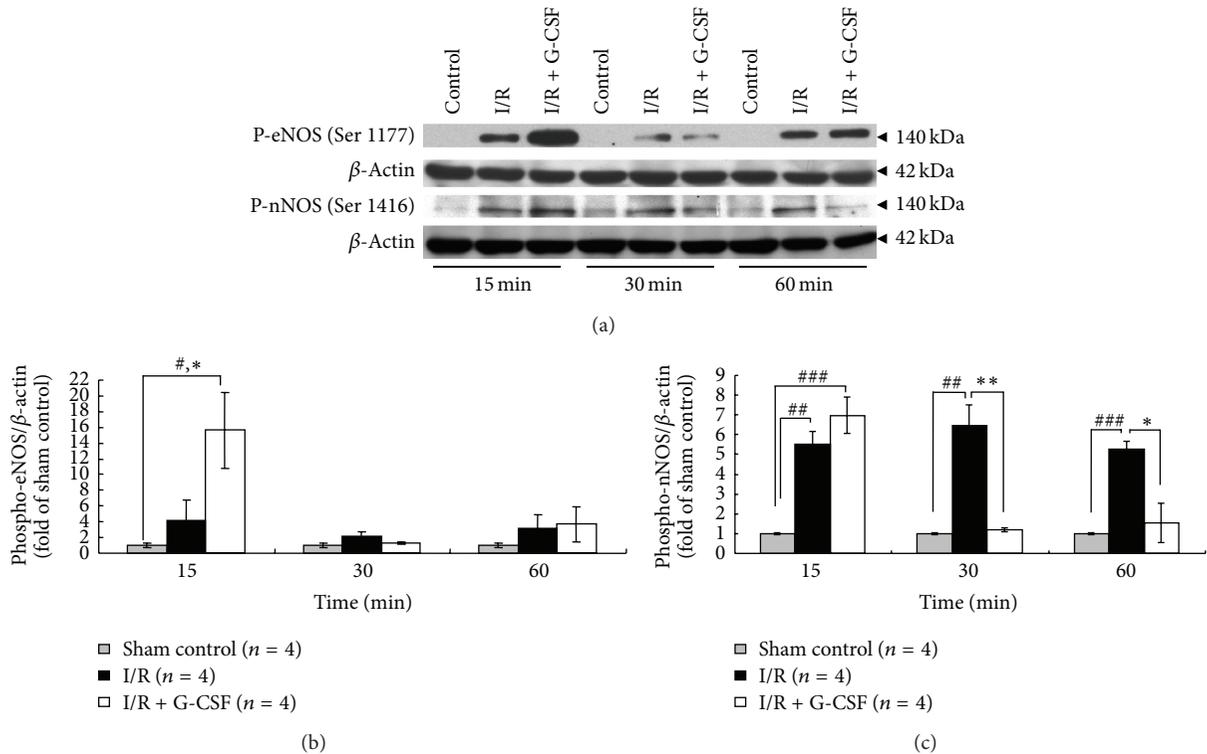


FIGURE 3: Activation of eNOS and nNOS in rats' striatal tissues during ischemia. (a) Representative changes of striatal phospho-eNOS (Ser1177) and phospho-nNOS (Ser1416) at 15, 30, and 60 minutes after ischemia in normal (sham control), I/R, and I/R + G-CSF treated rats. β -actin was loaded as internal quality control and used for normalization in densitometric analyses. Quantitative densitometry analysis showing relative expression of phospho-eNOS (b) and phospho-nNOS (c) as fold of sham control. * P < 0.05 and ** P < 0.01 versus I/R, # P < 0.05 and ## P < 0.01 versus sham control at 15, 30, and 60 min, respectively.

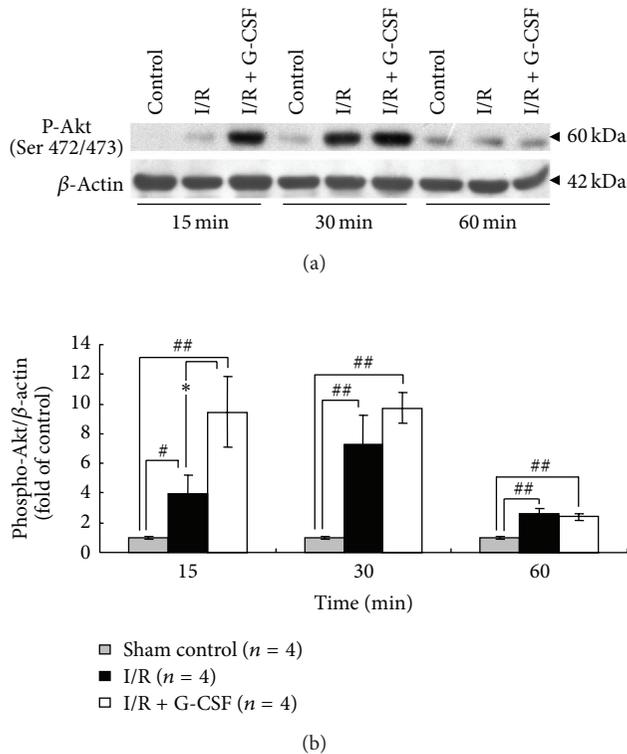


FIGURE 4: Activation of Akt in rats' striatal tissues during ischemia. (a) Representative changes of striatal phospho-Akt (Ser 472/473) at 15, 30, and 60 minutes after ischemia in normal (sham control), I/R, and I/R + G-CSF treated rats. β -actin was loaded as internal quality control and used for normalization in densitometric analyses. (b) Quantitative densitometry analysis showing relative expression of phospho-Akt as fold of sham control. * $P < 0.05$ versus I/R, # $P < 0.05$ and ## $P < 0.01$ versus sham control at each corresponding time point.

nNOS together contributed to a sharp NO increase in the early stage of brain ischemia.

Previous study has indicated that eNOS can be activated by the serine/threonine protein kinase Akt (protein kinase B) on serine 1177, leading to the production of NO [31], which plays an important role in protecting brain tissue by augmenting rCBF after cerebral ischemia [31]. To the best of our knowledge, there has been only one report attributing the ischemia-reperfusion protective effects of G-CSF to the activation of the Akt/eNOS pathway that was in the context of I/R in an isolated perfusion rat heart model [13]. We have expanded this to the more complex neural environment and in an *in vivo* context.

3.5. The Neuroprotective Effects of G-CSF on Total Infarct Volume and Neurological Deficits Were Blunted by L-NAME. Figure 5(a) shows representative brain slices from I/R (I), I/R + G-CSF (II), and L-NAME + I/R + G-CSF (III) treated rats stained with 2% TTC. Measurements of total infarct volume by 2% TTC staining at 24 hours after I/R indicated a 62% reduction in total infarct volume in I/R + G-CSF group

($104.15 \pm 24.72 \text{ mm}^3$) as compared to I/R group ($287.32 \pm 50.51 \text{ mm}^3$) (Figure 5(b), $P < 0.05$). Neurological deficit test also indicated that G-CSF treatment (I/R + G-CSF, $n = 4$) significantly reduced the mNSS (Figure 6. $P < 0.001$ on 1 and 14 days; $P < 0.05$ on 2, 3, and 7 days after the treatment as compared to I/R group, $n = 7$). L-NAME pretreatment (L-NAME + I/R + G-CSF, $n = 5$) blunted the neuroprotective effects of G-CSF in reducing total infarct volume (Figure 5(b), $P < 0.05$ as compared to I/R + G-CSF group) and mNSS (Figure 6, $P < 0.01$ at 1 and 3 days; $P < 0.05$ at 2 and 7 days; and $P < 0.001$ at 14 days as compared to I/R + G-CSF group).

3.6. Does G-CSF Still Have a Chance to Serve as a Stroke Drug? Although ample animal studies and several human trials have demonstrated the potential of G-CSF as a candidate for early stroke drug, the failure of AXIS 2 is a huge setback [32]. AXIS 2 was a European multicenter, randomized, and double-blind placebo-controlled Phase IIb trial. The aim of this trial was to show the clinical efficacy of infusing $135 \mu\text{g/kg}$ body weight G-CSF over a period of 72 hr, for the treatment of acute ischemic stroke which occurred within 9 hours of symptom onset. However, G-CSF failed to meet the primary (improvement on the modified Rankin scale after 90 days) and secondary (less than a half-point difference in the NIH Stroke scale after 90 days) endpoints in AXIS 2. As discussed by the authors, the reasons for the failure of G-CSF remain obscure. As opposed to 5 consecutive subcutaneous injections of $\sim 10 \mu\text{g/kg}$ body weight/day in treating neutropenia, the extraordinary high dose of G-CSF infusion in AXIS 2 was proved to be safe in a previous IIa trial, and thus the dose might not be the cause of failure.

The decrease in mean arterial blood pressure (MAP) and increase in heart rate were unexpected in G-CSF-treated patients. The authors speculated that the decrease in MAP was caused by the direct effect of G-CSF on the vasculature with a lowering of peripheral resistance. Since NO can cause vessel dilation, it will be interesting to learn if G-CSF, when given as early as possible after stroke onset, can help in the recovery of rCBF. Our current study also shows that a NO surge that occurs immediately after stroke is beneficial. It will also be of great interest to learn if G-CSF can exert its therapeutic effect when given simultaneously in the rt-PA therapy. Thus, it is still too premature to deny the application of G-CSF in early stroke therapy.

4. Conclusions

G-CSF is beneficial in terms of promoting early recovery of rCBF, reduction of total infarct volume, and neurological deficit. We have provided evidence supporting enhanced NO production via the activation of Akt/eNOS pathway as the probably mediator of such beneficial effects. Taken together, our results suggest that G-CSF may have the potential as a

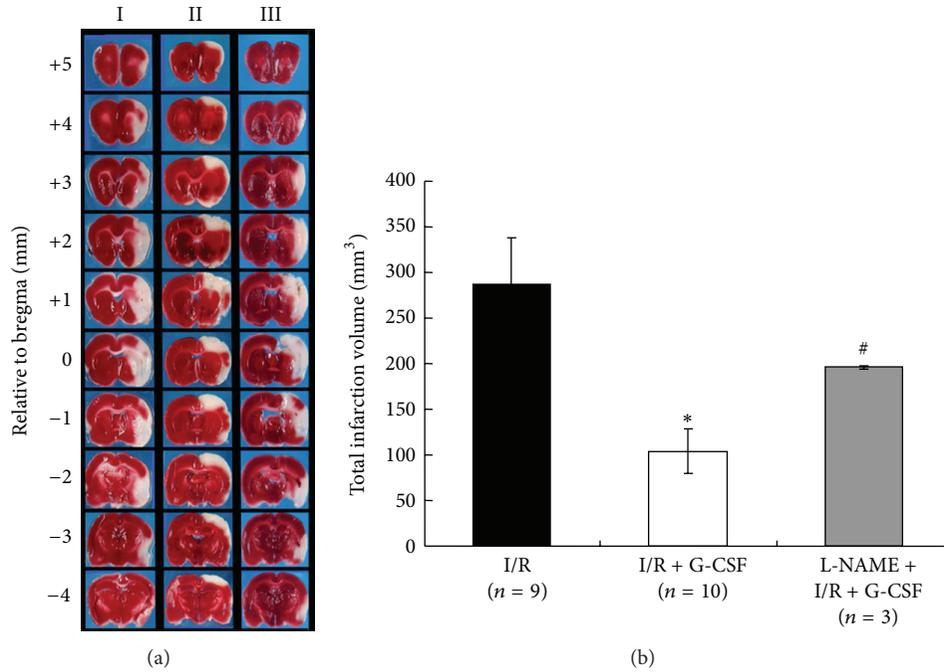


FIGURE 5: TTC staining of brain coronal sections at 24 hours after I/R. (a) TTC-stained coronal sections from I/R (Column I), I/R + G-CSF (Column II), and L-NAME + I/R + G-CSF (Column III) groups at 24 hours after I/R and (b) quantitative measurement of total infarct volumes. * $P < 0.05$ versus I/R and # $P < 0.05$ versus L-NAME + I/R + G-CSF, respectively.

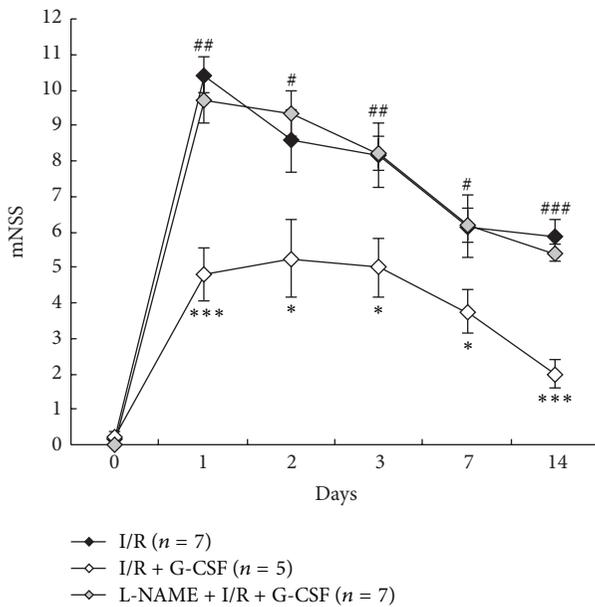


FIGURE 6: The modified Neurological Severity Score (mNSS) before I/R (0) and at 1, 2, 3, 7, and 14 days after I/R after various treatments. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ versus I/R, # $P < 0.05$, ## $P < 0.01$, and ### $P < 0.001$ versus I/R + G-CSF at each corresponding time points.

novel therapeutic agent or part of a therapeutic regimen for acute stroke.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Review Article

Endovascular Treatment of Venous Sinus Stenosis in Idiopathic Intracranial Hypertension: Complications, Neurological Outcomes, and Radiographic Results

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Introduction. Idiopathic intracranial hypertension (IIH) may result in a chronic debilitating disease. Dural venous sinus stenosis with a physiologic venous pressure gradient has been identified as a potential etiology in a number of IIH patients. Intracranial venous stenting has emerged as a potential treatment alternative. **Methods.** A systematic review was carried out to identify studies employing venous stenting for IIH. **Results.** From 2002 to 2014, 17 studies comprising 185 patients who underwent 221 stenting procedures were reported. Mean prestent pressure gradient was 20.1 mmHg (95% CI 19.4–20.7 mmHg) with a mean poststent gradient of 4.4 mmHg (95% CI 3.5–5.2 mmHg). Complications occurred in 10 patients (5.4%; 95% CI 4.7–5.4%) but were major in only 3 (1.6%). At a mean clinical follow-up of 22 months, clinical improvement was noted in 130 of 166 patients with headaches (78.3%; 95% CI 75.8–80.8%), 84 of 89 patients with papilledema (94.4%; 95% CI 92.1–96.6%), and 64 of 74 patients with visual symptoms (86.5%; 95% CI 83.0–89.9%). In-stent stenosis was noted in six patients (3.4%; 95% CI 2.5–4.3%) and stent-adjacent stenosis occurred in 19 patients (11.4%; 95% CI 10.4–12.4), resulting in restenting in 10 patients. **Conclusion.** In IIH patients with venous sinus stenosis and a physiologic pressure gradient, venous stenting appears to be a safe and effective therapeutic option. Further studies are necessary to determine the long-term outcomes and the optimal management of medically refractory IIH.

1. Introduction

Idiopathic intracranial hypertension (IIH) has long been associated with the hallmark clinical triad of headaches, papilledema, and visual loss in the absence of neurologic signs (with the exception of possible CN VI palsy), ventriculomegaly, or intracranial masses on CT or MRI [1]. While the incidence of IIH is relatively low among the general population at 1–2 per 100,000 [1], it can be as high as 19–21 per 100,000 in overweight, young adolescent to middle aged females [2]. To date, a variety of etiologies have

been suggested to explain the pathophysiology behind IIH, including meningeal inflammation, metabolic disturbances (e.g., hyper- or hypoadrenalism and hypoparathyroidism), medication effects (e.g., excess vitamin A, corticosteroids, and tetracycline), and cerebral venous hypertension [3].

The first line treatment for IIH consists of weight loss and/or medical therapy including diuretics such as acetazolamide. When medical treatment fails, surgical options include cerebrospinal fluid (CSF) diversion via ventriculo-peritoneal (VP) or lumboperitoneal (LP) shunting or optic nerve sheath fenestration. Recently, another etiology of

cerebral venous hypertension has garnered increasing attention as a putative cause of IIH, cerebral venous dural sinus stenosis. In medically refractory IIH patients with a physiologic pressure gradient across venous stenosis, cerebral venous stenting has emerged as an alternative treatment option to traditional surgical approaches. While numerous groups have begun to use cerebral venous stenting for the treatment of IIH, the overall safety and efficacy remain unclear. The aim of this paper is to review the available literature on cerebral venous stenting for IIH with specific regard to patient complications, neurological outcomes, and radiographic results.

2. Methods

2.1. Inclusion Criteria. Studies for this systematic review were selected based on the following criteria: (1) the study must include at least one patient treated with cerebral venous sinus stenting for IIH, (2) the study must include posttreatment outcomes data, and (3) the language of the study must be in English. Studies pertaining only to alternative treatments for IIH were excluded.

2.2. Literature Search. A systematic review of the literature was performed using PubMed and the following search strategy: “Idiopathic Intracranial Hypertension” OR “Pseudotumor Cerebri” OR “Benign Intracranial Hypertension” OR “Venous Sinus Stenting.” A filter was used to only return articles written in English language reported after 1980.

2.3. Literature Review and Data Extraction. Information related to patient demographics, disease characteristics, treatment parameters, and poststent complications and outcomes were recorded from the studies that met the inclusion criteria. Whenever possible, we gathered specific demographic information from each study including body mass index (BMI), lumbar puncture opening pressure, mean pre-stent pressure gradient across the stenosis, and mean poststent pressure gradient across the stent.

Recorded data included number and percentage of treatment related complications and clinical outcomes, including improvement or deterioration of headache, vision, papilledema, and/or tinnitus. Major technical complications were defined as those requiring an intracranial intervention or resulting in a permanent neurological deficit. Follow-up imaging results were reviewed for in-stent stenosis and adjacent or out-of-stent stenosis, including retreatment rates.

2.4. Statistical Analysis. The statistical analysis in this review was performed using Stata version 8.0 (StataCorp LP, College Station, TX). Descriptive statistics were obtained for complications, neurological outcomes, and radiographic outcomes.

3. Results

3.1. Patient and IIH Characteristics. The literature review yielded 17 studies comprising 185 patients who underwent 221 venous stenting procedures. The mean patient age was

34.6 years, 161 patients (87%) were female, and the mean BMI was 33.4 Kg/m². The most common presenting symptoms, in order of decreasing frequency, were headache in 89.7% (166/185 patients), papilledema in 63.6% (89/140 patients), visual decline in 60.7% (74/122 patients), and tinnitus in 50.9% (56/110 patients). The baseline patient and IIH characteristics are detailed in Table 1.

The mean opening pressure on lumbar puncture was 35.7 cmH₂O (95% CI 34.8–36.2 cmH₂O). The mean pre-stent pressure gradient was 20.1 mmHg (95% CI 19.4–20.7 mmHg) and the mean poststent pressure gradient was 4.4 mmHg (95% CI 3.5–5.2 mmHg). The overall mean change in gradient from pre-stent to poststent pressure gradient was 17.7 cmHg (95% CI 17.1–18.3 mmHg).

3.2. Periprocedural Complications. Complications were reported in 10 patients (5.4%; 95% CI 4.7–6.1%), including major complications in three patients (1.6%) and minor complications in seven patients (3.8%, Table 2). The major complications were two patients with subdural hemorrhages (SDHs) and one patient with both subarachnoid hemorrhage (SAH), ICH (intracerebral hemorrhage), and SDH. The minor complications were two patients with femoral artery pseudoaneurysms, two patients with transient hearing loss, one patient with a urinary tract infection (UTI), one patient with a syncopal episode, and one patient with a retroperitoneal hematoma. Four patients (2.1%; 95% CI 1.8–2.4%) required additional procedures as a result of complications, including craniotomy for SDH evacuation in two patients, external ventricular drain placement following SAH and SDH in one patient, and femoral artery stent placement for a pseudoaneurysm in one patient.

3.3. Neurological Outcomes. At a mean clinical follow-up of 22 months, patient improvement was noted for headaches in 130 of 166 patients (78.3%; 95% CI 75.8–80.8%), tinnitus in 52 of 56 patients (92.9%; 95% CI 88.7–97.1%), papilledema in 84 of 89 patients (94.4%; 95% CI 92.1–96.6%), and vision in 64 of 74 patients (86.5%; 95% CI 83.0–89.9%, Table 3).

3.4. Radiographic Outcomes. At a mean radiographic follow-up of 15.2 months, in-stent stenosis was noted in six patients (3.4%; 95% CI 2.5–4.3), but only one patient required retreatment (Table 4). Stent adjacent stenosis was more common, occurring in 19 patients (11.4%; 95% CI 10.4–12.4) and requiring treatment in 10 patients (6.0%; 95% CI 5.1–6.9).

4. Discussion

The etiology of IIH has long been debated in the literature and currently remains elusive [21–23]. Intracranial venous hypertension, whether attributable to thrombosis, obstruction, or stenosis, is among the purported mechanisms underlying IIH. [24]. We briefly discuss the current treatments for IIH patients failing best medical therapy and weight loss, which have had varying degrees of success, before critically analyzing the role of cerebral venous sinus stenting.

TABLE 1: Characteristics of patients and cases involved in stenting for IIIH.

Author/year	Number of patients	Number of stents	Age	Female gender	BMI (Kg/m ²)	CSF opening pressure (cm H ₂ O)	Mean prestent pressure gradient (mmHG)	Mean poststent pressure gradient (mmHG)	Mean gradient change (mmHG)
Higgins et al. 2002 [4]	1	1	30	1/1	30.1	35	18	3	15
Owler et al. 2003 [5]	4	4	27 (17-38)	3/4	30 (23-48)	29 (22-35)*	19 (12-25)	0.3 (0-1)	18.7
Higgins et al. 2003 [6]	12	14	33 (19-52)	12/12	36.9 (29-45)	33.7 (25-36)	18.9 (8-37)	11.3 (2-23)	7.6
Ogungbo et al. 2003 [7]	1	1	37	1/1	26.1	>40	25	NR	NR
Rajpal et al. 2005 [8]	1	1	15	0/1	26.9	37	25	NR	NR
Donnet et al. 2008 [9]	10	11	41 (28-60)	8/10	27.3 (22-37)	40.2 (29-59)	19.1 (12-34)	NR	NR
Paquet et al. 2008 [10]	1	1	60	1/1	NR	30	15	NR	NR
Arac et al. 2009 [11]	1	1	51	1/1	29	31	13	2	11
Bussière et al. 2010 [12]	10	13	34 (16-65)	10/10	35.9 (27-47)	NR	28.3 (11-50)	11.3 (2-23)	17
Zheng et al. 2010 [13]	1	1	34	1/1	26.1	40	22.5	6.5	16
Ahmed et al. 2011 [14]	52	60	34 (10-64)	47/52	>30 in 47	32.9 (25-73)^	19.1 (4-41)	0.6 (0-14)	18.5
Albuquerque et al. 2011 [15]	15	30	32.3 (15-51)	12/15	NR	NR	NR	NR	NR
Kumpe et al. 2012 [16]	18	19	37.9 (16-62)	12/18	31.6 (22.6-38)	39.6 (25-55)	21.4 (4-39)	2.6 (0-7)	18.8
Teleb et al. 2012 [17]	1	1	22	1/1	28	48	26	0	26
Radvany et al. 2013 [18]	12	12	39 (21-55)	11/12	32.6 (27.3-45.7)	39.4 (29-55)	12.4 (5-28)	1.3 (0-4)	11.1
Fields et al. 2013 [19]	15	15	34 (20-56)	15/15	39 (30-73)	NR	24 (13-40)	4 (0-9)	20
Ducruet et al. 2014 [20]	30	36	33 (14-52)	25/30	NR	NR	NR	NR	21.4 (10-56)
Characteristics	Number of patients	Number of stents	Mean age (95% CI)	Female gender (%; 95% CI)	BMI (95% CI)	CSF opening pressure (95% CI)	Mean prestent pressure gradient (95% CI)	Mean poststent pressure gradient (95% CI)	Mean gradient (95% CI)
Summary	185	221	34.6 (34.0-35.1)	161 (87.0; 0.86-0.89)	33.4 (32.6-34.3)	35.7 (34.8-36.2)	20.1 (19.4-20.7)	4.4 (3.5-5.2)	17.7 (17.1-18.3)

*Not reported in 1 patient.

^Not reported in 11 patients.

TABLE 2: Complications following stenting for IIH.

Author/year	Number of patients	Number of stentings	Complications	Complication rate	Complications requiring additional procedure
Higgins et al. 2002 [4]	1	1	0	0%	N/A
Owler et al. 2003 [5]	4	4	0	0%	N/A
Higgins et al. 2003 [6]	12	14	0	0%	N/A
Ogungbo et al. 2003 [7]	1	1	0	0%	N/A
Rajpal et al. 2005 [8]	1	1	0	0%	N/A
Donnet et al. 2008 [9]	10	11	0	0%	N/A
Paquet et al. 2008 [10]	1	1	0	0%	N/A
Arac et al. 2009 [11]	1	1	0	0%	N/A
Bussière et al. 2010 [12]	10	13	0	0%	N/A
Zheng et al. 2010 [13]	1	1	0	0%	N/A
Ahmed et al. 2011 [14]	52	60	2 major (SDH); 2 minor (transient hearing loss)	7.7%	2 (1 SDH, 1 SDH/ICH/SAH both requiring emergent craniotomy)
Albuquerque et al. 2011 [15]	15	30	1 minor RPH not requiring transfusion	3.3%	0
Kumpe et al. 2012 [16]	18	19	1 major (SAH/SDH); 2 minor (UTI and syncope)	16.7%	1 (SAH/SDH hematoma requiring EVD)
Teleb et al. 2012 [17]	1	1	0	0%	N/A
Radvany et al. 2013 [18]	12	12	0	0%	N/A
Fields et al. 2013 [19]	15	15	1 minor (femoral pseudoaneurysm)	6.7%	0 (femoral pseudoaneurysm resolved compression)
Ducruet et al. 2014 [20]	30	36	1 minor (femoral pseudoaneurysm)	2.8	1 (femoral pseudoaneurysm requiring femoral artery stent)
Characteristics	Number of patients	Number of stents	Complications	Complication rate % (95% CI)	Complications requiring additional procedure (%; 95% CI)
Summary	185	221	10	5.4% (4.7–6.1)	4 (2.1%; 1.8–2.4%)

SAH: subarachnoid hemorrhage.
SDH: subdural hemorrhage.
ICH: intracerebral hemorrhage.
RPH: retroperitoneal hematoma.

4.1. Surgical Interventions for IIH. Surgical therapies are typically considered after medical therapy has failed and generally consist of CSF diversion (serial lumbar puncture, lumboperitoneal shunt, or ventriculoperitoneal shunt) or optic nerve sheath fenestration (ONSF). With regard to CSF diversion procedures, LP shunting is often preferred in IIH patients due to their characteristic silt-like ventricles which increase the difficulty of ventriculoperitoneal shunt placement. However, CSF diversion is fraught with hardware failure and repeated need for revisions along with infections.

A recent review showed that, while LP and VP shunting are highly effective in mitigating IIH symptoms in the immediate postoperative period, both procedures have a fairly high failure rate. The revision rates for both forms of CSF diversion procedure were 60% for LP and 30% for VP shunts [25, 26].

ONSF is typically indicated in IIH patients with visual loss who endorse mild to no headaches. A small dural window created in the optic nerve sheath serves to drain CSF and relieve pressure on the optic disc, thereby helping to preserve vision. Another theory suggests that ONSF serves

TABLE 3: Neurologic outcomes following stenting for IIIH.

Author/year	Number of patients	Number of stents	Improved headache	Improved tinnitus	Improved papilledema	Improved vision	Follow-up
Higgins et al. 2002 [4]	1	1	1/1	NA	1/1	1/1	12
Owler et al. 2003 [5]	4	4	3/4	1/1	4/4	4/4	9.8 (5-12)
Higgins et al. 2003 [6]	12	14	7/12	NR	5/8	7/12	14.2 (2-26)
Ogungbo et al. 2003 [7]	1	1	1/1	NA	1/1	1/1	6
Rajpal et al. 2005 [8]	1	1	1/1	NA	1/1	1/1	6
Donnet et al. 2008 [9]	10	11	8/10	9/9	10/10	9/10	17.2 (6-36)
Paquet et al. 2008 [10]	1	1	1/1	NA	1/1	1/1	NR
Arac et al. 2009 [11]	1	1	1/1	0/1	NA	NA	2
Bussière et al. 2010 [12]	10	13	10/10	3/3	9/9	7/8	20.1 (4-60)
Zheng et al. 2010 [13]	1	1	1/1	NA	1/1	1/1	3
Ahmed et al. 2011 [14]	52	60	40/43	17/17	9/9	19/19	24 (2-108)
Albuquerque et al. 2011 [15]	15	30	12/15 (1: worse, 2: no change)	NR	NR	NR	20 (2-40)
Kumpe et al. 2012 [16]	18	19	10/12 (2: no change)	NR	15/16	NR	43.7 (11-136)
Teleb et al. 2012 [17]	1	1	1/1	NA	1/1	1/1	6
Radvany et al. 2013 [18]	12	12	5/12 (5: no change)	11/11	11/12	10/12	16 (9-36)
Fields et al. 2013 [19]	15	15	10/15 (1: no change, 2: worse, 2: different)	11/14	15/15	2/3	14 (1-49)
Characteristics	Number of patients	Number of stents	Improved headache (%; 95% CI)	Improved tinnitus (%; 95% CI)	Improved papilledema (%; 95% CI)	Improved vision (%; 95% CI)	Mean follow-up (95% CI)
Ducruet et al. 2014 [20]	30	36	18/26 (8: no change)	NR	NR	NR	23 (0-58)
Summary	185	221	130 (78.3; 75.8-80.8)	52 (92.9; 88.7-97.1)	84/89 (94.4; 92.1-96.6)	64/74 (86.5; 83.0-89.9)	22.0 (20.7-23.2)

TABLE 4: Radiographic outcomes following stenting for IHH.

Author/year	Number of patients	Number of stentings	Average radiographic follow-up (months)	Number of in-stent stenoses	Subsequent treatment	Number of out-of-stent stenoses	Subsequent treatment
Higgins et al. 2002 [4]	1	1	1	0	0	0	0
Owler et al. 2003 [5]	9	4	3	0	0	1	0
Higgins et al. 2003 [6]	12	14	NR	2	Thrombolytic therapy	NR	NR
Ogungbo et al. 2003 [7]	1	1	12	0	0	0	0
Rajpal et al. 2005 [8]	1	1	6	0	0	0	0
Donnet et al. 2008 [9]	10	11	6	0	0	0	0
Paquet et al. 2008 [10]	1	1	NR	NR	NR	NR	NR
Arac et al. 2009 [11]	1	1	2	0	0	0	0
Bussière et al. 2010 [12]	10	13	NR	NR	NR	NR	NR
Zheng et al. 2010 [13]	1	1	NR	NR	NR	NR	NR
Ahmed et al. 2011 [14]	52	60	NR	0	0	6	Restenting in 6 patients
Albuquerque et al. 2011 [15]	15	30	12.5	0	0	1	Restenting
Kumpe et al. 2012 [16]	18	19	25.3	0	0	4	Restenting in 1 patient
Teleb et al. 2012 [17]	1	1	12	0	0	0	0
Radvany et al. 2013 [18]	12	12	NA	0	0	2	Restenting in 2 patients and 1 patient requiring VPS
Characteristics	Number of patients	Number of stentings	Average radiographic follow-up (95% CI)	Number of in-stent stenoses (%; 95% CI)	Subsequent treatment (%)	Number of out-of-stent stenoses	Subsequent treatment
Fields et al. 2013 [19]	15	15	9	0	0	0	0
Ducruet et al. 2014 [20]	30	36	22	4	0	5	0
Summary	185	221	15.2 (13.6–16.8) ¹	6 (3.4; 2.5–4.3) ²	1 (0.6) [^]	19 (11.4; 10.4–12.4) ³	10 (6.0; 5.1–6.9) ³

¹Reported in 11 studies (N = 102).²Reported in 14 studies (N = 178).³Reported in 13 studies (N = 166).[^]Refers to 1 patient who received thrombolytic therapy. Not patients received restenting.

to elicit an inflammatory response that results in fibrosis of the optic nerve sheath, thereby preventing the transduction of intracranial pressure via the subarachnoid space to the optic disc. While ONSF often stabilizes vision function in the acute postprocedural period, it has been shown to have failure rates (defined as progressive vision loss after surgery) of 34% at 1 year and 45% at 3 years [15]. Thus, the current treatment options for IIH are limited by their lack of durability and relatively high long-term failure rates.

4.2. Role of Cerebral Venous Sinus Stenting in the Management of IIH. With the increasing recognition of cerebral venous stenosis as an etiology of IIH, dural venous sinus stenting has emerged as a potentially effective treatment. Recent publications have demonstrated promising clinical results with regard to headache and tinnitus resolution, papilledema reduction, and visual function improvement.

While the majority of the data focuses on headache improvement, more recent literatures have also focused on visual outcomes which may improve in a significant number of patients following stenting. However, many of the early studies simply state that treated patients' visual complaints improved without further quantification of pre- and post-procedural visual acuity or visual fields, and therefore it is hard to draw concrete conclusions from these studies [5–8, 13, 17]. More recent data have provided objective measures of ophthalmologic outcomes, including visual acuity and visual field testing [14, 18, 19]. As such, more rigorous ophthalmologic data will be needed in future studies to better substantiate the use of dural venous sinus stenting to improve vision in patients with IIH.

While venous stenting often obviates the need for CSF diversion, it is not without its own set of risks. Many of the reported complications arise from the angiography procedure rather than from stent placement. The most common complications were access related and include a retroperitoneal hematoma and 2 femoral pseudoaneurysms [15, 19, 20]. A more serious complication in the form of SDH and SAH was observed in 1 of 18 patients as reported by Kumpe et al. [16]. During stent placement of the right transverse sinus in this patient, there was stasis of flow in the right sigmoid sinus leading to a left SDH and SAH. The patient was managed successfully with an external ventricular drain. Similar complications were seen in a large series of 52 patients [14]. In this series, two patients had postprocedural SDHs. One patient developed a SDH after guidewire perforation of a dural sinus, while the other patient suffered a SDH along with SAH and intracerebral hemorrhage during emergent stent placement for fulminant IIH. Both patients underwent emergent craniotomies and made a full recovery. Although risks are inherent to any procedure, venous stenting for IIH remains a relatively safe procedure with numerous studies reporting no intraoperative complications [4–6, 11, 12, 18].

As with any stenting procedure, there exist complications inherently related to the stent, namely, in-stent stenosis. Two separate processes have been described for stent-related stenosis in the setting of IIH: in-stent stenosis and stent adjacent stenosis. Stent thrombosis may lead to in-stent stenosis or occlusion [27]. This, in general, would likely

cause the return of the presenting symptoms. However, stent thrombosis may theoretically be disastrous if the thrombus occludes the drainage of the vein of Labbe. The increasing use of periprocedural dual antiplatelet therapy has led to a decrease in the incidence of in-stent stenosis [15, 19], although it has not been totally eliminated [20]. Stent adjacent stenosis is defined as a venous sinus stenosis which develops adjacent to the stent, often in the segment from the torcula to the stent, and is somewhat unique to the dural venous sinuses following stenting. This phenomenon has been described in 19 cases in this review [14–16], of which 10 underwent further stenting. However, some groups were elected to not treat asymptomatic stent adjacent stenosis. The phenomenon of out-of-stent stenosis in IIH raises the question as to whether there exists an inherent pressure from the brain parenchyma itself that serves to push on the venous sinus, giving them a stenosed appearance. Thus, venous sinus stenosis may be a result of idiopathic increased intracranial hypertension rather than a cause of it. Long-term radiographic outcomes and further delineation of the pathophysiology behind dural venous sinus stenosis are indicated in future studies.

Finally, it is important to consider that radiographic evidence of venous sinus stenosis alone is inadequate to justify stenting for IIH. There must also be physiologic evidence of a significant pressure gradient across the stenosis in order for stenting to be clinically efficacious. In our literature review, we found the mean pre-stent pressure gradient to be 20 mmHg. Further studies are necessary to determine the optimal gradient for stenting in IIH patients.

4.3. Study Limitations. This review is limited by the heterogeneity of the case series of which it is comprised. Specifically, there were no reporting standards for the baseline clinical and radiographic characteristics and for the posttreatment outcomes. Additionally, all studies were retrospective, and the number of patients per series was relatively small. Finally, the stent type and design varied across different series, thus limiting further the generalizability of our findings. Given these limitations, venous sinus stenting for patients with medically refractory IIH in whom a radiographic venous sinus stenosis and physiologic pressure gradient are both evident is a Class IIa Recommendation, Level of Evidence C.

5. Conclusions

Cerebral venous dural sinus stenting affords a favorable risk-to-benefit profile for appropriately selected IIH patients who are refractory to medical management and are demonstrated to have both a venous sinus stenosis and a physiologic pressure gradient. The available literature demonstrates that venous stenting is effective, but further long-term, prospective evaluation of this treatment approach is necessary. Specifically, additional studies that define ophthalmologic and radiographic baseline parameters and outcomes are requisite for defining the optimal patient population. Additionally, further work is necessary to determine the best therapeutic option for IIH patients.

Conflict of Interests

The authors report no direct conflict of interests. Pascal Jabbour is a consultant for ev3, Codman, and Mizuho. Aaron S. Dumont is a consultant for ev3 and Stryker.

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Review Article

Unruptured Cerebral Aneurysms: Evaluation and Management

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The evolution of imaging techniques and their increased use in clinical practice have led to a higher detection rate of unruptured intracranial aneurysms. The diagnosis of an unruptured intracranial aneurysm is a source of significant stress to the patient because of the concerns for aneurysmal rupture, which is associated with substantial rates of morbidity and mortality. Therefore, it is important that decisions regarding optimum management are made based on the comparison of the risk of aneurysmal rupture with the risk associated with intervention. This review provides a comprehensive overview of the epidemiology, pathophysiology, natural history, clinical presentation, diagnosis, and management options for unruptured intracranial aneurysms based on the current evidence in the literature. Furthermore, the authors discuss the genetic abnormalities associated with intracranial aneurysm and current guidelines for screening in patients with a family history of intracranial aneurysms. Since there is significant controversy in the optimum management of small unruptured intracranial aneurysms, we provided a systematic approach to their management based on patient and aneurysm characteristics as well as the risks and benefits of intervention.

1. Introduction

Intracranial saccular aneurysms are acquired vascular abnormalities that cause outpouching of the arterial wall. They are often located at the bifurcation of the arteries in the anterior circulation of the Circle of Willis. There has been increased detection of unruptured intracranial aneurysms in clinical practice due to the frequent use of CT and MRI [1]. Therefore, in this review, we present a comprehensive overview of unruptured intracranial aneurysm with special regards to the predictors of rupture, the risks of medical management in comparison to clipping and coiling. We also provide family screening recommendations in patients with unruptured intracranial aneurysm. Furthermore, we discuss new endovascular techniques like flow diverting stents and their current indications.

2. Epidemiology

Intracranial aneurysms occur in 1-2% of the population and account for about 80–85% of nontraumatic subarachnoid hemorrhages [1]. Autopsy studies indicate prevalence in the adult population between 1% and 5%; however, 50% to 80% of all aneurysms do not rupture during the course of a person's lifetime [2]. Unruptured intracranial aneurysms are more common in women with a 3:1 ratio of women to men [3]. Intracranial aneurysms are sporadically acquired lesions; however, a rare familial form has been associated with conditions like autosomal dominant polycystic kidney disease, Marfan's syndrome, Ehlers-Danlos syndrome type IV, fibromuscular dysplasia, moyamoya disease, sickle cell disease, and arteriovenous malformations of the brain [4, 5]. Approximately 5% to 40% of patients

with autosomal dominant polycystic kidney disease have intracranial aneurysms, and 10% to 30% of patients have multiple aneurysms [4, 5]. An important risk factor for aneurysm is a family history. Patients with one affected family member have approximately a 4% risk of having an aneurysm, whereas patients with 2 or more affected first-degree family members have a 8%–10% risk of having an aneurysm [6]. Current guidelines recommend screening with intracranial magnetic resonance angiography for people with two immediate relatives with intracranial aneurysms and for all patients with autosomal dominant polycystic kidney disease [7]. The modifiable factors that may increase the risk for aneurysmal SAH include smoking, alcohol use, and hypertension [7]. The estimated incidence of subarachnoid hemorrhage (SAH) from a ruptured intracranial aneurysm in the United States is approximately 6–10/100,000 person-years [8]. Approximately 5% to 15% of cases of stroke are related to ruptured intracranial aneurysms [8]. Subarachnoid hemorrhage is more common in women than in men (2 : 1) with the peak incidence occurring in persons 50 to 60 years old [9]. The fatality rate for SAH is 30%–40%, and as high as 3 in 5 of those who survive SAH may be functionally dependent [6].

3. Pathology and Pathophysiology

The genetic etiology of intracranial aneurysm is complicated as demonstrated by a large meta-analysis of genetic studies which identified 19 single nucleotide polymorphisms associated with sporadic intracranial aneurysm. The strongest associations were found on chromosome 9 within the CDKN2B antisense inhibitor gene, on chromosome 8 near the SOX17 transcription regulator gene, and on chromosome 4 near the EDNRA gene [9]. Hypertension and smoking-induced vascular changes are involved in the process by which aneurysms form, grow, and rupture [4, 5]. The most common histologic finding is a decrease in the tunica media, the middle muscular layer of the artery, causing structural defects. These defects, combined with hemodynamic factors, lead to aneurysmal outpouchings at arterial branch points in the subarachnoid space at the base of the brain [10].

4. Natural History

Understanding the natural history of aneurysms is important in making treatment decisions. The International Study of Unruptured Intracranial Aneurysms (ISUIA) was a prospective cohort study that followed 1,692 patients with unruptured aneurysms that were 2 mm or larger (1,077 without prior history of SAH). ISUIA documented an overall annual aneurysmal rupture risk of 0.7% [12]. Two important factors in predicting risk of rupture include size and location. Various studies have shown that larger aneurysms have the greatest risk of rupture. However, other factors that can influence rupture risk include aneurysm location and patient factors such as age younger than 50 years, those with hypertension, and those with multiple aneurysms [12].

A Japanese prospective study reported the natural history of patients with aneurysms 3 mm or larger with an annual

rupture rate of 0.95% [14]. Furthermore, the risk of rupture increased with size, with a significant increase for aneurysms 7 mm or larger. Other risk factors for rupture included location on the anterior or posterior communicating artery and presence of a daughter sac [14]. A large meta-analysis from currently available literature demonstrates that other factors including age over 60 years, female sex, Finnish or Japanese descent, aneurysm size over 5 mm, posterior circulation location, and symptomatic unruptured aneurysms have a higher risk of rupture [26].

Findings from many retrospective studies have suggested that rupture risk is reduced in patients taking aspirin [27, 28]. However, it remains unclear whether the benefit of aspirin use in patients presenting with an unruptured intracranial aneurysm outweighs the potential risks, and a randomized double blinded clinical trial will be needed to answer this question with more certainty [29]. In a study of 747 consecutive patients with intracranial aneurysm presenting at a single hospital, the rate of hemorrhage was higher among those not taking aspirin (40%) than among those taking aspirin (28%), but the overall morbidity and mortality outcome of those experiencing subarachnoid hemorrhage was not affected by aspirin use [30]. In a case-control study of 1797 incident cases of intracerebral hemorrhage and subarachnoid hemorrhage, aspirin use was associated with a decreased risk of subarachnoid hemorrhage (odds ratio 0.82, 95% CI 0.67–1.00) compared with no aspirin use [31]. In an analysis of data from the ISUIA untreated cohort, patients who used aspirin most frequently had the lowest risk of aneurysm rupture during follow-up [32].

There are limited natural history data available for patients with familial intracranial aneurysm. ISUIA did not show that a family history was predictive of hemorrhage in a regression analysis. However, in the familial intracranial aneurysm study, 548 first-degree unaffected relatives of people with a familial history of intracranial aneurysm had MRA screening: 113 participants had 148 unruptured intracranial aneurysms, 5 of whom had an unruptured intracranial aneurysm that was 7 mm or larger in diameter. Two patients had aneurysmal rupture during follow-up, which represented an annual rupture rate of 1.2 per 100 patients (95% CI 0.1–4.3). The rupture rate in this cohort was 17 times higher than that for patients with an unruptured intracranial aneurysm in ISUIA after matching for aneurysm size and location. However, the small number of ruptures and large 95% CI precluded definitive conclusions regarding rupture rates in familial aneurysm [33].

Aneurysms presenting with subarachnoid hemorrhage tend to bleed again at a rate of 9% within the first 72 hours after the initial episode [34]. Therefore, patients with known intracranial aneurysms presenting with cranial-nerve palsies or brain-stem dysfunction should be evaluated and treated promptly because of the increased risk of rupture of 6% per year [35].

In a recent article, Greving et al. [11] proposed a practical risk score called PHASES score. It is used to predict a patient's risk of aneurysmal rupture based on population (geographical location), hypertension, age, size of aneurysm, earlier subarachnoid hemorrhage from another aneurysm,

TABLE 1: PHASES aneurysm risk score [11].

Population	
North American or European (except Finnish)	0 point
Japanese	3 points
Finnish	5 points
Hypertension	
No	0 point
Yes	1 point
Age	
Less than 70 years	0 point
Greater than or equal to 70 years	1 point
Size of aneurysm	
Less than 7.0 mm	0 point
7.0 mm–9.9 mm	3 points
10.0 mm–19.9 mm	6 points
Greater than or equal to 20 mm	10 points
Earlier subarachnoid hemorrhage from another aneurysm	
No	0 point
Yes	1 point
Site of aneurysm	
Internal carotid artery	0 point
Middle cerebral artery	2 points
Others like anterior cerebral artery, posterior communicating artery, or posterior circulation aneurysms	4 points
PHASES risk score	5-year risk of aneurysm rupture
Less than or equal to 2	0.4%
3	0.7%
4	0.9%
5	1.3%
6	1.7%
7	2.4%
8	3.2%
9	4.3%
10	5.3%
11	7.2%
Greater than or equal to 12	17.8%

and site of aneurysm. These predictors were selected based on a systematic review of and pooled analysis from 8382 participants in 6 prospective cohort studies with subarachnoid hemorrhage as outcome (readers should refer to Tables 1 and 2).

5. Clinical Presentation

Unruptured intracranial aneurysms may be incidental findings as a result of complaints unrelated to the aneurysm or detected as they grow and cause compression on adjacent brain structures [32]. Such compressions include middle cerebral artery aneurysms causing hemiparesis, visual field defect, or seizure, posterior communicating artery or basilar artery aneurysms causing third cranial nerve palsy, cavernous sinus aneurysms causing a cavernous sinus syndrome, basilar distribution aneurysms causing compression of the brainstem, and, on rare occasions, an embolus from the

aneurysmal sac causing transient ischemic attack or cerebral infarction due to distal embolisation [33]. Other cranial nerves can be involved, including trochlear and abducens nerves and the first division of the trigeminal nerve [36].

6. Diagnosis

The radiographic studies available to delineate the size and morphologic features of an intracranial aneurysm are CT angiography (CTA), magnetic resonance angiography (MRA), and angiography by direct intra-arterial catheterization (catheter angiography), which is considered the gold standard [37].

Several studies have evaluated the accuracy of detecting intracranial aneurysms by comparing CTA, MRA, and catheter angiography [38]. CTA uses thin-section contrast-enhanced CT with the aid of software generated images

TABLE 2: Summary of large studies evaluating the natural history of unruptured cerebral aneurysms.

Study design	Number of aneurysms and patients	Follow-up duration in years	Predictors of cerebral aneurysm rupture	Design flaws
International Study of Unruptured Intracranial Aneurysms (ISUIA) [12]: Retrospective Study in North America and Europe	1937 unruptured aneurysms in 1449 patients	8.3	(1) Size > 10 mm (2) Posterior circulation and posterior communicating artery aneurysms	(1) Selection bias
International Study of Unruptured Intracranial Aneurysms (ISUIA) [12]: Prospective Observational Study in North America and Europe	2686 unruptured aneurysms in 1692 patients	4.1	(1) Size > 7 mm (2) Previous subarachnoid hemorrhage from some other aneurysm (3) Posterior circulation and posterior communicating artery aneurysms	(1) Selection bias (2) Follow-up was <5 years for >50% of patients
Comprehensive Observational Cohort Study by Juvela and colleagues in Finland [13]	181 unruptured aneurysms in 142 patients	21	(1) Patient's age (inversely) (2) Cigarette smoking (3) Size > 10 mm	(1) Small total number of patients (2) Homogeneity of the study population
The Unruptured Cerebral Aneurysm Study of Japan (UCAS): Prospective Cohort Study by Morita et al. [14]	6697 unruptured aneurysms in 5720 patients	Not available	(1) Size > 7 mm (2) Location: anterior and posterior communicating arteries (3) Presence of daughter sac	(1) Selection bias (2) Homogeneity of the study population

to show cerebral vessels in three-dimensional views. These reconstructed images can be generated in a few minutes, and they allow evaluation of the vasculature in close relation to the brain and the bones of the skull base, therefore facilitating surgical planning [39]. Sensitivities of CTA range from 77% to 97% and specificities range from 87% to 100% [40]. Sensitivity for aneurysms smaller than 3 mm drops to a range of 40% to 91% [41]. The role of CTA is very limited in patients with impaired renal function, since a large bolus of contrast material is often administered. MRA is highly sensitive and specific for the detection of intracranial aneurysms. MRA has a sensitivity of 70% to 99%, and a specificity of 100% for aneurysms 3 mm or greater in diameter; however, the sensitivity diminishes for very small aneurysms (under 3 mm in diameter) to as low as 40% [42]. MRA is more difficult to use in critically ill patients because it takes considerably more time to perform.

Catheter angiography, with or without the advanced three-dimensional capability, is the gold standard which provides detailed evaluation of the aneurysm in its relation to other vessels. However, catheter angiography is more expensive and invasive than either MRA or CTA. Its risks, even in the hands of experienced operators, include neurologic complications occurring in 1.0% to 2.5% of cases, with permanent impairment in 0.1% to 0.5% [43]. Other associated risks include femoral-artery injury (0.05% to 0.55%), groin hematoma (6.9% to 10.7%), and adverse renal effects induced by contrast material (1% to 2%) [43].

Overall, brain MRA or CTA are the methods of choice for screening of unruptured aneurysms because of their noninvasive nature; however, a cerebral angiogram is sometimes used to better clarify the details of an aneurysm.

It should be noted that the ability of MRA and CTA to provide such morphological data is rapidly improving [44]. For those patients in whom contrast administration is contraindicated (including patients with renal failure in whom MRI-related gadolinium contrast is contraindicated), MRA is the screening method of choice because gadolinium contrast administration is not needed [45]. In 10% of cases of subarachnoid hemorrhage, cerebral angiogram may not detect any aneurysm. In cases in which the angiography is negative, it should be repeated in one to six weeks [46]. The proposed mechanism for the cause of subarachnoid hemorrhage without an identified aneurysm is hypertensive rupture of a small artery or vein. In these circumstances, an MRI of the brain and cervical spine with and without gadolinium should be obtained to rule out a thrombosed aneurysm, spinal arteriovenous malformation, dural arteriovenous fistula, or hemorrhagic tumor; however, the diagnostic yield is small [47, 48].

7. Management

Optimum management of an unruptured intracranial aneurysm should involve the comparison of the risk of aneurysmal rupture without any intervention with the risks of surgical clipping or endovascular treatment. The factors that should be considered include (1) aneurysmal factors, such as location, size, morphology, whether a thrombus exists within the aneurysm, and the presence of a daughter sac or multiple lobes, and (2) patient factors such as age, medical history, history of subarachnoid hemorrhage, and family history of subarachnoid hemorrhage [49].

There are three management options for unruptured cerebral aneurysms: conservative management, surgical clipping,

or endovascular treatment. Currently, there is a lack of prospective randomized controlled trials to guide therapy, particularly in comparing intervention with conservative management. Many published articles are retrospective in nature, and they lack objective short- and long-term assessment of outcomes [50].

Currently our best information regarding management of unruptured aneurysm is based on observed rates of complications in aneurysm treatment compared to the natural history of unruptured aneurysm [50].

7.1. Conservative Management. Conservative management is usually recommended for patients over the age of 60 years and for small (<7 mm) aneurysms, except in those with a strong family history of subarachnoid hemorrhage or a symptomatic aneurysm [51]. It should be noted that for patients with aneurysms of 7–12 mm in diameter, management is individualized, but many elderly patients with aneurysms in the anterior circulation can be considered for conservative management. For patients over the age of 60 years with aneurysms greater than 12 mm in diameter, an interventional procedure should be considered, while considering the patient's overall health status and the presence of factors that might increase surgical or endovascular risks [51].

It is imperative that all patients treated conservatively should be counseled about potential risk factors (such as hypertension and tobacco use) for aneurysm growth and rupture. Therefore, hypertension should be aggressively controlled, and smoking cessation should be strongly advocated for all patients who smoke. Alcohol should be used only in moderation.

Conservative management consists of routine periodic follow-up imaging with MRA or CTA and physician visits to review the studies. There is no recommended optimum interval, but a reasonable approach would be to repeat the MRA or CTA on an annual basis for about 3 years and then on several further occasions at a reduced frequency [44]. With regards to small unruptured and asymptomatic aneurysms of 2–3 mm in diameter, less frequent imaging can be performed if repeat imaging at 1 and 2 years shows stability of the aneurysm. Patients with aneurysm growth should be strongly considered for interventional treatment [45]. In a recent study using MRA to evaluate 173 unruptured aneurysms over a 4-year period, size at initial detection was a key predictor of aneurysm growth [44]. The overall frequency of aneurysm growth was 6.9% for aneurysms less than 8 mm in diameter, 25% for aneurysms 8–12 mm in diameter, and 83% for those greater than 12 mm in diameter [44]. Other predictors of aneurysmal growth demonstrated by a study which used MRA to assess 130 patients with 159 aneurysms in which 14 aneurysms grew included middle cerebral artery location, presence of more than one aneurysm, and aneurysm size greater than 4 mm [45]. The risk of aneurysm rupture after confirmation of aneurysm enlargement is not known with certainty. In a study in which CTA was used to evaluate 165 patients with 258 aneurysms, 18% of aneurysms grew [37]. The rate of aneurysmal rupture was 2.4% per patient-year in aneurysms with growth and 0.2% in those without growth. Independent predictors of aneurysm growth were

initial size of aneurysm and tobacco use [37]. A recent prospective Finnish cohort study by Korja et al. concluded that about 30% of all unruptured intracranial aneurysms rupture during a lifetime, and the risk factors for lifetime subarachnoid hemorrhage included current smoking, female sex, and aneurysm size of ≥ 7 mm in diameter [51].

There are few studies regarding the safety of antiplatelet agents and anticoagulants in patients with unruptured aneurysms. A Danish population-based case-control study demonstrated an increased association between SAH and dipyridamole use and new aspirin use, but not long-term aspirin use [27]. A case-control study utilizing the International Study of Unruptured Intracranial Aneurysms (ISUIA) suggested that aspirin use may have a protective effect against rupture and use of aspirin prior to rupture does not appear to worsen outcomes from SAH [15]. However, the use of anticoagulants has been associated with a poorer outcome from subarachnoid hemorrhage but not clearly associated with an increased risk for aneurysm rupture [29]. In patients with unruptured aneurysm, it is recommended that antiplatelet agents be used based on the patient's specific indication for such medication, while anticoagulants may be necessary due to specific indications; however, there should be careful consideration of risks and benefits and a thorough discussion with the patient.

7.2. Microsurgical Clipping. Microsurgical clipping requires access to the aneurysm via an open craniotomy. The aneurysm is dissected out and a tiny metallic clip is placed at the neck to isolate the aneurysm from the parent blood vessel. Surgical clipping is effective with complete occlusion obtained in greater than 90% of cases [46].

Surgical morbidity and mortality data are available from meta-analyses and prospective studies. Findings from one meta-analysis of 733 patients revealed a mortality rate of 1.0% and a major morbidity rate of 4% [49]. In a different meta-analysis of 2460 patients, a mortality of 2.6% and morbidity of 10.9% were reported; however publication bias was a limitation of this study [50]. Prospective data which was obtained from the International Study of Unruptured Intracranial Aneurysms (ISUIA) revealed a mortality of 2.3% at 30 days and 3.0% at 1 year for 798 patients undergoing surgical clipping [15]. Combined morbidity (which included substantial functional disability or severe cognitive impairment) and mortality from ISUIA was 17.5% in patients without previous intracranial hemorrhage at 30 days after surgical clipping and 13.6% in those patients with a previous hemorrhage from some other aneurysm [15]. Findings from a larger cohort of 1917 prospectively evaluated patients from ISUIA demonstrated a combined morbidity and mortality at 1 year of 12.6% for those without previous hemorrhage (death was 2.7%; functional disability only was 1.4%; impaired cognitive status was 5.5%; and both functional disability and impaired cognitive status was 2.8%) and 10.1% for those with previous subarachnoid hemorrhage from some other aneurysm (death was 0.6%; functional disability only was 0.9%; impaired cognitive status was 7.1%; and the status of both functional disability and impaired cognitive was 1.5%)

[15]. Overall, morbidity and mortality were the highest in patients older than age of 50 years and with aneurysms that were large or in the posterior circulation [15]. The risks of microsurgical clipping include hemorrhage (0.25%), incomplete occlusion (5%), and recurrence (1.5%) [49].

In a recent meta-analysis by Kotowski and colleagues, clipping of unruptured intracranial aneurysms was associated with a mortality of 1.7% and a morbidity of 6.7% from a systematic review of 60 studies with 10,845 aneurysms in 9845 patients [19]. In this meta-analysis, morbidity rates were noted to be higher in large aneurysms (>25 mm) or posterior circulation aneurysms (readers should refer to Table 3).

7.3. Endovascular Management. The different endovascular techniques include (1) packing the aneurysm with coils, with or without adjunct techniques such as balloon inflation or stent placement at the aneurysm neck for more difficult cases; (2) use of flow diverting stents; and (3) use of liquid embolic agents.

The most common form of endovascular management is the deployment of the detachable coils into the aneurysm via microcatheter. These coils cause local thrombosis and isolation of the aneurysm from the parent artery. Patients that are ideal candidates for the use of coils are aneurysms with a narrow neck (<4 mm) and low dome-to-neck ratio (<2) [52]. Adjunct techniques such as balloon inflation or stent placement at the aneurysm neck are increasingly used in some of the more difficult cases such as wide neck (>4 mm) or high dome-to-neck ratio (>2) [20]. Adjunctive techniques for coil embolization prevent coils from protruding through the aneurysm neck into the parent artery, therefore reducing the risk of thromboembolic complications.

Flow diverting stents such as pipeline embolization device (Covidien, Irvine, CA) are indicated for large unruptured saccular or fusiform intracranial aneurysms (>10 mm) of the anterior circulation from the petrous segment to the superior hypophyseal segment [20]. Pipeline embolization devices (Covidien, Irvine, CA) consist of tightly braided mesh that allow flow into vessel branches, but cause stagnation of blood in the sac which results in the occlusion of the aneurysm [20]. Patients need to be pretreated with dual antiplatelet therapy (aspirin and clopidogrel). The recommendation is for the patient to be on lifelong daily aspirin (81–325 mg) and clopidogrel therapy is continued for a duration of 3 to 6 months after procedure [20]. The results of a multicenter retrospective study of the pipeline embolization device were recently published showing a 30-day morbidity and mortality of 6.3% and a long-term neurologic morbidity and mortality of 8.4% [53]. The morbidity and mortality were the highest in the posterior circulation group at 16.4% and the lowest in the internal carotid artery aneurysm (with size <10 mm) group at 4.8% [53]. The pipeline embolization study included a total of 793 patients with 906 aneurysms; when patients with ruptured aneurysm (9% of cases) were excluded, the overall morbidity and mortality for unruptured aneurysms was 5.7% [53].

Onyx HD-500 (ev3 Neurovascular) is an embolic agent that is indicated for large, saccular, wide necked aneurysms that are not amenable to surgical clipping or endovascular coiling. However, the use of liquid embolic agents (Onyx

HD-500; ev3 Neurovascular) for large and giant intracranial aneurysms has declined due to higher risk of unfavorable outcomes. In a systematic review of the literature on the safety of endovascular treatment of unruptured aneurysms by Naggara and colleagues, procedure related poor outcomes occurred in 4.7% of patients, with higher risk of 8.1% in the subset of patients that received liquid embolic agents [20]. Cerebral Aneurysm Multicenter European Onyx (CAMEO) Trial was a prospective observational study that evaluated the use of Onyx in 97 patients with 100 aneurysms and it demonstrated a permanent neurologic morbidity of 8%, procedure related morbidity of 2%, and a delayed parent vessel occlusion rate of 9% [54].

Data from meta-analysis of existing literature suggests that the risk of unfavorable outcomes from endovascular management is approximately 4% to 5%, with a risk of mortality of 1% to 2% [20]. The 1-year morbidity rate was 6.4% and the mortality rate was 3.1% in 451 patients treated with endovascular coiling in the ISUIA study [12, 15]. Of note, the baseline characteristics of the endovascular group were different from the surgery group (which included older patients, larger aneurysms, and larger number of posterior circulation aneurysms); therefore, the results are not directly comparable. The risk of poor outcome with endovascular procedure was higher with aneurysm diameter greater than 12 mm and posterior circulation location.

There are no randomized clinical trial data that directly compare surgical clipping of aneurysm with coiling of unruptured aneurysms. Hwang and colleagues recently performed a meta-analysis of 24 studies to compare the effects of endovascular clipping and neurosurgical clipping in 31,865 patients with unruptured intracranial aneurysm [55]. Hwang et al. concluded that coiling was superior to clipping in the short term (≤ 6 months) in terms of disability and complications [55]. They demonstrated that a higher disability with clipping using the Glasgow Outcome Scale (OR, 2.38; 95% CI, 1.33–4.26) and Modified Rankin Scale (OR, 2.83; 95% CI, 1.42–5.63) in comparison to coiling and clipping resulted in higher disability in the short term (≤ 6 months) (OR on the Glasgow Outcome Scale, 2.72; 95% CI, 1.16–6.34), but not in the long term (>6 months) (OR for Glasgow Outcome Scale, 2.12; 95% CI, 0.93–4.84) [55]. Furthermore, clipping had 2.5 times more neurological and cardiac complications than coiling since the odd ratios (ORs) for neurological and cardiac complications were higher with clipping (1.94 with a 95% confidence interval [CI] of 1.09–3.47 and 2.51 with a 95% CI of 1.15–5.50) [55]. The limitations of the study by Hwang include the use of only observational studies and the study did not evaluate outcomes based on size and locations of aneurysms.

The risks of endovascular management include those associated with catheter angiography such as groin hematomas, infection, reactions to contrast material, and pseudoaneurysms [56]. Other risks include thromboembolism (2.5%), arterial dissection (0.7%), and parent artery occlusion (2%) [22]. Aneurysms treated with coils may require further treatment due to partially coiled aneurysm which may tend to recur and hemorrhage [22] (readers should refer to Table 4).

TABLE 3: Summary of large studies evaluating the microsurgical clipping of unruptured cerebral aneurysms.

Study	Important findings
International Study of Unruptured Intracranial Aneurysms (ISUIA) [12, 15]	Overall, morbidity and mortality were the highest in patients older than age 50 years and with aneurysms that were large or in the posterior circulation. In a cohort of 1917 prospectively evaluated patients, combined morbidity and mortality at 1 year was 12.6% for those without prior hemorrhage (death was 2.7%; functional disability was 1.4%; impaired cognitive status was 5.5%) and 10.1% for those with previous subarachnoid hemorrhage from some other aneurysm (death was 0.6%; functional disability was 0.9%; impaired cognitive status was 7.1%)
Britz et al. [16]	Surgical clipping in 4619 patients was associated with higher survival estimates (hazard rate of death 30%) and low neurologically related causes of death (2.3%)
Ogilvy and colleagues at Massachusetts General Hospital [17]	Treatment of 604 unruptured aneurysms showed an overall morbidity and mortality of 15.9% and 0.8%, respectively. Treatment risk for large aneurysms was 5% in the anterior versus 15% in the posterior circulation in the elderly, while treatment risk was 2% in young patients with aneurysmal size <10 mm
Moroi and colleagues at the Research Institute for Brain and Blood Vessels [18]	Treatment of 549 unruptured aneurysms showed a mortality and morbidity of 0.0% and 0.6% for aneurysms <10 mm and a mortality and morbidity of 1.2% and 6.1% for aneurysms >10 mm
Meta-analysis using Cochrane Database by Kotowski et al. [19]	Analysis of 60 studies (from 1990 to 2011) with 9845 patients with 10,845 aneurysms showing a mortality rate of 1.7% and an overall morbidity rate of 6.7%. Significant risk factors for poor surgical prognosis included aneurysm size >10 mm and posterior circulation aneurysms ($P < 0.001$)

TABLE 4: Summary of large studies evaluating the endovascular management of unruptured cerebral aneurysms.

Study	Important findings
International Study of Unruptured Intracranial Aneurysms (ISUIA) [12]	The 1-year morbidity rate was 6.4% and the mortality rate was 3.1% in 451 patients treated with endovascular coiling. The risk of poor outcome with endovascular procedure was higher with aneurysm diameter greater than 12 mm and posterior circulation location
Meta-analysis by Naggara et al. [20]: retrospective analysis of 97 studies from 2003 to 2011 with 7172 patients	Mortality rate of 1.8% and overall unfavorable outcomes rate (including death) of 4.7%. Endovascular treatment became safer over time with reduction in the rate of poor outcomes from 5.6% before 2000, 4.7% between 2001 and 2003, and 3.1% after 2004. Risk of unfavorable outcomes was 4.9% with coil embolization, 8.1% with liquid embolization agents, and 11.5% with flow diversion
Analysis of treatment by endovascular approach of nonruptured aneurysm (ATENA) by Pierot et al. [21]: prospective study on 739 unruptured aneurysms (<15 mm) treated in 27 centers in Canada and France	Morbidity and mortality at 1 month were 1.7% and 1.4%, respectively. Complications included intraoperative rupture rate of 2.6%, device-related complication rate of 2.9%, and thromboembolism rate of 7.1%
Murayama and colleagues [22]: retrospective study of 916 unruptured aneurysms treated with coil embolization	Rate of recanalization was 20.9%. The recanalization rate for small aneurysms (<10 mm) with narrow necks (<4 mm) was 5.1%, whereas, in small aneurysms with wide necks (>4 mm), it was 20.0%. The recanalization rate was 35.0% in large aneurysms (11–25 mm) and 59.1% in giant aneurysms (>25 mm)
Benes and colleagues [23]: analysis of 151 unruptured aneurysms treated with coil embolization in 131 patients	Combined morbidity and mortality rate of 1.5% at 6 months. Thromboembolic complication rate of 7.6%

7.4. Clipping versus Coiling versus Conservative Management. In general, microsurgical clipping is used for young patients (<50) with small aneurysms (<10 mm) in the anterior circulation unless such a patient has significant medical comorbidities that may increase their surgical risk. Moreover,

clipping may be favored over coiling in some wide-necked aneurysms or aneurysms with branches arising from the neck or body. Furthermore, endovascular coiling is ideal for patients with several medical comorbidities with increased surgical risk or patients with aneurysms that have narrow

TABLE 5: Summary of large studies evaluating the treatment risk of unruptured cerebral aneurysms.

Study	Important findings
Alskehlee et al. [24]: review of a cohort of 3,738 clipped unruptured aneurysms versus 3,498 coiled unruptured aneurysms from the National Inpatient Sample Database from 2000 to 2006	(i) Mortality rate was 1.61% (for clipped aneurysms) versus 0.57% for coiled aneurysms ($P < 0.0001$) (ii) Rate of acute ischemic stroke was 6.71% (for clipped aneurysms) versus 2.92% for coiled aneurysms ($P < 0.0001$) (iii) Rate of intracerebral hemorrhage was 2.38% (for clipped aneurysms) versus 1.37% for coiled aneurysms ($P < 0.002$)
McDonald et al. [25]: review of a cohort of 1,388 clipped unruptured aneurysms versus 3,551 coiled unruptured aneurysms from Premier Perspective Database from 2006 to 2011	(i) Mortality rates were similar in both clipping and coiling with odds ratio of 1.43 ($P < 0.47$) (ii) Clipping had a higher likelihood of unfavorable outcomes: odds ratio (OR) for discharge to long term care was 4.78 ($P < 0.0001$); OR for ischemic complications was 3.42 ($P < 0.0001$); OR for postoperative neurological complications was 3.39 ($P < 0.0001$); OR for hemorrhagic complications was 2.16 ($P < 0.0001$); OR for ventriculostomy was 2.10 ($P < 0.032$)

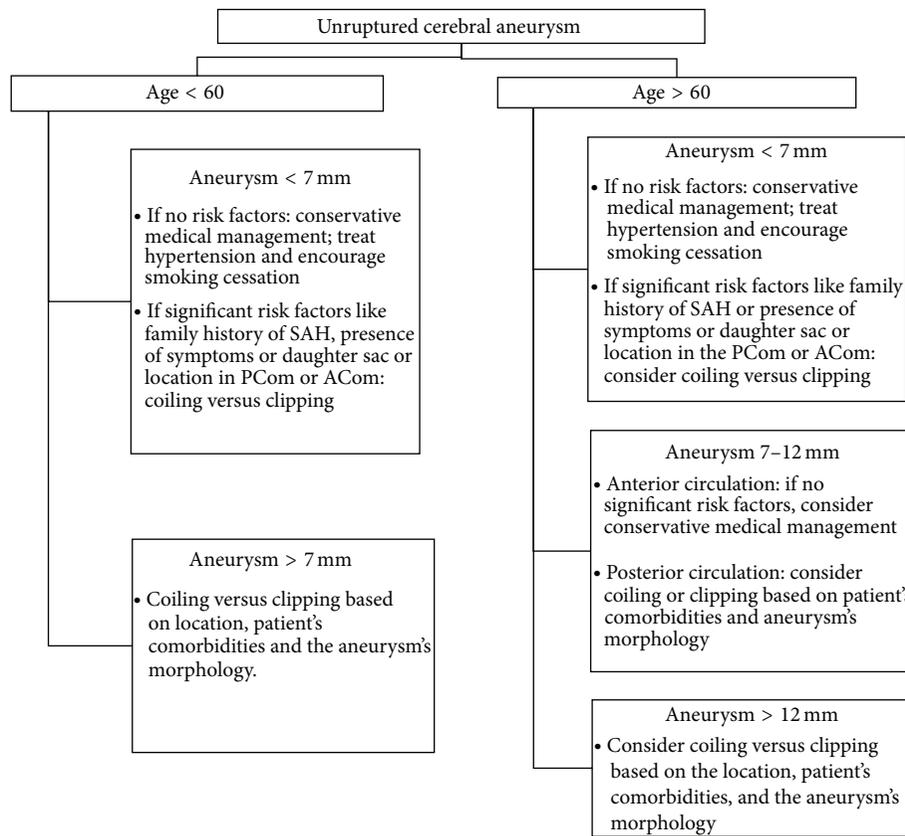


FIGURE 1: Flow chart for the management of unruptured cerebral aneurysm.

necks. Aneurysms with wide necks may be coiled using stent assisted coiling or balloon angioplasty assisted coiling. Pipeline embolization (Covidien, Irvine, CA) is ideal for carotid cavernous aneurysms as well as large and giant internal carotid artery aneurysms (readers should refer to Table 5 and Figure 1).

8. Conclusion

Unruptured intracranial aneurysms are currently being detected at a higher rate because of increased use of imaging

techniques. Once they are detected, we need to compare the aneurysm's natural history to the risk of intervention while considering the aneurysm location, size, morphology, age, clinical presentation, and medical comorbidities. These are factors that will also determine the type of interventional technique to pursue if the patient is a candidate for intervention. After an exhaustive review of the literature, the optimum management of small unruptured intracranial aneurysm remains unclear. Currently, we do not have well defined risk of rupture specific to aneurysmal size or location. Furthermore, we need randomized clinical trial that will directly

compare clipping with coiling of unruptured aneurysm. Moreover, we need more data on evolving endovascular techniques like flow diverting stents.

Abbreviations

CTA: CT angiography
 ISUIA: International Study of Unruptured Intracranial Aneurysms
 MRA: Magnetic resonance angiography
 SAH: Subarachnoid hemorrhage.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Hemifacial Spasm and Neurovascular Compression

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Hemifacial spasm (HFS) is characterized by involuntary unilateral contractions of the muscles innervated by the ipsilateral facial nerve, usually starting around the eyes before progressing inferiorly to the cheek, mouth, and neck. Its prevalence is 9.8 per 100,000 persons with an average age of onset of 44 years. The accepted pathophysiology of HFS suggests that it is a disease process of the nerve root entry zone of the facial nerve. HFS can be divided into two types: primary and secondary. Primary HFS is triggered by vascular compression whereas secondary HFS comprises all other causes of facial nerve damage. Clinical examination and imaging modalities such as electromyography (EMG) and magnetic resonance imaging (MRI) are useful to differentiate HFS from other facial movement disorders and for intraoperative planning. The standard medical management for HFS is botulinum neurotoxin (BoNT) injections, which provides low-risk but limited symptomatic relief. The only curative treatment for HFS is microvascular decompression (MVD), a surgical intervention that provides lasting symptomatic relief by reducing compression of the facial nerve root. With a low rate of complications such as hearing loss, MVD remains the treatment of choice for HFS patients as intraoperative technique and monitoring continue to improve.

1. Clinical Features

HFS starts with tonic-clonic contractions of the orbicularis oculi muscle, resulting in involuntary eyelid closure and eyebrow elevation. Over time, the contractions progress to the region affecting the frontalis (i.e., muscles of the forehead), platysma (i.e., muscles of the neck), and orbicularis oris (i.e., muscles of the mouth) muscles [1–5]. Eventually, the patient may develop sustained contractions of all involved muscles, causing a severe, disfiguring grimace with partial closure of the eyes and lifting of the mouth corners in the “tonus phenomenon” [3]. The majority of HFS cases occur unilaterally with an estimated 0.6% to 5% occurring bilaterally [6].

Some patients will report worsening of spasms with fatigue, situations of anxiety, and changes in position of the head (e.g., head to one side or the other on the pillow at night) [7]. One study also found that HFS-related headaches were associated with increased spasm severity [8]. Another

study suggested that HFS patients have a higher chance than the general American population (15.1% versus 1.34%, $P < 0.001$) of presenting with rosacea, a chronic condition characterized by facial erythema, fine telangiectasia, papules ocular irritation, and rhinophyma [9].

2. Epidemiology

HFS is prevalent in 9.8 per 100,000 persons [10]. The average age of onset for HFS is 44 years. Women and Asian populations have an increased susceptibility to HFS though valid prevalence data is scarce [11–13]. This issue is due to HFS underdiagnosis, misdiagnosis, and absence of population-based data [14]. A study of 203 family physicians in 2004 found that 90.6% were unable to diagnose HFS correctly and that 46.3% did not know how to manage HFS [15]. Worldwide estimates for the prevalence of HFS are 14.5 per 100,000 women and 7.4 per 100,000 men [16, 17].

Families with HFS present with autosomal dominant inheritance and low penetrance although there have been only a few reported cases [18]. In addition, the genetic susceptibility is poorly defined as there is not a clear relationship between HFS and single-nucleotide polymorphisms in genes related to vascular compression [19].

3. Pathophysiology

The accepted underlying pathophysiology of HFS suggests that the disease process is caused by facial nerve root entry zone myelin breakdown and ephaptic transmission, which is the passage of neural impulses through artificial chemical or chemical synapses. The root exit zone of the facial nerve is defined as the transition point between central (oligodendrocytes) and peripheral (Schwann) cell myelination [20, 21]. This segment is sheathed by only an arachnoidal membrane and lacks both interfascicular connective tissue separating fibers and epineurium; these features increase this segment's vulnerability to compression [21]. Compared to similar disorders of the trigeminal, glossopharyngeal, and vagus nerves, a study correlated the length and volume of central myelin portions of these nerves with the incidence of the nerves' corresponding diseases [22]. One study suggested that the root exit zone was primarily involved in only 23% of its studied HFS patients whereas compression of a more proximal segment of the facial nerve when it emerges from the pontomedullary sulcus was implicated in 73% [23].

Ectopic excitation can result from an area along the nerve that generates impulses independently of the natural synapse when the excitation threshold is low due to processes such as demyelination. One study examined orbicularis oris muscle response using EMG after supraorbital nerve stimulation and lateral spread tests with diazepam injections; the study results showed consistent latent muscle responses, which implicate ectopic excitation and ephaptic transmission [24].

Two hypotheses for the hypotheses of the HFS pathophysiology exist. The nuclear/central hypothesis suggests that injury to the facial nerve causes regressive medullary changes with functional connective reorganization in the facial nucleus, causing nuclear hyperexcitability because of dendritic spike generation [20]. The peripheral hypothesis suggests that clinical symptoms result from ectopic impulse generation and "cross-talk" between fibers at site of the lesions [20]. However, these hypotheses fall short with abnormal muscle response (AMR) data. When using electrophysiological monitoring stimulating one branch of the facial nerve while recording from muscles innervated by other branches of the facial nerve, HFS patients generate a characteristic wave with a latency of approximately 10 milliseconds, which is defined as the AMR [25, 26]. Theoretically, the latency of the AMR should equal the sum of the latency of the stimulus delivered to the facial nerve branch and recorded at the vascular compression site as well as the latency from direct facial root stimulation at the site of vascular compression and the resulting muscle depolarization [27]. However, the sum of these latencies is 2 milliseconds less than the expected total [28], which cannot be explained by the central or peripheral hypotheses.

Another hypothesis is the sympathetic hypothesis. The adventitia of arteries contains sympathetic endings and is worn down in HFS, causing neurotransmitters to induce ectopic action potentials that travel to the neuromuscular junction and induce involuntary contraction of facial muscles [27]. Using HFS rat models and electrophysiological monitoring, neurotransmitter released from autonomic nervous endings in the adventitia of offending vessels induced ectopic action potentiation in demyelinated facial nerve fibers [29].

4. Etiology

The etiology of HFS can be divided into two types: primary and secondary. Primary HFS is defined by vascular compression of the facial nerve root entry zone in the posterior fossa [30, 31]. Implicated arteries include the anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), and vertebral artery (VA). Anatomic variations in vasculature such as lateral deviation of one or both vertebral arteries occurred on the ipsilateral side of HFS in 86.4% cases, making these variations a HFS risk factor [32]. The pattern of neurovascular compression can be divided into six different categories: (A) loop type, where the vascular itself creates the compression, (B) arachnoid type, where arachnoid trabeculae between the vessel and brainstem cause the vessel to tether to the nerve, (C) perforator type, where the perforating arteries from the compressing vessel tether the vessel to the brainstem, (D) branch type, where the nerve is caught between the compressing vessel and its branches, (E) sandwich type, where the nerve is sandwiched between two different vessels, and (F) tandem type, where one vessel compresses another vessel that compresses the nerve [33]. Multiple vessel compressions have been observed in 38% of HFS cases [23]. However, many patients present without an identifiable etiology [34]. Some studies have shown a higher prevalence of hypertension in patients with primary HFS compared to patients with other neurological diseases [1, 35, 36]. The association suggests that hypertension leads to arterial vessel ectasia and contributes to neurovascular compression of the facial nerve [1].

Secondary HFS occurs with damage anywhere along the facial nerve from the internal auditory canal to the stylomastoid foramen [30]. Cases of secondary HFS have been linked to cerebellopontine angle (CPA) tumors and vascular malformations with other case linked to facial nerve trauma, demyelinating lesions, and vascular insults [34]. CPA tumors occur rarely; in a study of 2,050 HFS cases, only nine patients had HFS that was attributable to CPA tumors, which included two vestibular schwannomas, five meningiomas, and two epidermoid tumors [37]. Mechanisms of HFS in this study also differed with six cases identifying offending vessels as well as individual cases of tumor encasement of the facial nerve, hypervascular tumor compression of the facial nerve, and a large tumor compressing the brain stem causing contralateral facial nerve compression [37]. Young onset HFS has been linked to Chiari type I malformations, which has been attributed to these patients' narrow and shallow posterior fossa that crowd cranial nerves and vascular structures inside the cerebellopontine angle cistern [38, 39].

Collectively, these underlying issues of secondary HFS are thought to cause neural dysfunction and/or irritation of the facial nerve pathway [40]. Hearing loss, weakness of upper and low facial muscles, and preferential involvement of the orbicularis oculi and frontalis muscle were significantly more common in secondary HFS compared with primary HFS cases [7]. In a study of 252 patients, 78.5% presented with primary HFS whereas 21.5% presented with the secondary form [7]. Additional studies support that primary HFS is approximately 4 times more common than secondary HFS [30, 41].

5. Diagnosis

The diagnosis of HFS is made clinically. The “Babinski-2 sign,” “other Babinski sign,” or “brow-lift sign” is a physical exam maneuver that is positive when a patient lifts his/her eyebrow with ipsilateral eye closure, signaling the synchronized activity of the frontalis and orbicularis oculi muscle during HFS [42–44]. This technique has been shown in one study to have high sensitivity (86%), specificity (100%), and interrater reliability (92%) for HFS diagnosis [45].

EMG, MRI, and computerized tomography (CT) are used to confirm the diagnosis and differentiate primary from secondary HFS. Of these modalities, T2-weighted MRI sequences and high resolution fast imaging employing thin section steady-state free precession MR images are most commonly used to display possible vascular compressions [21]. Fusion MR imaging that combines steady-state MR imaging and three-dimensional time-of-flight MR angiography has been shown to assist in describing patient-specific anatomy at the root exit zone of the facial nerve [46]. EMG can also be useful to differentiate HFS from other abnormal facial movement disorders; in HFS, spontaneous, high-frequency synchronized firing is seen on EMG [3]. Additional diagnostic techniques such as a CT angiogram are useful for microsurgical planning. A recent study also suggested that the hemodynamic changes may be detectable using color-duplex ultrasound, showing a higher mean blood flow velocity in PICA and AICA arteries on the HFS side compared to that of the contralateral face [47]. An analysis using three-dimensional MR volumetric analysis found that HFS patients have lower posterior fossa CSF volumes compared to that of matched controls, suggesting that smaller posterior fossa CSF space may be an HFS risk factor [48].

All these diagnostic techniques help differentiate HFS from other craniofacial dyskinesias such as blepharospasm (BSP), tic disorders, myokymia, and synkinesis in addition to other disorders such as partial motor seizures, craniocervical dystonia (Meige syndrome), tardive dyskinesias (TD) and neuromyotonia. Other conditions such as psychogenic HFS, facial myoclonus, oromandibular dystonia, and hemimasticatory spasm can masquerade as HFS, resulting in diagnostic difficulty [34]. One case of moyamoya disease presented as HFS and was identified due to facial nerve compression with compensatory posterior circulation vessel enlargement [49]. In addition, psychogenic HFS was found in 2.4% of patients evaluated for HFS in one study and can lead to unnecessary medical and/or surgical intervention [50].

Comorbidity between HFS and other craniofacial dyskinesias can occur. Trigeminal neuralgia (TN) is irritation of the trigeminal nerve that causes facial pain. It can present concurrently with HFS in a syndrome called tic convulsif. Studies have shown that HFS can follow Bell's palsy, which is facial paralysis from dysfunctional facial nerve caused by brain tumor, stroke, myasthenia gravis, and Lyme disease [34]. HFS has also been reported to occur as a result of facial nerve demyelination in multiple sclerosis patients.

6. Medical Treatment

The standard medical treatment for HFS is botulinum neurotoxin (BoNT) injections. Having been used since the early 1980s, BoNT injections provide low-risk symptomatic relief in 85% of HFS patients, making it the treatment of choice for patients with high anesthetic risk and those who refuse surgery [21]. One study suggested that BoNT-A also helped improve hemifacial spasm-related headaches [8].

BoNT's mechanism of action is to block calcium-mediated release of acetylcholine at the synaptic junction. Two serotypes are available: BoNT-A and BoNT-B, as well as four different commercial formulations: abobotulinumtoxinA, onabotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB [51]. After injection, BoNT is cleaved by trypsin into heavy and light chain components [52]. At this point, the BoNT toxin is internalized into presynaptic nerve terminals, where the heavy chain binds synaptic vesicle protein 2, trisialoganglioside 1b, and synaptotagmin-1 [53]. The light chain then binds to the SNARE complex and cleaves target proteins such as synaptosomal-associated proteins of 25 kDa (SNAP-25) and synaptobrevin-2 to prevent exocytosis of neurotransmitters from the presynaptic terminal, leading to muscle paralysis [54].

BoNT-A is the primary serotype used for HFS treatment. BoNT-A injections occur in several sites in the pretarsal and preseptal portions of the facial nerve and are effective with a mean onset of action of 3 to 5 days. In one longitudinal multicenter center study, the effectiveness of BoNT-A in relieving HFS symptoms remained unchanged in the first and tenth year with patients needing statistically similar doses [55]. However, the injections must be repeated every 3 to 6 months. Tolerance can develop in some cases, but the treatment is generally well tolerated. Local complications of these injections include ptosis, blurred vision, and diplopia that may improve after days to weeks [14]. Repeated injections also can cause atrophy of target muscles, which may lead to injection of the contralateral face for cosmetic reasons [54]. Despite the effectiveness and low complication rate of BoNT-A, the need for repeated injections incurs a high economic cost and provides only symptomatic relief. Comparatively, BoNT-B is less commonly used. In an open-label single dose study, BoNT-B serotype was also shown to be well tolerated with 40% of subjects responding to treatment [56].

Pharmaceuticals such as anticonvulsants and GABAergic drugs may be used as alternative to BoNT injections. These drugs are generally less effective compared to BoNT at treating HFS. No controlled studies have found demonstrated long-term effectiveness of these medications, limiting their

treatment utility. However, they can be used for symptomatic relief in early HFS patients who have mild and infrequent symptoms as well as patients who decline BoNT injections and/or surgical intervention.

7. Surgical Treatment

As an alternative to BoNT injections, microvascular decompression (MVD) provides a curative treatment with long-term relief of symptoms by alleviating vascular compression of the facial nerve root. The underlying principle of MVD is to separate the nerve-vessel conflict rather than isolate it with prostheses; important intraoperative considerations include prompt identification of the neurovascular conflict site, sharp dissection of arachnoids for maximal nerve root visualization, and electrophysiological monitoring to distinguish offending vessels [57]. MVD has excellent results with long-term success rates between 83% and 97% of cases [58].

An analysis of twenty-two papers representing 5,685 patients treated with MVD for HFS found that an average of 91.1% of patients had complete resolution of symptoms over a median 2.9-year follow-up period [59]. Even with a first-time MVD failure, patients in one study who elected for repeated MVDs had a cure rate of 85% and did not suffer a higher rate of complication with a mean follow-up of 54.48 months [60]. Another small study found no significant difference between elderly and young patients in cure rate (96.3% versus 89.4%) and complication rate [61].

Before MVD, MRI imaging is used to identify the offending vessel and exclude structural pathology such as meningioma, acoustic neuromas, or epidermoid tumors. One study showed that preoperative assessment of HFS using T2-weighted MR cisternography predicted 79.1% of offending vessel invagination into the brainstem, allowing for better preoperative planning [62].

Under general anesthesia, the patient is typically placed in either supine or the lateral decubitus position [63]; a craniotomy inferior of the transverse sinus and medial of the sigmoid sinus is performed to expose the dura [14]. Once identified, the offending vessel can be mobilized and separated from the facial nerve root using shredded Teflon implants [64]. After the facial nerve is free of vascular contact, symptom resolution may occur immediately due to decreased compressive force [65]. Symptom resolution could be delayed, which is thought to be from remyelination at the microinjury site or normalization of the facial motor nucleus response [59, 66]. At the end of the MVD procedure, the dura is closed after irrigating the cerebellopontine angle and verifying that the Teflon implants are immobile. The senior authors (KRB/EM) replace the bone flap and perform a bone substitute cranioplasty [14].

Intraoperative EMG monitoring of facial nerve AMR increases safety of the operation and improves MVD outcomes. Outcomes of MVD can be optimized when the full length of the facial nerve is confirmed to be clear of the offending vessel, all offending vessels double-checked to be removed from the nerve, and AMRs disappear [67]. One study found that patients had a fourfold greater chance of HFS cure if AMR was abolished intraoperatively using EMG

surveillance [3]. In the 38% of HFS patients with multiple neurovascular compression, AMR and ZL-Response (ZLR), an alternative intraoperative EMG, used simultaneously as intraoperative monitoring, has been suggested to provide more useful information than AMR alone especially in situations when AMR is unavailable or unstable; the study reported 92% HFS resolution rate in HFS patient with multiple neurovascular compressions using this method [68]. Monitoring lateral spread response (LSR) also correlates with MVD. Several studies show that the disappearance of LSR during decompression predicted favorable outcomes [69–71] whereas the disappearance of LSR during dural opening or after CSF drainage before decompression correlated with worse outcomes [72].

Individual surgical methods vary. One postoperative study with an average follow-up term of 13 years suggested a “supine, no retractor” system having fewer adverse effects during general anesthesia with lower risks of postoperative nausea/dizziness, peripheral nerve palsy, and deafness [73]. Techniques to preserve the lesser occipital nerve during the lateral suboccipital craniotomy portion of MVD have also been described and reduce the incidence of sensory disturbances in the occipital region [74]. Compressions of the facial nerve outside the root exit zone have been described and shown that entire-root-decompression technique provides improved outcomes compared to decompression of just the root exit zone [75]. Emphasis must also be placed on mobilizing offending arterioles in addition to larger arteries. One study of 69 patients with intraoperative EMG found that nine patients who had artery mobilization had persistent AMRs, which resolved after offending arterioles were also separated from the facial nerve [76]. In reexploratory surgeries, two factors that may have complicated the initial decompression include inadequate exposure of the root exit zone and the use of unshredded Teflon implants, which can be easily dislodged [64].

Resolution of HSF after MVD may take several months to several years with small percentage of patients who fail to improve. In these patients, failure to improve may be attributed to inadequate decompression of the offending vessel, presence of a previously unidentified secondary offending vessel, or implant compression/migration against the facial nerve [77]. Generally, complications of MVD are uncommon and generally transient [59]. In some cases, MVD can result in serious complications, which are thought to be caused by facial nerve stretching during cerebellar retraction, iatrogenic injury to surrounding structures, or prosthesis compression [78]. The most common are deafness (2% to 20% of cases) or partial hearing loss, defined by one study as pure tone audiometry of more than 10 dB at frequencies of 4 and 8 kHz (26.6%); follow-up and repeat audiological examination studies are still lacking [79]. The use of brainstem auditory evoked potential monitoring (BAEPs) during MVD may warn surgeons of cochlear nerve damage intraoperatively by following the latency of Wave 5, which corresponds to the brainstem auditory pathways from the cochlear nucleus to the inferior colliculus [78].

A few cases of cerebrospinal fluid (CSF) leakage, cerebellar injury, and lower cranial nerve complications have

been reported as well as life-threatening complications, such as space-occupying hemorrhages and cerebellar/brainstem infarctions [61]. A retrospective comparison study suggested that CSF leakage occurs with postoperative use of closed-suction drainage [80]. Calcium phosphate cement following retromastoid craniectomies has been suggested to decrease the rate of complications such as CSF leaks with satisfactory cosmetic outcomes [81]. Overall, serious complications following MVD were reported in less than 1% of cases [21]. HFS recurrence can occur in 4% to 10% of patients [21] and has been associated with arterial hypertension [82]. MVD can also be used to treat the rare patients with coexistent HFS, trigeminal neuralgia, and glossopharyngeal neuralgia [83] as well as patients with cerebellopontine angle tumors when combined with tumor removal [84].

Hospital-wide protocols are also optimizing patient outcomes and containing costs. After one institution implemented enhanced-recovery perioperative protocols and diagnosis-specific clinical pathways in patients undergoing MVD for HFS and trigeminal neuralgia, it reported decreased operating room times, hospital stay length, and a reduction in rates of complications and readmissions [85]. Concurrently, a retrospective study at the same institution reduced surgical care episodes costs by 25% by decreasing duration of operations and simplifying intraoperative monitoring intraoperatively while reducing ICU and total hospital stay length postoperatively [86].

Overall, MVD remains the treatment of choice for patients with HFS as the development of intraoperative technique and monitoring continues to improve.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Auditory Dysfunction in Patients with Cerebrovascular Disease

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Auditory dysfunction is a common clinical symptom that can induce profound effects on the quality of life of those affected. Cerebrovascular disease (CVD) is the most prevalent neurological disorder today, but it has generally been considered a rare cause of auditory dysfunction. However, a substantial proportion of patients with stroke might have auditory dysfunction that has been underestimated due to difficulties with evaluation. The present study reviews relationships between auditory dysfunction and types of CVD including cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, cerebrovascular malformation, moyamoya disease, and superficial siderosis. Recent advances in the etiology, anatomy, and strategies to diagnose and treat these conditions are described. The numbers of patients with CVD accompanied by auditory dysfunction will increase as the population ages. Cerebrovascular diseases often include the auditory system, resulting in various types of auditory dysfunctions, such as unilateral or bilateral deafness, cortical deafness, pure word deafness, auditory agnosia, and auditory hallucinations, some of which are subtle and can only be detected by precise psychoacoustic and electrophysiological testing. The contribution of CVD to auditory dysfunction needs to be understood because CVD can be fatal if overlooked.

1. Introduction

Auditory function is complex, as it anatomically necessitates the transmission of an auditory signal from the ear to the auditory cortex and further processing to facilitate the perception and recognition of sound. Hearing disturbances profoundly affect quality of life and can occasionally be a cause of life-threatening disorders of the central nervous system. Auditory dysfunction is usually masked by other neurological issues and it can be difficult to evaluate in patients with cerebral stroke. Cerebrovascular disease (CVD) is the most prevalent neurological disorder and it can cause various types of auditory dysfunction. This study reviews current understanding of interactions between CVD and auditory dysfunction.

2. Review

2.1. Cerebral Infarction and Cerebral Ischemia

2.1.1. Bitemporal Infarction and Ischemia. The clinical syndrome of cortical deafness with bitemporal infarction has become established since it was first described in 1883 [1].

Cortical auditory disorders considerably vary and the variety of descriptions, such as auditory agnosia [2], apperceptive agnosia [3], pure word deafness [4], central deafness [5], and reversible cortical (central) auditory dysfunction [6, 7], indicates substantial overlap and thus a spectrum of related auditory processing disorders. The central auditory nervous system consists of cortical, subcortical, and interhemispheric connections [8]. Differences between syndromes might depend on the degree to which the primary cortical processing, accessory, and efferent auditory systems are involved [9].

2.1.2. Anterior Inferior Cerebellar Artery (AICA) Infarction.

An acute ischemic stroke in the distribution of the AICA is associated with facial weakness, hypalgesia, ataxia, vertigo, hearing loss, and nystagmus. Some patients lack or may not be aware of the symptom associated with brainstem or cerebellar signs. Among them, sudden hearing loss is a common sign of an AICA infarct [10–12]. The major responsible focus is the cochlear injury, which results in sudden unilateral deafness and is frequently associated with tinnitus. Cerebellar infarction is relatively infrequent and comprises 2.3% of all patients with acute stroke involving the posterior inferior

cerebellar artery (PICA; 49%) and AICA (20%) regions [13]. Magnetic resonance imaging (MRI) in one study found that the most common site affected by an AICA infarction was the middle cerebellar peduncle [10]. A sensorineural hearing loss was found in 92% of AICA infarctions in that series. The most common mechanism of AICA infarction is an atheroma or thrombus in the parent basilar artery that blocks the AICA [14]. An auditory disturbance has also been identified as a prodrome of AICA infarction [15, 16]. The AICA supplies the dorsolateral pons, middle cerebellar peduncle, inner ear, vestibulocochlear nerve, and anterior inferior cerebellum including the flocculus [17, 18]. Because the blood supply to the peripheral auditory system arises from the internal auditory artery that is ordinarily a branch of the AICA, partial ischemia in the AICA territory could lead to an isolated acute auditory syndrome such as hearing loss and tinnitus [15]. Sudden deafness with an AICA infarction is usually due to a dysfunction of the cochlea resulting from ischemia to the inner ear [10]. Because symptoms and signs of cerebellar infarcts are very similar to benign peripheral labyrinthine disorders, many patients with cerebellar infarcts are likely to be overlooked unless they are assessed by CT/MRI [13]. The possibility of AICA infarction particularly in elderly patients with sudden deafness and risk factors for CVD should be considered, even if classic brainstem or cerebellar signs are absent.

2.1.3. Non-AICA Origin Posterior Circulation Infarction. Huang et al. described seven patients with sudden bilateral hearing loss caused by vertebrobasilar occlusive disease [19]. Toyoda et al. described two patients with basilar artery occlusion in whom bilateral hearing loss warned of impending stroke [20]. Sudden deafness due to right vertebral artery dissection has also caused vertebrobasilar ischemic stroke [21]. Sudden deafness due to non-AICA territory infarction is mostly associated with an infarct in the territory of the PICA [22]. The labyrinthine artery (auditory artery and internal auditory artery) usually originates from the AICA, but it can occasionally originate from the PICA or directly from the basilar artery [23]. Non-AICA territory posterior circulation infarcts result in unilateral and/or bilateral acute hearing loss. We should take this pathology into consideration especially in case of bilateral acute hearing loss.

2.1.4. Cerebral Venous Thrombosis (CVT). There are several reported cases of CVT affecting the eighth cranial nerve. CVT presenting as multiple lower cranial nerve palsies including eighth nerve was reported [24]. Kim et al. reported CVT mimicking acute unilateral vestibulopathy [25]. Assessment by MRI identified extensive CVT involving the superior longitudinal sinus, the straight sinus, and the proximal portion of both transverse sinuses in a patient with CVT sustained reversible bilateral sensorineural hearing loss [26]. Crassard et al. described a patient with lateral sinus thrombosis who presented with acute hearing loss without vertigo or imbalance. Cochlear venous blood collected by the cochlear vein drains through the labyrinthine vein into the inferior petrosal sinus or directly into the transverse sinus. Thrombosis of the transverse sinus might increase cochlear pressure and induce

anoxic changes as a result of impaired drainage or thrombosis extending to the cochlear or labyrinthine veins [27].

2.2. Intracerebral Hemorrhage (ICH)

2.2.1. Bilateral ICH. Cortical deafness is a rare condition that occurs with bilateral temporal lobe lesions [1] or with bilateral subcortical lesions interrupting the ascending auditory pathways [28]. In cortical deafness, patients appear deaf, although some reflex responses, such as turning towards a sudden loud sound, may be preserved. With time, some auditory capacities may reemerge. Other patients remain permanently deaf [8].

Cortical deafness can follow bilateral hypertensive putaminal hemorrhage [29–31]. Bilateral hypertensive putaminal hemorrhage caused cortical deafness in two patients, possibly due to complete transaction of the acoustic radiation and cell degeneration in the medial geniculate body with putaminal hemorrhage on both sides and an auditory system that might have been dominant in the contralateral hemisphere [29]. Bilateral damage due to acoustic radiation of the temporal lobe without involving the medial geniculate body might have caused the cortical deafness in a patient described by Nishioka et al. [30].

Auditory agnosia refers to impaired perception restricted to certain classes of sounds. Word deafness, the most striking type of auditory agnosia, is the incapacity to recognize speech sounds [8]. Pure word deafness, inability to understand spoken words, despite intact hearing, speech production, and an ability of reading, is rare [4]. Word deafness mostly occurs as a result of bilateral temporal lesions, interrupting the connections between the two primary auditory cortices to Wernicke's area. Pure word deafness is produced by a posterior unilateral temporal lesion [8]. In contrast to sensory aphasia, reading and writing are preserved in word deafness because they are not fed by auditory input.

2.2.2. Cerebellar Hemorrhage. Acute vestibular syndrome due to cerebellar hemorrhage is similar to those of acute cerebellar infarction. Surgical evacuation of a subpial hematoma partially improved hearing loss and tinnitus that comprised the initial symptoms of a cerebellar hemorrhage [32]. Crossed pontocerebellar fibers as well as the cochlear and vestibular nerves might have been damaged by hemorrhage of the middle cerebellar peduncle. The right acoustic nerve was remarkably swollen by the hematoma [32].

2.2.3. Brain Stem Hemorrhage. Central pontine hemorrhage was associated with auditory dysfunction in four patients [33]. Damage to the medial superior olivary nuclei and to the trapezoid body involving both afferent and efferent fibers was responsible for the symptoms. Bilateral total deafness due to a single pontine hemorrhage involved an inactivated trapezoid body in a patient [34] whose other pontine auditory structures were spared. All of the above patients were conservatively treated with medication and the symptoms were reversible. The auditory symptoms associated with brain stem stroke include hearing loss, phantom auditory perceptions (auditory hallucinations), and hyperacusis [8].

Smaller brain stem hemorrhage involving the caudal pons can cause hearing impairment and hallucinations that can be either unilateral or bilateral [35]. Hyperacusis is the least common of the auditory complaints; it has been reported for a patient with a bilateral tectal midbrain hemorrhage [36]. Peduncular hallucinations can occur with midbrain strokes, but they are predominantly visual with an occasional minor auditory component, such as seeing people who are “whispering” [37]. Sometimes central auditory disorders in stroke are initially mistaken for acute psychosis [8].

Bilateral ICH, cerebellar, and brain stem hemorrhage are relatively frequent in elderly patients, and the degree and type of auditory dysfunction might considerably vary from a complete bilateral hearing loss to a partial or unilateral hearing disturbance and even auditory hallucinations. Thus, the incidence of auditory dysfunction due to bilateral ICH, cerebellar, and brain stem hemorrhage might be underestimated or misdiagnosed as presbycusis. Symptoms can be subtle and/or transient and thus difficult to diagnose. Thus, auditory function should be carefully assessed in elderly patients during the acute and chronic phases.

2.3. Subarachnoid Hemorrhage (SAH)

2.3.1. Cerebral Aneurysm. Distal AICA aneurysms can cause auditory disturbances and cause SAH and complete ipsilateral deafness. The reported incidence of aneurysms of AICA is about 0.1% of all cerebral aneurysms; only 56 patients with such aneurysms have been described in the literature [38, 39]. Among them, intracanalicular (internal auditory artery) aneurysms are extremely rare, as only six patients have been documented [40–45] and all of them were deaf. Most distal AICA aneurysms present as SAH (82.5%) and less frequently as only cerebellopontine mass signs (17.5%) [39]. The cause of acoustic nerve palsy can be ischemic [46, 47], direct nerve compression [46], or the presence of hemosiderin after SAH within the inner ear [48]. If the internal auditory artery aneurysm compresses the auditory nerve, the aneurismal sac should be removed to achieve good recovery of nerve function [38]. The technical difficulty of neck clipping in this site may be attributed to its location and to the adherence of the aneurismal neck to the surrounding structures [39]. Castaigne et al. were the first to successfully treat an intrameatal aneurysm surgically in 1967 [40], and Hitzelberger and Gardner presented another case the following year [49] and then Hori et al. surgically trapped an intrameatal aneurysm [42].

Central deafness has been linked historically to bihemispheric involvement of the temporal lobe, with more recent findings suggesting that compromise of other cortical and subcortical structures and brain stem can also result in this disorder [50]. Individual with central deafness often presents with a rather dramatic auditory deficit. These patients often demonstrate inconsistent or no responses to sound [50].

Subarachnoid hemorrhage affecting both inferior colliculi can cause central deafness [50]. The bilateral involvement of auditory structures within the midbrain can result in this condition.

2.3.2. Cerebral Vasospasm. A patient with SAH who developed sudden bilateral deafness [51] also experienced sudden onset of headache, nausea, and vomiting 9 days before referral to a hospital, where an old infarction was identified in the left temporal lobe before the occurrence of SAH. Hence, cortical deafness in this patient was caused by vasospasm contralateral to the previous infarction. Unilateral deafness that occurred after the rupture of a right vertebral artery dissecting aneurysm resulted from ischemia in the territory of the right internal auditory artery due to vasospasm [52].

Tabuchi et al. discovered a reversible cortical auditory dysfunction that was caused purely by bilateral cerebral vasospasm after aneurismal SAH [6]. Acute bilateral deafness that appeared 7 days after SAH onset was reversed by improving the cerebral vasospasm. This case suggests that transient ischemia involving the bilateral auditory cortices and auditory radiations can cause this unusual symptom [6]. A partly reversible central auditory dysfunction induced by cerebral vasospasm after SAH improved over a period of 6 months [7]. Whereas cortical deafness might have been associated with bilateral lesions of the temporal cortex, central auditory dysfunction was partly reversible in this patient after prominently unilateral right temporal lesions. The author considered the roles of interthalamic connections and less severe vasospasm of the left MCA that transiently impaired the left thalamocortical auditory pathways [7].

2.4. Cerebrovascular Malformation

2.4.1. Arteriovenous Malformation (AVM). Surgical excision of an AVM within the internal auditory canal (IAC) that caused sensorineural hearing loss did not affect complete deafness in one patient [53]. A cerebellar AVM was totally extirpated 122 days after initial symptoms resembling those of ear disease appeared, including unilateral facial palsy, hearing impairment, and tinnitus [54]. Sudden deafness has also arisen as a manifestation of a right temporoparietooccipital AVM, the rupture of which caused SAH [55]. An AVM can be life threatening if overlooked and thus it should be considered when hearing is disturbed.

2.4.2. Dural Arteriovenous Fistula (DAVF). Dural arteriovenous fistulae usually between the external carotid artery and dural venous structures are a rare entity accounting for 10%–15% of all cranial AVMs. Spontaneous closure (regression) of a DAVF in the middle ear has been associated with acute hearing loss [56]. Intraosseous DAVF of the skull base, possibly as a consequence of compression of the cochlear nerve or vasculature by a draining vein or nidus of the DAVF, has been associated with hearing loss [57].

2.4.3. Cavernous Angioma (Cavernoma). Intrapetrous cavernous angioma involving the facial nerve is a well-known ontological entity [58]; however, cavernous angiomas rarely occur in the IAC. These tumors originate from the capillary bed of the epineurium surrounding the nerve and can either compress or infiltrate the nerve. These lesions can cause severe and progressive sensorineural hearing loss, tinnitus,

facial nerve palsy, or vertigo even when they are relatively small [59]. All the patients initially presented with progressive sensorineural hearing loss, which can be caused by cavernous angiomas of the IAC [53, 59–62]. Cavernous angioma within the IAC can be attached to the facial, acoustic, or intermediate nerve. They are very rare and only 40 cases have been histologically proven and described in the literature [62]. A diagnosis must be based on the patient's symptoms together with CT and MR imaging features. Surgery is the treatment of choice and surgical approaches vary, depending on the size of the lesion, its location, and the severity and duration of preoperative hearing loss [59]. Such angiomas must be surgically extirpated while avoiding complications arising from bleeding into surrounding structures [62]. A prompt surgical treatment in acutely symptomatic patients provides a chance of complete regression of the clinical symptoms.

2.4.4. Venous Angioma (Developmental Venous Anomaly). A venous angioma arising within the IAC and expanding to the brainstem has caused a unilateral profound sensorineural hearing loss [63]. Hearing loss in this outpatient was incidentally discovered in the right ear. T2-weighted MRI revealed hypointense large tubular structures of the IAC that extended to the contralateral side of the brainstem across the right cerebellopontine angle area and multiple branching structures in the cerebellar hemispheres with intense contrast enhancement were consistent with venous angioma. Observation of the lesion was recommended until other intracranial complications developed [63]. Venous angiomas are low-flow, low-resistance lesions that are less likely to hemorrhage, the estimated overall risk of which is 0.22% per year [64]. The morbidity and mortality rates of surgical or radiosurgical removal or obliteration of venous angiomas to eliminate risk for hemorrhage are significantly higher compared with the natural history. Thus, observation is the recommended primary mode of therapy [64].

2.4.5. Capillary Telangiectasia. Capillary telangiectasia is often found incidentally on MRI or at autopsy and may be associated with minor neurologic symptoms, but there has been little evidence about whether such lesions are responsible for these symptoms [65]. Sensorineural hearing loss and tinnitus abruptly developed in a patient with capillary telangiectasia of the pons that might have affected the auditory and vestibular central pathways in the right midpons [65]. Capillary telangiectasias are usually <2 cm in diameter, and they are most frequently located in the pons [66]. These lesions show slight contrast enhancement and an obvious gradient-echo signal loss on MR images, except when a draining vein is present. Capillary telangiectasias have often been incidentally discovered and treated conservatively [67], but they have also been associated with hemorrhage and progressive and aggressive neurological deterioration [68, 69].

Sudden deafness defined as a sudden loss of hearing due to unknown causes is often treated with vasodilators and drugs to improve blood flow. However, cerebrovascular malformations must be ruled out by MRI because their presence

would contraindicate the administration of vasodilators and drugs to improve blood flow.

2.5. Moyamoya Disease (MMD). Cortical deafness due to bilateral temporal subcortical hemorrhages associated with moyamoya disease (MMD) gradually improved and completely disappeared within two months [70]. Damage to the bilateral auditory radiation might have played a role in the cortical deafness arising in this patient.

Diffuse ischemic damage to the subcortical white matter including areas of the temporal lobes as well as multiple and focal cortical infarctions in both cerebral hemispheres determined by MRI in a 3-year-old boy with MMD and central deafness suggested thalamocortical dysfunction and disconnection between higher brainstem and cortical auditory areas [71]. Sudden unilateral hearing loss that was possibly caused by vascular occlusion resulting from thrombotic narrowing or blockage by plaque presented as the first symptom of MMD [72]. Therapy with high-dose steroids and a vasodilator resulted in only mild improvement [72].

Moyamoya disease is principally a bilateral progressive cerebrovascular disorder that can plausibly cause cortical and/or central deafness, either via ischemic or hemorrhagic lesions. The possibility of MMD should be considered especially in children, young adults, and East Asians with sudden hearing loss.

2.6. Superficial Siderosis (SS). Superficial siderosis is associated with sensorineural hearing loss although it is generally considered to be rare and presumably underdiagnosed [73, 74]. SS of the central nervous system results from hemosiderin deposition in the subpial layers of the brain and spinal cord due to recurrent and persistent bleeding into the subarachnoid space [75]. Thus, SS might be associated with CVD. The source of bleeding remains unknown in about one-third of patients [76]. Sensorineural deafness (95%), cerebellar ataxia (88%), and pyramidal signs (76%) characterize SS [75].

Cerebellar Bergmann cells, microglia, and superficial astrocytes take up subarachnoid blood and then heme oxygenase intrathecally breaks down heme to free iron, which is cytotoxic as it produces reactive oxygen species. Both iron and heme products cause neurodegenerative injury [77]. Damage to the acoustic nerve can be prominent due to the nerve having a long course through the CSF within the pontine cistern and its investment in numerous microglial cells that become hemosiderin-laden [78].

The diagnostic modality of choice for SS is MRI [79], which can show characteristic marginal T2 hypointensity around the brain stem, cerebellum, and spinal cord. Vascular malformations associated with SS include cerebral AVM, spinal AVM, spinal AVF, cerebral aneurysms, and cavernous malformations [80–84]. However, bleeding sources might remain undetectable regardless of extensive neuroimaging. A 1995 survey of world literature revealed that the underlying cause of SS was identified in 34 of 63 patients [75].

Treatment options for SS have not been established. Surgical exclusion of a bleeding source is one therapeutic approach to stop SS progression, assuming that the bleeding

source is identified. With respect to hydrocephalus, a CSF shunt is indicated when consciousness is disturbed [75]. Proposed medical treatments include iron chelators, desferrioxamine, trientine, and steroid [85, 86]. Deferiprone, which is a lipid-soluble iron chelator that can penetrate the blood-brain barrier, can improve the clinical symptoms and deposition of hemosiderin [87, 88] and thus provides hope for treating SS [89].

SS has been associated with cerebral amyloid angiopathy (CAA), which is an important cause of intracerebral hemorrhage in elderly patients [90, 91].

Compared to the well-described classical type of SS, which mainly affects brain stem and posterior fossa, SS in CAA showed a preference for the cerebral convexity and only exceptionally occurred in the infratentorial compartment [91]. SS might be recognized within the spectrum of CAA [92].

2.7. Auditory Function during the Chronic Stage of CVD. Risk of hearing loss is increased among elderly patients with stroke compared with the general population [93]. Stroke might result in disordered auditory processing [94] and one report describes auditory neglect in patients after cerebral stroke [95]. A substantial proportion of patients develop extreme auditory functional limitations not limited to speech sounds after stroke of the auditory brain [96]. Auditory function should also be evaluated during the chronic stage of CVD and the real incidence of auditory dysfunction in CVD should be elucidated.

3. Conclusion

Auditory dysfunction is a common clinical symptom that can profoundly affect the quality of life of affected individuals. As the aging population increases, more patients will present with CVD accompanied by auditory disturbances. Henceforth, CVD will probably become an important contributor to the differential diagnosis of auditory dysfunction. General physicians need to understand this likelihood.

Conflict of Interests

The author has no personal, financial, or institutional interests in any of the drugs, materials, or devices described in this paper.

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Review Article

Brain AVMs: An Endovascular, Surgical, and Radiosurgical Update

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Brain arteriovenous malformations (bAVMs) are complex vascular lesions. Despite multiple studies, several classifications, and a great interest of the scientific community, case selection in AVM patients remains challenging. During the last few years, tremendous advancements widened therapeutic options and improved outcomes spreading indications for patients harboring lesions deemed inoperable in the past. Anatomical and biological case specific features, and natural history with a focus on presenting symptoms should be evaluated case by case and always kept in mind while planning a therapeutic management for a bAVMs. A multidisciplinary approach is strongly recommended when dealing with bAVMs and should involve physicians expertise in this kind of challenging lesions. The goal of this paper is to provide a focused review of the most recent acquisitions and therapeutic strategies regarding surgical, endovascular, and radiosurgical treatment.

1. Introduction

Brain arteriovenous malformations (bAVMs) structure consists of a primary pial arterial supply converging into a nidus directly connected to a venous drainage network without interposition of a capillary bed. Blood flow in bAVM is turbulent, characterized by high velocities and low resistances completely ignoring the natural equilibrium dictated by cerebral hemodynamic autoregulation. Other peculiar features include a tendency to bleed and to develop vascular anomalies such as aneurysms and venous ectasia [1].

Clear data concerning bAVM epidemiology are still unavailable although an estimation of their incidence is set on values between 0,001% and 0,5% [1, 2]. At least 1-2% of all the hemorrhagic strokes are the result of a bleeding bAVM. Among patients harboring such vascular lesion, 12% will experience symptoms during their lifetime [2]. The annual hemorrhagic risk for unruptured bAVM reaches 2%–4% [3]; following a first rupture event this risk increases,

achieving 6%–8% during the first year and then it drops to the aforementioned initial values [1]. Morbidity and mortality are fixed around, respectively, 80% and 10%–30% [4, 5].

Etiopathogenesis of bAVM is controversial: some authors theorized how they may develop during intrauterine life and some others advocated an angiopathic reaction following either a cerebral ischemic or hemorrhagic event as the "primum movens" of their development [1]. In 2009, Kim et al. [6] advocated the activity of matrix metalloproteinases (MMP-9) and antigenic and inflammatory factors, such as interleukin-6, as a possible cause of bAVM rupture. More specifically, being a proteolytic enzyme, MMP-9 demolishes proteins found in the extracellular matrix (ECM) and it has been found at high concentrations in bAVM nidus. Therefore MMP-9 is probably involved in a series of alterations ultimately leading to vessels wall fragility and thus higher susceptibility to rupture [7]. bAVMs are extremely frequent in certain group of patients afflicted by particular hereditary diseases such as the hereditary hemorrhagic telangiectasia,

TABLE 1: Grading systems for AVMs.

Spetzler-Martin grading system for AVMs [9]		Spetzler-Ponce grading system for AVMs [10]		Grading score proposed by Lawton [11]		
Points	Class	Spetzler-Martin grade			Points	
Size of nidus			Age (years)			
Small (<3 cm)	1	A	I, II	Surgical resection	<20	1
Medium (3–6 cm)	2	B	III	Multimodality treatment	20–40	2
Large (>6 cm)	3	C	IV, V	No treatment	>40	3
Location			Unruptured presentation			
Noneloquent site	0			No		0
Eloquent site	1			Yes		1
Pattern of venous drainage			Diffuse			
Superficial only	0			No		0
Deep	1			Yes		1

Parkes-Weber syndrome, Wyburn-Mason syndrome, and Cobb syndrome. The location of a bAVM influences profoundly its hemorrhagic risk; indeed deep seated lesions in the proximity of the basal ganglia or in the periventricular regions are more likely to bleed. Moreover the presence of a deep venous drainage, associated aneurysms or venous varices, and venous stenosis or arteriovenous fistula are other factors contributing to an even higher risk of hemorrhage [4, 8]. Conversely, accordingly to a recently published meta-analysis [8], male sex, small brain AVMs, and those with strictly deep venous drainage were associated with lower case fatality.

2. Treatment Options

Numerous classifications have been proposed in an effort to provide neurosurgeons and neurointerventionists with a reliable instrument to support therapeutic choices when dealing with bAVM. In 1986, Spetzler and Martin [7] introduced a classification systems based on dimensions, location, and type of venous drainage which estimated surgical risk for bAVMs (Table 1). Subsequently in 2011, Spetzler himself and Ponce proposed a 3-category classification for bAVM [10]. Lawton et al. [11] brought their contribution including variables such as patient age, hemorrhagic presentation, nidus diffuseness, and deep perforating arterial supply. Despite those efforts, an adequate classification is still unavailable mostly due to the fact that the complexity of bAVM hampers any attempt of simplification using parameters either arbitrary chosen or selected on the basis of their statistical significance. Factors such as the presence of intranidal or perinidal aneurysms, varicose or stenotic veins, turbulent flow, pial fistula, or wall-shear stress may not be as decisive as the currently used parameters for bAVM classification; nonetheless they ultimately influence bAVM hemorrhagic risk. These classifications have been used in the past and partly are still being used nowadays to support bAVM therapeutic management.

bAVM therapeutic approach is multidisciplinary: a cure may be achieved thanks to surgery, radiosurgery, neurointerventional surgery, or a combination of the three. More specifically, the endovascular management for bAVM may include interventions providing a reduction of bAVM nidus dimension in a presurgical setting, reduction prior to radiosurgery, or elimination of certain, often associated, vascular anomalies such as aneurysms, venous varices, and fistulas. Supporting evidences on the behavior of bAVMs managed conservatively performed through mere observation and radiological follow-up may be a viable option considering the risk of complications entailed with the treatment of these complex and unpredictable lesions. A recently published clinical trial called ARUBA [12] (a randomised trial of unruptured brain arteriovenous malformations) brought decisive evidences toward a more “cautious” attitude concerning bAVMs treatment; however, the study presented some weaknesses, among which the lack of distinction between different kinds of treatment (patients randomized in the “interventional” group were mostly treated via the endovascular route, which is known to be keen to complications) and the investigators themselves advocated the need of further research and follow-up in order to confirm their findings. Details on ARUBA are reported at the end of the present review paper for the purpose of completeness (see the appendix).

3. Microsurgical Treatment

The gold-standard in bAVM management is surgery whenever viable. According to published patient series, in 94%–100% of the cases an angiographic cure with low morbidity rates (from 1% to 10%) can be obtained in small (nidus < 3 cm) bAVMs when surgery is performed by expert vascular neurosurgeons [1]. These percentages greatly vary when dealing with bigger lesions located in critical or eloquent brain regions: for instance in IV and V grade bAVMs, according to Spetzler and Martin classification, an angiographic cure may

be obtained only in, respectively, 22% and 17% of the cases [1]. According to Hartmann et al. [13], during a long conducted follow-up in surgically treated patients, 3% sustained disabling neurologic deficits versus 32% of treatment-related new nondisabling neurological deficits. A recently published meta-analysis described complications leading to permanent neurological deficits or death occurring in a mean of 7.4% (range, 0%–40%) patients after microsurgery; successful brain AVM obliteration was achieved in 96% (range, 0%–100%) patients with this kind of treatment [8]. Surgery may be part of a multimodal therapeutic management involving a preliminary endovascular approach in order to reduce nidus volume and curing or mitigating eventual additional vascular anomalies as the ones already mentioned. Most often, neurosurgeons expect from their neurointerventional colleagues a selective embolization of the deep arterial feeders sited in the opposite site of the surgical operation field prioritizing the use of Onyx rather than glue to improve surgical resectability.

Interesting results have been drawn from studies focusing on patients treated with a combination of surgery and radiosurgery [11]: the rationale behind this type of approach lies on the possibility to surgically approach bAVMs, previously deemed inoperable, after either a partial or global reduction of their dimensions through radiosurgery. Conversely the latter may be used as an adjuvant therapy after surgery.

Tremendous improvements of the neurosurgeon armamentarium have further widened the range of therapeutic options. Killory et al. [15] described how the use of green indocyanine would allow visualizing residual portions of bAVMs during surgery maximizing surgical outcomes. Moreover a drastic technical amelioration has been brought by the introduction of nonstick bipolar forceps and Thulium laser. The effects of adenosine, such as asystole, known to be used during surgery for aneurysms, have found new applications for the management of bAVMs, especially when trying to reach deep sited portions of the lesion or to deal with massive intraoperative bleeding. The recent breakthrough of newly acquired 3D technology applications in surgery may soon allow real-time fusing of angiographic or MRI images with the surgical operation field playing a synergic role with other imaging tools such as neuronavigation, tractography, and functional MRI to further boost progress toward a better understanding of bAVMs anatomy and consequently better surgical outcomes.

4. Endovascular Treatment

Even though the final goal of bAVM therapy is the complete obliteration of its nidus, this is not always possible. An endovascular approach may be adopted in at least five possible scenarios: indeed an embolization may be performed either prior to surgery/radiosurgery, or to treat vascular anomalies with a bAVM, as a curative therapy or in a palliation setting (i.e., mitigation of blood flow steal symptoms) [14]. Embolic agents are numerous, each with peculiar advantages and limitations. Among the most commonly used n-butyl cyanoacrylate (n-BCA), ETOH, PVA/Embospheres, coils and, more recently, Onyx, a biocompatible polymer

of ethyl vinyl alcohol copolymer dissolved in an organic solvent (dimethyl sulfoxide) which allows significant AVM volume reduction and, in some cases, angiographic and anatomic cure [16] (Table 2). The introduction of microcatheters equipped with detachable tips (Apollo, Covidien, USA; Sonic, Balt, France) changed radically the techniques used to inject embolic materials as these devices are far less susceptible to complications due to entrapment of the microcatheter itself allowing better efficacy of the endovascular treatment. Unfortunately, at present, these microcatheters with detachable tips are still unavailable in the United States.

Despite the intra-arterial route is the most commonly used, during the last few years a transvenous approach has been developed with reported good results so far [17, 18]. Traditionally, endovascular neurosurgeons have always been reluctant when considering such an option mostly due to the risk of hemorrhagic complications derived from any manipulation of the venous side of a bAVM when its core is still patent. The transvenous route can be chosen only in selected cases, for instance when it is not possible to navigate the microcatheter through small and tortuous arteries to reach the AVM nidus, in case of high-flow venous side aneurysm occlusion or when surgery or radiosurgery is not viable. Two aspects of the endovascular transvenous approach are worth citing here: the progressive and controlled lamination of Onyx within the draining vein and the transvenous rapid nidus occlusion with the retrograde filling of all its arterial feeders, which may prevent hemorrhagic complications. In a swine experimental study, Masoud [19] showed how induced hypotension would support a transvenous embolization: indeed it allows the embolic material to reach retrogradely the arterial side with more ease providing better results in terms of nidus obliteration for AVM.

An innovative injection technique for Onyx has been recently proposed by Chapot et al. [20] and presented under the name of “pressure-cooker” technique. Normally, good results with Onyx injection are obtained by creating a plug in the vascular lumen just proximal to the microcatheter tip and then start injecting. In Chapot’s technique an antireflux plug is created by trapping the detachable part of an Onyx-compatible microcatheter with coils and glue in order to obtain wedge-flow conditions, thereby enabling a better understanding of macrofistulous AVMs and a more comprehensive, forceful, and controlled Onyx embolization. With the same rationale, double lumen balloons (Scepter XC, Microvention, USA) may play a role in bAVMs endovascular therapy; more specifically the inflation of a balloon proximal to the Onyx injection site may avoid the need for a plug and its associated risks. Main limitation of this technique lies in the difficulty encountered while navigating the dual-lumen balloon into distal arterial feeders, especially small ones because these vessels can often be accessed only with flow-directed microcatheters or small microcatheters and an overpenetration of the nidus with negative hemodynamic consequences, especially with venous penetration [21].

Regarding morbidity and mortality of an endovascular approach, complications leading to permanent neurological deficits or death occurred in 6.6% (range, 0%–28%) after

TABLE 2: Embolic materials.

Embolitic material	Advantages	Limitations
N-butyl cyanoacrylate (n-BCA)	<ul style="list-style-type: none"> (i) Great penetration potential into bAVMs nidus. (ii) Permanent embolization with durable occlusion of the embolized vessel or pedicle. (iii) Deliverable through small, flexible, and flow-directed catheters causing minimal trauma even in distal vessels of the cerebrovascular system. (iv) Easy and quick delivery, infusion generally takes less than 1 minute. (v) Radiolucent, must be mixed with a radiopaque agent (i.e. ethiodized oil: lipiodol, ethiodol). Usual ratios for the mixture are 1.5 : 1 to 3 : 1 (oil-to-NBCA) with nonnegligible margin of error. (vi) Radiolucent. Follow-up angiograms and eventual indications for further endovascular surgery are not hampered by radiological artifacts from the first intervention. 	<ul style="list-style-type: none"> (i) Experience is required to judge the best fitted ratio for NBCA/Ethiodol for each different scenario. (ii) Adhesive-tendency to adhere to the catheter, making withdrawal traumatic or impossible. (iii) High level of expertise is required to control the injection to achieve adequate nidal obliteration preventing venous dissemination. (iv) Far higher consistency than ONYX. In case of packed AVM it cannot be removed piecemeal with scissors.
Onyx	<ul style="list-style-type: none"> (i) Nonadhesive, (ii) Great radiopacity—enhanced angiographic control during injection. (iii) Lesser consistency than NBCA. In a packed AVM can be removed piecemeal with scissors. 	<ul style="list-style-type: none"> (i) DMSO component of the mixture may induce vasospasm and angioneclerosis. (ii) Tantalum powder must be mixed with the agent to provide radiopacity. (iii) Great radiopacity—follow-up angiograms and eventual subsequent endovascular procedures are hampered by radiological artifacts.
Ethanol (ETOH)	<ul style="list-style-type: none"> (i) Sclerosant-dehydration and disruption of endothelium surface with fractures of the vessel walls to the level of the internal elastic lamina resulting in acute thrombosis. (ii) Great penetration potential. 	<ul style="list-style-type: none"> (i) Risk of significant brain edema. (ii) It may induce pulmonary precapillary vasospasm possibly leading to cardiopulmonary collapse. (iii) Great penetration potential-high level of experience is required to perform ETOH embolization safely.
Polyvinyl alcohol (PVA)/Embospheres	<ul style="list-style-type: none"> (i) Penetration potential depends on particle size allowing the adoption of different strategies in function of case specific angiographical features. (ii) Once injected particles expand obstructing vessels with higher diameters than the catheters. (iii) Particles are far more controllable than embolic liquid agents during injection. 	<ul style="list-style-type: none"> (i) Particulate embolization requires a microcatheter with an internal diameter larger than the particle itself. (ii) During mixing process, PVA particles may fragment contaminating the mixture with smaller “dangerous” emboli. (iii) Risk of particles to clump up and/or catheters to be clogged due to particles high friction coefficient. Potential risk of vascular perforation. (iv) The choice of the particles’ size depends on operator’s interpretation of the superselective angiogram. (v) Nonpermanent embolization effects—particles may be absorbed or degraded by endogenous lytic agents. Risk of recanalization. Best fitted for presurgical embolization purposes rather than stand-alone endovascular curative procedures.
Coils	<ul style="list-style-type: none"> (i) Detachable coils are most useful for the initial embolization of large fistulae. (ii) Poor penetration potential if compared to particulates or liquid embolic agents-risk of distal dissemination is relatively contained. 	<ul style="list-style-type: none"> (i) Potential for vascular perforation. (ii) Poor penetration potential.

embolization while successful bAVM obliteration occurred in 13% cases (range, 0%–94%) [8]. Future advancements in bAVMs endovascular management may be brought by new embolic materials with peculiar features specifically conceived, for example, to reduce radiopacity after their use and thus allowing better visualization during following endovascular procedures if needed.

5. Radiosurgical Treatment (RS)

Radiosurgery has been building its success in selected cases of high grade bAVMs (mostly IV and V grade lesions according to Spetzler and Martin classification) considered inoperable or highly prone to severe or even fatal complications if treated with other kinds of approaches. Radiosurgery retains at least

two limitations: the latency of postoperative results and the iatrogenic morbidity. Latency for devascularization results reaches usually 2 years' time from radiosurgery (can be up to 4 years), a period during which patients are unfortunately exposed to hemorrhagic risks comparable to nonoperated patients with comparable vascular lesions. The second limitation concerns the structures adjacent to the radiosurgical target volume which may be affected by radiations, leading to an iatrogenic morbidity.

Complete obliteration is observed in 50%–90% of the cases and its rate is inversely proportional to the bAVM nidus size [5, 22, 23]. Once considered as cured, a hemorrhagic event may occur in less than 1% of patients [24]. Radiation dosage and correct interpretation of the malformation anatomy have a decisive influence on cure percentages: one should constantly keep into account both risks and benefits when choosing dosage/volume ratios, tailoring each procedure case by case and striving to reach, at least, a <3% risk of perilesional tissular damage [25]. A thorough evaluation of benefits and risks must be conducted before choosing the selected variables. MRI and angiography are the gold standard for treatment planning: to achieve the best result, occlusion of the malformation with minimal risk of adverse events, it is of paramount importance to precisely locate the arteriovenous shunt. Moreover isodose areas corresponding to perilesional tissues should be 50% to 80% less than those centered to the AVM core in order to minimize iatrogenic morbidity [26].

Radiosurgery may be burdened by complications leading to permanent neurological deficits or death in 5.1% (range, 0%–21%) of the cases [8]. In an effort to reduce the likelihood of such adverse events, a pharmacological therapy including steroids, pentoxifylline, and vitamin E may be adopted; in selected cases anticoagulant drugs, barbiturates, hypothermia, or hyperbaric oxygen therapy may be used [25]. 21-aminosteroids have shown their beneficial effects providing inhibition of lipid peroxidation triggered by induced free radicals, known to cause cellular and, ultimately, vascular damage; unfortunately though, they do not influence cellular reactions involved in the necrotic process.

Even though bAVMs embolization often precedes radiosurgery, recently acquired data have shown how such a conduct may worsen radiosurgical outcomes: indeed obliteration percentages in patients receiving partial embolization prior to radiosurgery are definitely worse than patients harboring nonoperated malformations [25]. The pathophysiological mechanism behind this evidence is still obscure; probably the occlusion of the main arterial feeders with the smaller ones left untouched may lead to an angiogenetic reaction triggered by ischemia. Moreover a partial embolization may induce recruitment of new vascular subsystems thereby crippling radiosurgery benefits [25]. Furthermore, Onyx (Covidien, Irvine CA), whose popularity is increasingly growing as the embolic material of choice for vascular malformations management, disrupts radiosurgery planning stages as its strong radiopacity creates radiological artifacts preventing acquirement of a complete understanding of bAVMs anatomy which is, as already stated above, of the utmost importance for the success of the procedure. bAVMs presenting with

pial fistulas retain a superior hemorrhagic risk and appear to be refractory to radiosurgery; those associated with extra or intranidal aneurysms are more likely to bleed with a 5-years 10-fold estimated hemorrhagic risk if compared with bAVMs not presenting with such additional vascular anomalies [25]. For such complex cases, as for bAVMs in general, a multidisciplinary approach is strongly recommended.

Appendix: ARUBA. The recently published ARUBA study [12] is a randomized study that evaluates the risks of treatment of unruptured arteriovenous malformations compared to those implied by a conservative management. Adult patients (≥ 18 years) with an unruptured brain arteriovenous malformation were enrolled into this trial at 39 clinical sites in nine countries. Patients were randomised to medical management with interventional therapy (i.e., neurosurgery, embolisation, or stereotactic radiotherapy, alone or in combination) or medical management alone (i.e., pharmacological therapy for neurological symptoms as needed).

The study, started on April 4, 2007, was stopped in advance on April 15, 2013, because the increased risk of treatment was evident compared to natural history. This study is based on the assumption that the natural history of intact AVMs is less dangerous than commonly considered; therefore the risks of any treatment are not justified. This study has raised several criticisms: the main one concerns the nature of the treatment that has been compared with natural history: there is no distinction between the kind of treatment, which was mostly endovascular, a treatment that is already known to imply several complications. On a case study of 223 patients evaluated, of its planned 400, 114 assigned to interventional therapy and 109 to medical management, only 18 were treated surgically. Mean follow-up was 33 months. The primary outcome of death or stroke was seen in 11 patients (10%) in the conservative group and 39 patients (29%) in the interventional group. However, the long-term results remain unknown. The ARUBA investigators plan to continue to follow up this group to determine whether the differences persist.

The study also confirms that the risk of bleeding in case studies collection is around 3% per year in unruptured malformations.

6. Conclusions

Innovation defined by the technological development including new embolic materials, catheters, and techniques resulted in a safer and more effective treatment of brain AVMs. In order to obtain the best therapeutic outcomes, a multimodal, case-tailored approach should be adopted. Anatomical and biological case specific features, natural history with a focus on presenting symptoms should be evaluated case by case and always kept in mind while planning a therapeutic management for bAVMs. All patients should be evaluated by physicians with expertise in endovascular embolization, microneurosurgical resection, and radiosurgery. Despite multiple studies, several classifications and a great interest by the scientific community, case selection in AVM patients remain challenging.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Cerebral Arteriovenous Malformations: Evaluation and Management

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There has been increased detection of incidental AVMs as result of the frequent use of advanced imaging techniques. The natural history of AVM is poorly understood and its management is controversial. This review provides an overview of the epidemiology, pathophysiology, natural history, clinical presentation, diagnosis, and management of AVMs. The authors discussed the imaging techniques available for detecting AVMs with regard to the advantages and disadvantages of each imaging modality. Furthermore, this review paper discusses the factors that must be considered for the most appropriate management strategy (based on the current evidence in the literature) and the risks and benefits of each management option.

1. Introduction

AVMs are abnormalities of the intracranial vessels that constitute a connection between the arterial and venous systems and lack an intervening capillary bed. Hemorrhagic presentation of AVM is associated with significant morbidity and mortality; it is an independent predictor of future hemorrhage. The gold standard for diagnosis of AVM is cerebral angiography. However, the evolution of noninvasive imaging techniques has led to the increased diagnosis of unruptured AVM which now presents with new challenges with regard to their management. This review paper provides a comprehensive review of the literature with presentation of the risks and benefits of the different management options available for AVM such as medical management, microsurgical resection, stereotactic radiotherapy, and endovascular embolization. Furthermore, the clinical presentation of patients with AVM and how it relates to the preferred management option are discussed in detail.

2. Epidemiology

Approximately 2% of AVMs are multiple and the remainder are solitary [1]. According to reports, 0.1% of the population harbors an AVM [2, 3]. Both sexes are affected equally. AVMs are the leading cause of nontraumatic intracerebral hemorrhage in people less than 35 years old [4]. Most lesions reach attention in patients in their 40's and 75% of the hemorrhagic presentations occur before the age of 50 years [2]. According to autopsy studies, only 12% of AVMs become symptomatic during life [5].

3. Pathology and Pathophysiology

AVMs have three components: feeding arteries, nidus, and draining veins [6]. The gross features of an AVM include the presence of single or multiple direct arteriovenous connections that permit high-flow arteriovenous shunting through small feeding arteries that lack a muscularis layer and the absence of a capillary bed. Consequently, this high-flow shunt

can produce structural changes in the feeding and draining vessels which results in arterial smooth muscle hyperplasia associated with fibroblasts and connective tissue elements known as fibromuscular cushions [6]. The microscopic features of AVMs are variable and depend on the portion of the lesion that is sampled. The venous elements have thin collagenous walls and the arterial feeders have muscular elastic walls. The parenchymal elements within the AVM tend to be hemosiderin stained, gliotic, and nonfunctional. Some lesions may have vascular or interstitial calcification [7].

4. Natural History

AVMs are congenital lesions that occur sporadically. The familial incidence of brain AVMs is rare, and only a few reported cases in the literature; however there is an association with other abnormalities like Osler-Weber-Rendu disease and Sturge-Weber syndrome [8, 9]. Cerebral AVMs account for 1.4% to 2% of hemorrhagic strokes [10, 11]. The estimated prevalence of AVM varies from less than 10 to 18 per 100,000 [12, 13]. Brain AVMs are found incidentally on 0.05% of brain MRI screens [14].

The natural history of asymptomatic brain AVMs remains poorly understood and conflicting information can be found on symptomatic lesions in the literature. Although scientists have not reliably identified anatomic predictors, spontaneous obliteration may be more likely to occur in small AVMs (less than 2.5 cm) that present with hemorrhage and have fewer arterial feeders [15]. This phenomenon is more likely to occur with AVMs drained by a single draining vein and associated with smaller AVMs and a hemorrhagic presentation [16].

5. Clinical Presentation

Cerebral AVMs may present with intracranial hemorrhage, seizures, headaches, and long-term disability; the most common presenting symptoms are hemorrhage and seizures [17].

5.1. Intracranial Hemorrhage. The annual incidence of hemorrhage of unruptured and untreated brain AVMs is of 2% to 4% with approximately 38% to 71% of patients with brain AVMs presenting with intracranial hemorrhage [17]. There are conflicting data in regard to association of age and risk of hemorrhage; however, the initial presentation of hemorrhage most commonly occurs in patients between the ages of 20 and 40 [18, 19]. Although conflicted data exists in regard to the effect of gender on hemorrhage, evidence seems to support no effect of gender on the risk of hemorrhage [20, 21].

There is data to suggest that hemorrhagic presentation is a significant independent predictor of future hemorrhage. Ondra and colleagues [22] over a 24-year period had a prospectively followed cohort of unoperated symptomatic patients with brain AVMs and found a mean time interval of 7.7 years between initial presentation and subsequent hemorrhage. Brown Jr. and colleagues [2] found that the risk of subsequent hemorrhage fell from 32.9% during the first year to 11.3% per year in subsequent years among patients with hemorrhage as the initial presentation. A study from Toronto [17] found an annual risk of hemorrhage of 9.65%

during the first year and 3.67% after 5 years from the initial hemorrhagic presentation.

Other potential risk factors for hemorrhage include (1) AVM with exclusively deep venous drainage (typically defined as drainage through the periventricular, galenic, or cerebellar pathways), (2) AVM associated with aneurysms, (3) AVMs that are deep in location, and (4) AVM that is infratentorial in location [17]. Brain AVMs are heterogeneous since each AVM's unique feature of microanatomy and vascular architecture may provide a unique clinical outcome. The risk of hemorrhage varies from 0.9% per year in patients without risk factors like hemorrhagic presentation, deep AVM location, or deep venous drainage and may be as high as 34.4% in patients with these factors [23, 24]. In a prospective study of 678 patients, the overall hemorrhage rate of brain AVMs with associated aneurysms was 6.93% per year compared with 3.99% per year for patients without associated aneurysms [17]. The risk of hemorrhage remains present until complete AVM obliteration; therefore partial endovascular embolization of an AVM does not completely reduce the risk of hemorrhage to zero [17].

5.2. Seizures. Seizures occur in about 18% to 40% of brain AVMs with favorable response to treatment with antiepileptic drugs [17, 25]. The type of seizure most commonly associated with AVMs is generalized seizures (30%) [26]. There is no significant association of hemorrhage with initial presentation with seizure, focal neurological deficits, or headaches as demonstrated by Brown Jr. et al. [2]. Furthermore, patients presenting with seizure are not more likely to suffer an AVM rupture during follow-up [17]. For instance, in the Toronto-based prospective study of 678 patients, the hemorrhage rate for patients presenting with seizure was 4.16% per year, which was close to the rate for the entire cohort (4.61%) [17].

5.3. Headache. Headaches occur in approximately 5% to 14% of patients with brain AVMs and these headaches are not distinctive. They can be unilateral or bilateral and can have migrainous features with and without aura [22, 26]. Currently, there are no studies to evaluate the rate of response to pharmacologic treatment and AVM obliteration.

5.4. Focal Neurologic Deficits (FNDs). Focal neurologic deficits (FNDs) occur in 1% to 40% of patients with brain AVMs [3]. Only 5% to 15% manifest progressive deficits unrelated to hemorrhage [6]. The pathophysiology of these deficits is multifactorial and includes vascular steal phenomenon and/or venous hypertension. The vascular steal phenomenon is centered around the perinidal arterial steal, which results from the high-flow shunting through the AVM and leads to low blood pressure in the feeding arteries and surrounding brain tissue [27]. Furthermore, venous dilatation may lead to mass effect and compression of brain tissue therefore resulting in FNDs [28]. The Columbia AVM Database (with 5,735 patients) found an independent association of FND with increasing age, female gender, deep brain location, and venous ectasia without any association with lobar location, size, arterial supply, or venous drainage pattern [28].

6. Imaging

Conventional cerebral angiography is the gold standard in the evaluation of AVM angioarchitecture, and it shows the following essential features: the feeding arteries, location of nidus, draining veins, morphology, presence, and location of associated aneurysms, venous varices, and vasculopathic stenotic segments on arteries and veins. These features are important because they are commonly used for treatment planning [29]. One of the important angiographic features is the visualization of the AVM during the arterial phase of an early draining vein since this feature confirms the presence of an arteriovenous shunt. Intraventricular hemorrhage as a result of AVM rupture is secondary to the apex of the nidus (seen as a wedge-shaped arrangement of tangled vessels on cerebral angiography) projecting toward the ventricular surface. Furthermore, in the presence of hemorrhage, mass effect can be appreciated on an angiography. It is important to note that a thrombosed AVM may not be detected on a cerebral angiography.

Other imaging modalities which are often the initial studies used to evaluate symptoms that are not specific to AVMs include CT, CT angiography, MRI, and magnetic resonance angiography. However, these imaging techniques are limited in their sensitivity and ability to provide detailed imaging of AVM architecture [29]. Each imaging technique provides its own unique strength: CT angiography provides better vascular detail of AVMs, whereas MRI and magnetic resonance angiography provide greater visualization of surrounding structures adjacent to the nidus. Furthermore, MRI can detect thrombosed vessels as hyperintense signals and show any associated hemorrhage at various stages of evolution. T2-weighted and GRE sequences are the most sensitive to breakdown products. MRI can be important for preoperative planning because it allows for an appropriate surgical approach while demonstrating the relationship of the AVM and important parenchymal structures.

7. Management

An important factor that must be considered during the treatment decision-making process is to compare the risks of all treatment modalities against the natural history risks of AVMs. Management of cerebral AVMs includes observation with medical management, microsurgical resection, stereotactic radiotherapy, and endovascular embolization. Invasive treatment modalities are the reasonable choice for ruptured cerebral AVMs due to the high rate of morbidity and mortality, and the goal of treatment is eradication of the AVM. The factors that dictate treatment options (which may include single or multimodal therapy) are operator skill, AVM size and location, surgical or endovascular accessibility, venous drainage, and presence of high-risk features, such as a feeding artery aneurysm [30].

However, the appropriate treatment modalities for unruptured AVMs present a challenging clinical dilemma because of a poorly defined natural history and the seemingly low annual hemorrhage rates. This clinical conundrum led to the development of ARUBA which aims to compare the

TABLE 1: Spetzler-Martin Grading Scale for AVMs.

Characteristic	Number of points assigned
Size of AVM	
Small (<3 cm)	1 point
Medium (3–6 cm)	2 points
Large (>6 cm)	3 points
Location	
Noneloquent site	0 points
Eloquent site*	1 point
Pattern of venous drainage	
Superficial only	0 points
Deep component	1 point

* Sensorimotor, language, visual cortex, hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles, or cerebellar nuclei.

natural history with modern multimodal therapy. ARUBA (a randomized trial of unruptured brain arteriovenous malformations) was the first randomized controlled trial to evaluate surgical intervention versus medical management for unruptured cerebral AVMs. However, errors in study design, execution, short length of follow-up, and a relative lack of information regarding the treatment arm and the enrollment process invalidate the authors' conclusions [30].

7.1. Observation with Medical Management. Conservative treatment is considered for management of asymptomatic AVMs. Furthermore, it may include management of associated symptoms, general medical care, and surveillance imaging of an AVM. Time intervals for surveillance imaging are not well defined and may include MRI brain imaging annually or biennially. Specific medical care may include management of hypertension, headache, and seizures. Similar outcomes in seizure frequency have been reported in an observational study comparing conservative management and AVM treatment [31].

7.2. Microsurgical Resection. In 1986, Spetzler and Martin introduced a grading system for AVMs based on the nidus size, location in relation to eloquent cortex, and venous drainage pattern (see Table 1); site includes sensorimotor, language, visual cortex, hypothalamus, thalamus, internal capsule, brainstem, cerebellar peduncles, and cerebellar nuclei [32]. The Spetzler-Martin Scale is used to estimate the risk of surgical resection of an AVM with higher grades being associated with greater surgical morbidity and mortality [33]. Microsurgery is the gold standard for definitive treatment of AVMs. Microsurgical excision of the AVM involves a craniotomy, careful dural opening with circumferential nidus dissection until complete AVM resection is achieved. Postoperative angiography is performed to demonstrate complete AVM excision. The advantage of microsurgical resection is the high rate of complete obliteration, while the limitations of this approach include anatomic accessibility, edema from retraction, intraoperative rupture, resection of normal brain tissue, and feeding vessel thrombosis. Microsurgical adjuncts to help facilitate a better surgical outcome include the

use of mapping, corticography, stimulation, and functional MRI [34]. A meta-analysis comprising 2425 patients treated between 1990 and 2000 showed a surgical mortality of 3.3% and a permanent postoperative morbidity of 8.6%, with an increasing morbidity-mortality rate associated with an increasing Spetzler-Martin grade [35].

The cure of AVM in adults is definitive with complete microsurgical resection and angiographic confirmation of obliteration. However, AVMs in children are more dynamic and may have the ability to regenerate after negative angiographic studies [36].

7.3. Stereotactic Radiosurgery. Radiosurgery involves the delivery of localized high-dose radiation to the AVM to induce a vascular injury, which leads to gradual sclerosis of the blood vessels with eventual obliteration over a period of 2 to 3 years. Successful treatment with radiosurgery depends on AVM size, grade, location, angioarchitecture, density of the nidus, and radiation dosage. AVMs smaller than 3.5 cm are ideal for obliteration [37]. The time from treatment to obliteration ranges from 2 to 3 years during which the patient has no protection from hemorrhage because of the delay from the effects of radiation. It was reported by Hernesniemi and colleagues [38] that the risk of hemorrhage during the initial 2 years after radiosurgery was 4.8% per year, which compares favorably with the natural history of AVMs.

However, this is less favorable with microsurgical resection. About 2 to 5 years after radiosurgery, the risk of hemorrhage is slightly higher at 5.0% per year but not significantly different from the natural history of AVMs. However, it should be noted that Pikus and colleagues demonstrated that microsurgically treated grade I to III AVMs had higher incidence of obliteration with statistically significant fewer postoperative hemorrhages, neurological deficits, and deaths when compared with stereotactic radiosurgery [39]. A multicenter analysis of 1255 patients receiving radiotherapy reported 102 (8%) patients developed a neurologic deficit after radiosurgery [40].

The advantages of radiosurgery include a noninvasive therapy and reasonable obliteration rates. The disadvantages of radiosurgery include the risk of bleeding during the latency of 1 to 2 years, neurologic deficits from edema and necrosis of normal brain tissue, and individual sensitivity to radiation and unknown long-term outcome.

7.4. Endovascular Embolization. Endovascular treatment of brain AVMs involves the delivery of liquid embolics, such as n-butyl cyanoacrylate and ethylene vinyl alcohol copolymer (Onyx) and platinum embolic coils via superselective catheterization with flow-guided ultrathin microcatheters. Often times, it is performed as preoperative embolization to surgical resection or in conjunction with stereotactic radiotherapy. Preoperative embolization can reduce the size of an AVM for microsurgical excision, and it has been shown to have acceptable rates of clinically significant complications (approximately 6.5%) [41].

Embolization may be performed as an adjunctive treatment to reduce the size of the AVM before radiosurgery. In certain cases, small malformations may be completely

obliterated by embolization alone and large AVMs may undergo near-complete obliteration. Furthermore, palliative embolization may be used in selected cases to stabilize progression of neurologic deficits or attempt seizure control in cases where AVMs are not amenable to microsurgical excision or radiotherapy.

The advantages of endovascular therapy include a minimally invasive approach, possible immediate occlusion, and intraprocedure angiographic evaluation. The disadvantages of endovascular therapy include incomplete embolization, unintended vessel embolization, intracranial hemorrhage, and normal perfusion pressure breakthrough, leading to edema or hemorrhage [42].

8. Conclusion

The increasing use of advance imaging techniques will increase the incidence of asymptomatic AVMs. At the present moment, we do not fully understand the natural history of AVMs to precisely predict which AVMs will likely bleed and what the most appropriate optimal treatment option will be, single or multimodal therapy. In the future, we certainly need well designed randomized controlled trials to compare different treatment modalities and their outcomes.

Abbreviations

ARUBA: A randomized trial of unruptured brain AVMs
AVM: Arteriovenous malformation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Intravenous Flat-Detector Computed Tomography Angiography for Symptomatic Cerebral Vasospasm following Aneurysmal Subarachnoid Hemorrhage

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The study evaluated the diagnostic accuracy of intravenous flat-detector computed tomography (IV FDCT) angiography in assessing hemodynamically significant cerebral vasospasm in patients with subarachnoid hemorrhage (SAH) with digital subtraction angiography (DSA) as the reference. DSA and IV FDCT were conducted concurrently in patients suspected of having symptomatic cerebral vasospasm postoperatively. The presence and severity of vasospasm were estimated according to location (proximal versus distal). Vasospasm >50% was defined as having hemodynamic significance. Vasospasms <30% were excluded from this analysis to avoid spectrum bias. Twenty-nine patients (311 vessel segments) were measured. The intra- and interobserver agreements were excellent for depicting vasospasm ($k = 0.84$ and 0.74 , resp.). IV FDCT showed a sensitivity of 95.7%, specificity of 92.3%, positive predictive value of 93.6%, and negative predictive value of 94.7% for detecting vasospasm (>50%) with DSA as the reference. Bland-Altman plots revealed good agreement of assessing vasospasm between the two tests. The discrepancy of vasospasm severity was more noted in the distal location with high-severity. However, it was not statistically significant (Spearman's rank test; $r = 0.15$, $P = 0.35$). Therefore, IV FDCT could be a feasible noninvasive test to evaluate suspected significant vasospasm in SAH.

1. Introduction

Symptomatic cerebral vasospasm (SCV) causes delayed ischemic neurologic deficit which can be associated with poor neurologic outcomes in patients with subarachnoid hemorrhage (SAH) [1]. Cerebral vasospasm following SAH has a morbidity and mortality rate of 10% to 30% [2]. Consequently, early detection and prompt management are required before ischemic brain injury occurs by vasospasm. The current treatment regimen for symptomatic vasospasm includes primary medical and secondary endovascular treatments. With the advances in endovascular technologies, intra-arterial (IA) vasodilators infusion or transluminal balloon angioplasty (TBA) have been increasingly performed for refractory vasospasm [3, 4]. Although there is no time limit for initiation of endovascular treatment, effectiveness can be achieved

with a therapeutic time window of 2 hours after developing vasospasm [5]. In particular, significant vasospasm that is refractory to medical treatment requires early endovascular intervention. However, decision-making for endovascular intervention can be time-consuming. Current imaging modalities, such as transcranial Doppler ultrasonography (TCD), magnetic resonance angiography (MRA), and computed tomography angiography (CTA), cannot be directly connected to endovascular intervention. In addition, clinical diagnostic steps to differentiate cerebral vasospasm from other medical conditions including intracranial hemorrhage, hydrocephalus, seizure, infection, or delirium can delay endovascular procedure.

Intravenous flat-detector computed tomography (IV FDCT) is an emerging technology that enables CT-like images from a C-arm biplane angiography system. Image

intensifiers used to be used to produce CT-like images from C-arm system. However, concerns that arose included low dynamic range and distorted images with high contrast. The high dynamic range and higher dose efficiency of the flat panel detector can clearly delineate vasculature [6]. Psychogios et al. [7] reported that high-resolution IV FDCT images are comparable to those of multidetector row CT angiography (MDCTA). IV FDCT is feasible to estimate intra- and extracranial stenosis with cerebral angiography as the reference [8, 9]. The prominent feature of IV FDCT is its application during neurointerventional procedures. White et al. [10] and Struffert et al. [11] reported that IV FDCT is useful to detect periprocedural complications and acute cerebral infarction. In addition, subsequent endovascular procedures can be conducted after identifying unexpected complications on the same angiographic suite without patient transfer. Therefore, IV FDCT could potentially improve clinical outcome in SAH patients by providing time saving benefits in identifying and treating significant cerebral vasospasm. However, to the best of our knowledge, no statistical analysis regarding the accuracy of IV FDCT compared with cerebral angiography in estimating cerebral vasospasm has been conducted. The aim of this study was to evaluate the diagnostic accuracy of IV FDCT in measuring cerebral vasospasm >50% with digital subtraction angiography (DSA) as the reference.

2. Material and Methods

2.1. Study Design. This investigation was conducted in patients suspected of having symptomatic vasospasm after aneurysm obliteration from January 2007 to October 2012 at a single center. Thirty-four SAH patients with Fisher grade III were enrolled in this cohort. Their mean age was 59.3 ± 14.7 years and 11 (37.9%) patients were male. Hypertension and a history of smoking were found in 8 (27.6%) and 5 (17.2%) patients, respectively. The mean vasospasm occurrence was 6.8 days (range 4–12 days) after ictus. Surgical clipping of 18 aneurysms (60%) and coil embolization of 12 aneurysms (40%) were performed (Table 1). Distribution of clip counter was as 11 single clips, six double clips, and one triple clip. Five cases used mini clips and 21 cases used nominal clips. Every surgical clipping was conducted with a Yasargil-Titanium Aneurysm Clip (Aesculap AG, Tuttlingen, Germany). No larger (>20 mm) [12] or fenestration clip was used in this study.

Intravenous nimodipine (Samjin Pharm, Seoul, Republic of Korea; 20 mcg/kg/h) was administered to prevent cerebral vasospasm (Figure 2). All patients were monitored by daily TCD examinations in the neurointensive care unit. Symptomatic vasospasm was suspected in the newly developed neurological deficit (e.g., impaired or deteriorated consciousness, dysphasia, motor weakness, or sensory changes) associated with elevated TCD velocity or when the Lindegaard ratio was met [13] after excluding other causes (e.g., aneurysm rebleeding, intracranial or surgery associated hematoma, hydrocephalus, electrolyte disturbance, procedure related infarct, seizure, or infection). Confirmation and calculation of vasospasm severity were made based on DSA findings. After diagnostic angiography, IV FDCT was performed

TABLE 1: Clinical characteristics of 29 Fisher grade III SAH patients harboring 30 aneurysms.

Variables	Number (%)
Male	11 (37.9%)
Age*, years	59.3 ± 14.7
Hypertension	8 (27.6%)
Smoking	5 (17.2%)
Location	
A-com	8 (26.7%)
Pericallosal	3 (10%)
MCABF	7 (23.3%)
M1	1 (3.3%)
P-com	5 (16.7%)
BA	3 (10%)
VA	1 (3.3%)
PICA	2 (6.7%)
Methods	
Surgical clipping	18 (60%)
Coil embolization	12 (40%)

*Mean \pm SD.

Note: A-com indicates anterior communicating artery; BA, basilar artery; MCABF, middle cerebral artery bifurcation; M1, M1 segment of middle cerebral artery; P-com, posterior communicating artery; PICA, posterior inferior cerebellar artery; SAH, subarachnoid hemorrhage; and VA, vertebral artery.

simultaneously to ascertain the change in vessel size before endovascular intervention. The images, given as maximum intensity projection (MIP) images gained by IV FDCT, were reconstructed and matched with the corresponding DSA images. If images of preoperative IV FDCT were unavailable, normal proximal arterial diameter was used as the reference to measure vasospasm severity. All vessel diameters were calculated with an electric ruler by two endovascular neurosurgeons blinded to clinical information. The following vessels were measured for analysis: both distal intracranial internal carotid artery (ICA), A1, A2, M1, M2, P1, P2, and V4, located just proximal to PICA, and the mid-point of the basilar artery. Cases of hypoplastic segments [14] or poor image quality for interpretation due to artifact were excluded for analysis. The concordance of IV FDCT with DSA was evaluated according to location (proximal versus distal). Proximal located vessels included distal ICA, M1, A1, P1, and BA. The vasospasm severity was categorized into three groups: none or mild (<30%), moderate (30–50%), and severe (>50%) [15]. Vessel narrowing >50% was defined as hemodynamically significant cerebral vasospasm [12]. Vasospastic vessels <30% were excluded from this analysis to avoid spectrum bias [8, 16]. This study was approved by the Institutional Review Board and informed consent was always obtained (number 2011-45).

2.2. Image Acquisition. Eighty milliliters of PAMIRAY250 contrast agent (Iopamidol; Dong kook Pharm., Seoul, Republic of Korea) with 40 mL of saline was infused through an anterior cubital vein with a flow rate of 5 mL/s. IV FDCT data acquisition was conducted according to the following

protocol: 0.4 of increment, 200° of total angle, 538 of total projections, radiation dose of 35 mGy, acquisition time of 20 seconds rotation, and 18 seconds X-ray time delay. Postprocessing of the IV FDCT data was performed on a Leonardo DynaCT dedicated work station equipped with InSpace 3D software (Siemens, Erlangen, Germany) [8]. The software adapted system-specific filter algorithms to adjust beam hardening and ring artifact, radiation scatter, and truncated projections. A volume dataset of a batch of about 400 slices in a 512 × 512 matrix and voxel size of 0.1 × 0.1 × 0.1 mm³ was reproduced. IV FDCT raw data were reconstructed in axial, coronal, and sagittal directions of maximal intensity projection (MIP) images with various slice thicknesses, mainly 15 mm. All IV FDCT and DSA were performed with the AXIOM Artis zee Biplane system (Siemens, Erlangen, Germany).

2.3. Statistical Analyses. The intra- and interobserver agreements, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of IV FDCT to identify hemodynamic significant vasospasm were calculated. The Bland-Altman method was used to assess the diagnostic accuracy of IV FDCT according to location. Receiver operating characteristic (ROC) curves were estimated for defining vasospasm >50% including all vessel segments (≥30%) with DSA as the reference. Analyses were performed with SPSS version 18 (SPSS, Chicago, IL) and MedCalc software (Medcalc, Ostend, Belgium).

3. Results

Of 34 Fisher grade III patients suspected of having symptomatic vasospasm, 29 patients harboring 30 aneurysms demonstrated angiographic evidence of vasospasm. A total of 311 vessel segments in 29 patients were analyzed. The locations of aneurysms were the anterior communicating artery (Acom; *n* = 8, 26.7%), middle cerebral artery (MCA; *n* = 8, 26.7%), posterior communicating artery (Pcom; *n* = 5, 16.7%), basilar artery (BA; *n* = 3, 10%), and vertebral artery (VA; *n* = 1, 3.3%). Eighty-five vasospastic vessel segments (≥30% luminal narrowing) were observed (Table 2). ACA territory comprised vasospasm (*n* = 45, 53.0%) followed by MCA territory (*n* = 30, 35.3%). Hemodynamically significant vasospasm was observed in 46 vessel segments. The intra- and interobserver agreements were excellent for depicting vasospasm (*k* = 0.84 and 0.74, resp.). IV FDCT demonstrated a sensitivity of 95.7% (95% CI 85.2–99.5%), specificity of 92.3% (95% CI 79.1–98.4%), PPV of 93.6% (95% CI 82.5–98.7%), and NPV of 94.7% (95% CI 82.3–99.4%) for identifying vasospasm >50% with DSA as the reference (Table 3). Bland-Altman plots revealed good agreement of estimating vasospasm severity between IV FDCT and DSA according to location (proximal versus distal) (Figures 1(a) and 1(b)). Discrepancy of vasospasm severity (DSA-IV FDCT, %) was more notable in the distal location with higher-grade vasospasm. However, it was not statistically significant (Spearman’s rank test; *r* = 0.15, *P* = 0.35). ROC curves for detecting vasospasm >50% in all vessel segments (≥30% luminal narrowing) are depicted in

TABLE 2: Distribution of vasospastic vessel segments (>30% luminal narrowing) demonstrated by digital subtraction angiography.

Variables	Number of vasospastic segments (%)
ICA	5 (5.9%)
A1	22 (25.9%)
A2	23 (27.0%)
M1	16 (18.8%)
M2	14 (16.5%)
P1	3 (3.5%)
P2	1 (1.2%)
BA	1 (1.2%)
Total	85

Note: ICA indicates internal carotid artery; A1, A1 segment of anterior cerebral artery; A2, A2 segment of anterior cerebral artery; M1, M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; P1, P1 segment of posterior cerebral artery; P2, P2 segment of posterior cerebral artery; BA, basilar artery; and V4, V4 segment of vertebral artery.

TABLE 3: Accuracy of IV FDCT in identifying hemodynamic significant vasospasm (>50%) compared with DSA.

	Seen on DSA	Not seen on DSA	Total
Seen on IV FDCT	44	3	47
Not seen on IV FDCT	2	36	38
Total	46	39	85

Note: numbers are vessel segments.

Figure 1(c). The area under the curve was 0.996. The cut-off value of IV FDCT >48% had a sensitivity of 93.6% (95% CI 82.5–98.7%) and specificity of 94.7% (95% CI 82.3–99.4%) in detecting vasospasm >50%. The cut-off had to be set at >46% to attain 100% sensitivity for identifying hemodynamic significant vasospasm.

4. Discussion and Conclusion

Early identification and treatment for symptomatic vasospasm are crucial after obliteration of cerebral aneurysms. Although medical treatment has been used as a first-line therapy [17], endovascular treatment has been performed for vasospasms that prove refractory to medical therapy. In addition, distal vasospasm can be treated by mechanical angioplasty. Santillan et al. [3] reported that balloon angioplasty decreases the need for chemical angioplasty in patients with distal cerebral vasospasm. Considering the tissue at risk concept [18], which is the penumbra area that will be restored with early reperfusion from an ischemic state, prompt endovascular intervention after diagnosis could be beneficial for significant cerebral vasospasm. Ideal radiologic test for SCV requires a shorter acquisition time, high diagnostic accuracy with fewer artifacts, subsequent connection to the endovascular procedure, and less radiation exposure. TCD, MRA, and CTA have been conducted widely for the evaluation of cerebral vasospasm. TCD has been used for screening vasospasm due to its relative simple procedure and availability [19]. Vora et al. [20] showed that only patients with low (<120 cm/s)

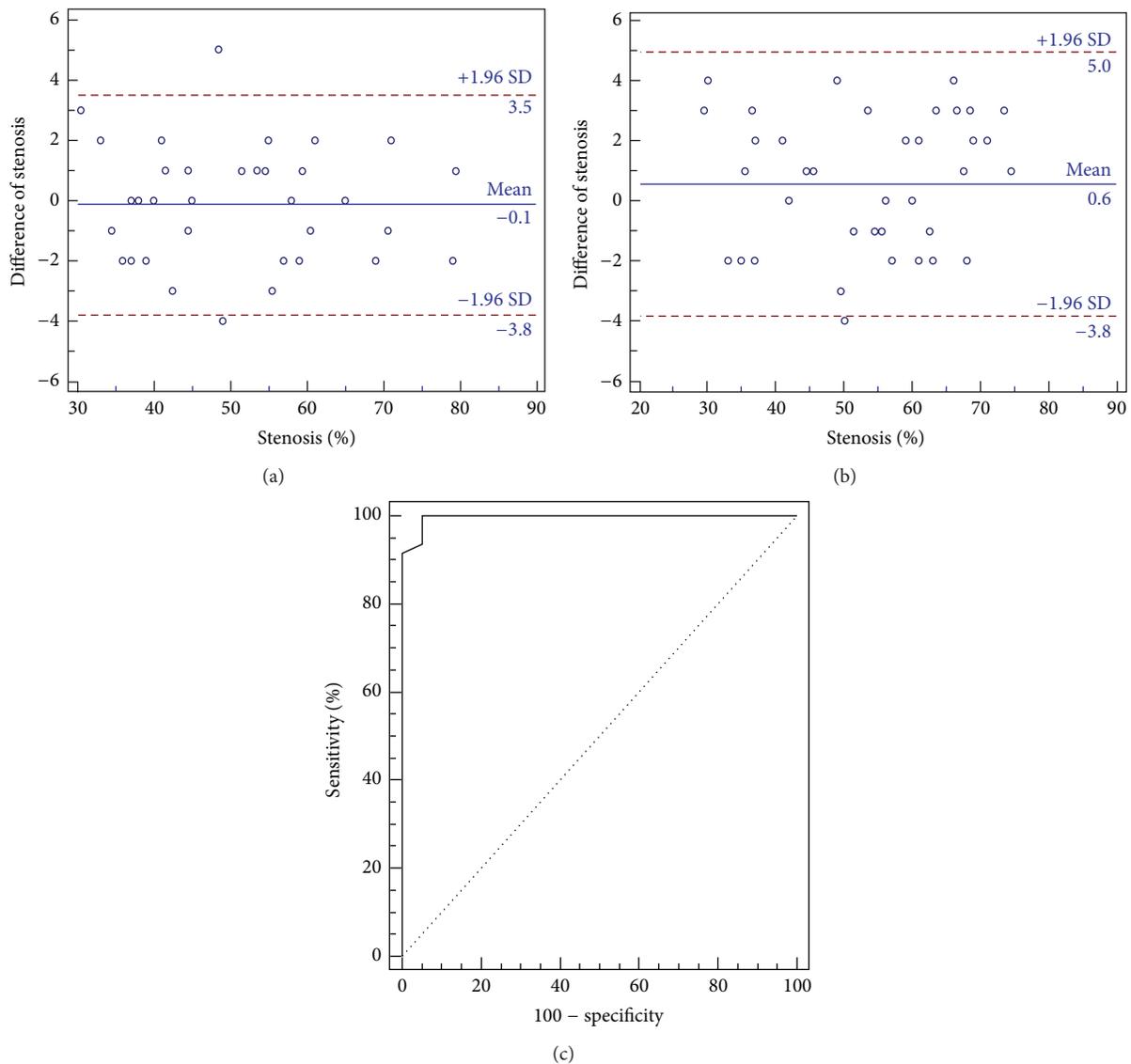


FIGURE 1: Bland-Altman plot reveals excellent concordance of measuring vasospasm severity according to locations such as proximal (a) and distal (b). (c) Receiver operating characteristic curves for detecting vasospasm (>50%) in all vessel segments (>30%). The area under the curve is 0.996. IV FDCT >48% has a sensitivity of 93.6% and specificity of 94.7% in detecting hemodynamic significant vasospasm (>50%) with DSA as the reference (proximal arteries include distal internal carotid artery, M1 segment of the middle cerebral artery, A1 segment of the anterior cerebral artery, P1 segment of the posterior cerebral artery, and basilar artery).

or very high (≥ 200 cm/s) MCA velocities correlate with the absence or presence of the significant vasospasm. Nakae et al. [21] reported that an increase in the mean blood flow velocity ratio of the ipsilateral to contralateral MCA is more valuable than absolute flow velocity in predicting vasospasm. However, TCD has limited value in estimating vasospasm in other arteries except for MCA [22] and vasospasm under intermediate velocities (120–200 cm/s) [20]. In addition, interpretation of the result can be limited by the examiner's expertise and narrow window [23]. Accordingly, MRA or CTA has been performed to ascertain the vasospasm. Time-of-flight (TOF) MRA is the standard technique to evaluate cerebral vasculature. Grandin et al. [24] showed a good

agreement between MRA and DSA in depicting vasospasm following SAH. In their study, MRA had a sensitivity of 92%, specificity of 98%, and negative predictive value of 98%. However, sensitivity for vasospasm of the ICA and MCA was 25% and 56%, respectively. Some disadvantages for the evaluation of cerebral vasospasm are metallic artifacts by clip, coil, stent, and devices of craniotomy site after operation [25] and longer acquisition time, which can be less favorable with fluctuations in neurologic conditions. In addition, overestimation of the arterial stenosis due to turbulent flow [26] or image degradation due to methemoglobin in the subarachnoid space [2] can be of concern. CTA is a fast and reliable method to detect cerebral vasospasm.

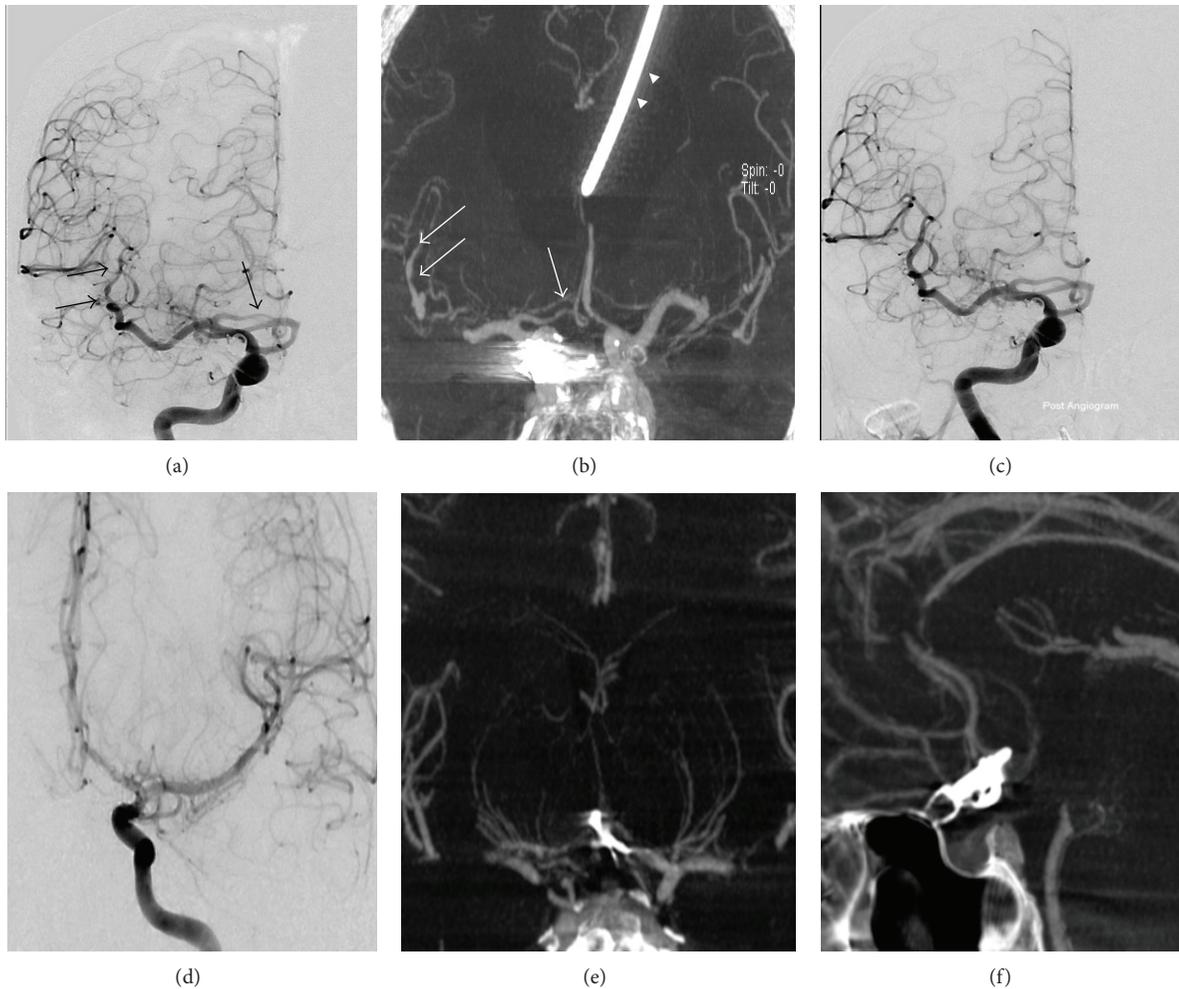


FIGURE 2: An 81-year-old female was transferred for ruptured aneurysm of the posterior communicating artery. (a and b) Digital subtraction angiography (DSA) and IV FDCT taken 5 days after the coil embolization revealed moderate vasospasm of the M2 and A1 (arrows) (arrowhead indicates a catheter of the extraventricular drainage). (c) DSA after chemical angioplasty using nimodipine shows the improvement of blood flow. A 22-year-old male was transferred for ruptured aneurysm of the anterior communicating artery. (d, e, and f) DSA and selective coronal and axial maximal intensity projection image of IV FDCT show no evidence of vasospasm.

Greenberg et al. [27] reported that CTA had 79.6% sensitivity, 93.1% specificity, 18.1 positive likelihood ratio, and 0.2 negative likelihood ratio in estimating cerebral vasospasm. Yoon et al. [12] showed that MDCTA had 97.5% accuracy, 98.1% sensitivity, and 98.0% specificity in detecting vasospasm over 50%. The agreement for proximal and distal segments of the vasospasm was 97.3% and 96.1%, respectively. Nevertheless, technical challenges including proper timing of bolus injection and beam-hardening effect can produce images of suboptimal quality [28]. In our study, IV FDCT showed a high sensitivity (95.7%) and specificity (92.3%) in detecting hemodynamically significant vasospasm. Discrepancies of vasospasm severity according to location, such as anterior or posterior, were not observed. Although more vasospastic vessels were underestimated in the distal location with higher grade stenosis, it was not statistically significant ($P = 0.35$). Such a phenomenon can be explained by the characteristics of the radiologic tools. Stenosis measurement by DSA may be influenced by flow velocity

and contrast dilution. Accordingly, increased blood velocity due to hypertensive treatment and contrast dilution due to hypervolemic therapy may exaggerate the degree of vasospasm. In addition, IV FDCT can generate images that are more uniformly distributed than DSA [29, 30]. Therefore, IV FDCT may underestimate the degree of vasospasm of the higher stenotic vessels in the distal location compared with DSA.

Simultaneous endovascular intervention without patient transfer could be beneficial in patients with vasospasm refractory to medical treatment. Although there is no therapeutic time window for vasospasm, early intervention within 2 hours has been effective in reversing vasospasm [5]. In our institution, suspected hemodynamically significant vasospasm in SAH patients with Fisher grade III is indicated for urgent endovascular intervention. Fisher et al. [31] correlated thick blood clot of the subarachnoid space, defined as Fisher grade III, with the occurrence of the symptomatic vasospasm. Wilson et al. [32] also showed

that the degree of SAH thickness was feasible to predict symptomatic vasospasm. From our experience, about 65% of SAH patients with Fisher grade III show reversal of angiographic vasospasm ($\geq 80\%$ of normal luminal diameter). All endovascular procedures were conducted with 2 hours after onset of symptomatic vasospasm. Accordingly, further study is necessary to see whether IV FDCT is a useful method to improve neurologic outcome in a large cohort of high-risk SAH patients for cerebral vasospasm. Another advantage of IV FDCT is that it can provide real-time scanning images. Accordingly, other medical conditions mimicking vasospasm also can be evaluated. The clinical diagnosis of the cerebral vasospasm consists of consecutive steps to exclude other conditions, such as hydrocephalus, rebleeding of the aneurysm, intracranial hematoma, hydrocephalus, cerebral infarction, electrolyte disturbance, and seizure. Thus, cerebral vasospasm can be more clearly depicted. In addition, physicians can manage adverse events during the procedure without delay. White et al. [10] reported IV FDCT as having marked value in decision making for 40.9% of the patients during periendovascular period. In their study, extensive leakage of the contrast medium through the perforation site by microcatheter, hematoma, and enlarged ventricle size was clearly evident. Adverse events during intrahospital transfer can also be prevented. Although, there was no statistical analysis about risk reduction in patient transfer from the diagnosis (CT or MRI rooms) to the treatment (angiography suite), an accident rate up to 71% can occur in intensive care unit patients during the conveyance for radiologic tests [33]. Because patient monitoring during transfer is usually accomplished by inexperienced examiners including interns, prompt, and proper management it cannot be performed in an emergent situation [34]. Therefore, IV FDCT could have the potential to decrease unnecessary complications during transfer.

IV FDCT can provide good depiction of the various vascular territories with collateral flow in a single acquisition [35, 36] and vascular calcification. Accordingly, screening with IV FDCT can reduce the procedural time and contrast dose. It can also be helpful to select treatment methods. With good spatial resolution of approximately 0.1 mm [37], IV FDCT has shown good delineation of intracranial stent [38]. Buhk et al. [39] suggested that IV FDCT can be feasible to evaluate aneurysm after stent remodeling. Kalender and Kyriakou [40] reported that IV FDCT showed better spatial resolution than MDCTA by comparing modulation transfer time (MTF) and visual estimate of bar pattern phantom according to different pixel binning. Nevertheless, increased noise level and decreased low-contrast resolution can be of concern. Regarding radiation dose, IV FDCT has a lesser or compatible radiation dose compared with that of MDCTA. Bai et al. [41] reported the lesser effective radiation dose of 1.18 mSv in IV FDCT of 20 s scan compared with 1.89 mSv in MDCTA. Considering a conventional brain CT of 60 mGy [42], IV FDCT can allow intracranial image with lesser radiation exposure of 35 mGy.

Because cerebral blood volume can be estimated with the same acquisition [11], detection of cerebral vasospasm anatomically and functionally could be obtained. Struffert

et al. [43] showed a high correlation between abnormal CBV lesion on IV FDCT and stroke volume on follow-up MDCT. Nevertheless, lower temporal resolution of IV FDCT than that of conventional perfusion CT can be a limitation. Because the lower temporal resolution attributes to the broader time attenuation curve with lower peak, CBV and CBF can be overestimated [44].

Image degradation by metal artifact can be a concern in detection of cerebral vasospasm. Psychogios et al. [45] reported that long axis of a clip placed parallel or perpendicular to the rotational plane can generate metal artifact. Besides clip direction, larger clip and multiplicity are associated with image degradation [45]. The latter authors did not recommend IV FDCT as a routine radiologic test following postclipped aneurysms, because poor-quality images were observed in 30% of cases. Buhk et al. [39] also reported that IV FDCT cannot routinely replace the role of DSA in detecting residual neck after endovascular intervention. Because large coil mass causes an amorphous signal within the coil mass, accurate detection of residual filling cannot be obtained in the images of IV FDCT [39]. In our series, seven patients (24.1%) experienced poor-quality images (surgical clipping, $n = 5$; coil embolization, $n = 2$) for identifying the presence of residual neck or parent vessel patency due to metal artifacts. In particular, multiple clips were associated with image degradation. Nevertheless, the presence of vasospasm can be seen through the various reconstructed images. Motion artifact also can occur in patients of compliance. Accordingly, a newly developed algorithm for metal artifact reduction and methods to increase C-arm rotation time with decreased angular sampling are needed.

The distinctive feature of this study is that two tests were conducted simultaneously to mitigate the possibility of vessel change. Vasospasm in SAH patients tends to have a hemodynamic nature. Moreover, vessel diameters can be affected during the medical treatments by maintaining hypertensive and/or hypervolemic status. Therefore, measurement of the vessel size at a different period may produce inaccurate results.

There are some limitations in this study. First, the small number of patients and single center experience are limitations. In addition, vasospastic vessels $\geq 30\%$ of the posterior circulation were not sufficiently enrolled. Second, the possibility of selection bias can be a concern. We think that clinical change in Fisher grade III SAH patients associated with elevated TCD velocity could contribute to the relative high prevalence of the cerebral vasospasm in our cohort. Nevertheless, the result might not apply to general SAH patients. Third, safety issue associated with additional contrast and radiation cannot be fully investigated. This method may result in an increased radiation dose and increased contrast rather than just specific, focused DSA runs. Accordingly, further studies are needed to elucidate the safety of the additional contrast and radiation in a large population.

In conclusion, IV FDCT could be feasible for detecting hemodynamic significant vasospasm. We do not advocate the superiority of IV FDCT more than other noninvasive tests in detecting cerebral vasospasm. We believe that IV FDCT could also be a feasible noninvasive test for the

evaluation of suspected hemodynamic significant vasospasm in SAH patients who would benefit from early endovascular treatment. A multicenter study including direct comparison of IV FDCT to the other noninvasive tests is needed.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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