

Management of aneurysmal subarachnoid hemorrhage

Michael N. Diring, MD, FCCM, FAHA

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain complications of subarachnoid bleeding.
2. Describe management of patients with aneurysmal subarachnoid bleeding.
3. Use this information in a clinical setting.

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Objective: Acute aneurysmal subarachnoid hemorrhage (SAH) is a complex multifaceted disorder that plays out over days to weeks. Many patients with SAH are seriously ill and require a prolonged intensive care unit stay. Cardiopulmonary complications are common. The management of patients with SAH focuses on the anticipation, prevention, and management of these secondary complications.

Data Sources: Source data were obtained from a PubMed search of the medical literature.

Data Synthesis and Conclusion: The rupture of an intracranial aneurysm is a sudden devastating event with immediate neurologic and cardiac consequences that require stabilization to allow for early diagnostic angiography. Early complications include rebleeding, hydrocephalus, and seizures. Early repair of the an-

eurysm (within 1–3 days) should take place by surgical or endovascular means. During the first 1–2 weeks after hemorrhage, patients are at risk of delayed ischemic deficits due to vasospasm, autoregulatory failure, and intravascular volume contraction. Delayed ischemia is treated with combinations of volume expansion, induced hypertension, augmentation of cardiac output, angioplasty, and intra-arterial vasodilators. SAH is a complex disease with a prolonged course that can be particularly challenging and rewarding to the intensivist. (*Crit Care Med* 2009; 37: 432–440)

KEY WORDS: aneurysm; subarachnoid hemorrhage; vasospasm; hypertension; treatment; endovascular

Acute aneurysmal subarachnoid hemorrhage (SAH) is a complex multifaceted disorder that plays out over days to weeks. The initial hemorrhage can be devastating and up to a quarter of patients die before reaching medical attention (1).

Those who survive the initial bleed are at risk for a host of secondary insults including rebleeding (2, 3), hydrocephalus (4), and delayed ischemia neurologic deficits (5, 6). The management of patients with SAH focuses on the anticipation, prevention, and management of these secondary complications, and hence can be particularly challenging and rewarding to the intensivist.

Intracranial aneurysms account for ~85% of cases of nontraumatic SAH (7). The other causes include bleeding from other vascular malformations (arteriovenous malformations), moyamoya syndrome, coagulopathy, and, rarely, extension of an intracerebral hematoma. In up to one fifth of cases, no source of bleeding is identified (8, 9).

Epidemiology

In the United States, over 30,000 persons each year experience an SAH. Intracranial aneurysms are found in 2% to 5% of all autopsies; fortunately, however, the incidence of rupture is only 2–20 of 100,000 individuals per year (10). Hemorrhage is more frequent in women than men (ratio, 3:2) (11, 12) older than 40, but the reverse is true in those younger than 40. Peak rupture rates occur between the ages of 50 and 60 years (3).

Risk factors for SAH include hypertension, cigarette smoking (13–16), heavy alcohol consumption (17, 18), and a history of SAH in first-degree relatives (19, 20). Having three or more affected rela-

Professor of Neurology, Neurosurgery, Anesthesiology, and Occupational Therapy, Washington University School of Medicine, St. Louis, MO.

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tives triples the risk of SAH. In 8680 asymptomatic individuals, magnetic resonance imaging detected an overall incidence of aneurysms in the general population of 6.8% rising to 10.5% in those with a family history of SAH (21). The specific genes involved have not yet been identified.

Pathophysiology

Both congenital and acquired factors are considered important in aneurysm development. Aneurysms have been associated with connective tissue disorders and polycystic kidneys, and are frequently found on feeding vessels of arterial venous malformations (22, 23). Acquired factors that may contribute include atherosclerosis, hypertension, and hemodynamic stress (22, 23).

The majority of aneurysms are found in the circle of Willis at the base of the brain near bifurcations. Only about 15% of aneurysms occur in the posterior (vertebro-basilar) circulation. The most common sites of ruptured aneurysms are the takeoff of the posterior communicating artery from the internal carotid artery (41%), anterior communicating artery/anterior cerebral artery (34%), and middle cerebral artery (20%) (7). Up to 20% of patients have multiple aneurysms (24).

Presentation

The classic presentation of acute aneurysm rupture is the instantaneous onset of a severe headache (25), which the patient often describes as the “worst headache of my life,” nausea, vomiting, and syncope followed by a gradual improvement in level of consciousness (26). Focal neurologic signs are unusual but may occasionally be seen due to mass effect from a giant aneurysm, parenchymal hemorrhage, subdural hematoma, or a large localized subarachnoid clot. In addition, third and sixth cranial nerve palsies may be present because of aneurysmal compression of the nerve or increased intracranial pressure, respectively. Seizures at onset may be reported (27), but it is not clear how many of these episodes represent true epileptic events vs. simple abnormal posturing.

Initial and Evaluation Management

The initial steps in the evaluation of a patient with suspected SAH should focus

on airway evaluation, early computed tomography (CT) imaging, blood pressure control, serial assessment of neurologic function, and preparation for angiography. The patient’s clinical status is assessed using the Hunt and Hess Scale (28) and World Federation of Neurologic Surgeons Scales (29) (Table 1).

A noncontrast CT scan within 24 hours detects >95% of SAHs (30). Blood appears as a high-density signal in the cisterns surrounding the brainstem and the basal cisterns. CT may be falsely negative if the volume of blood is very small, if the hemorrhage occurred several days prior, or if the hematocrit is extremely low. The amount of subarachnoid blood is graded (31–33) and is an important predictor of vasospasm risk (Fig. 1). Early hydrocephalus is suggested by enlarge-

ment of the third ventricle and of the temporal horns of the lateral ventricles.

If CT is normal and suspicion of SAH remains strong, a lumbar puncture should be performed (34). The presence of xanthochromia may be helpful in distinguishing a traumatic lumbar puncture from a true SAH especially if it is detected by spectrophotometry (35–37).

Conventional catheter angiography remains the gold standard for detection of intracranial aneurysms and should be performed as soon as practical to facilitate early repair of the ruptured aneurysm. CT angiography has recently improved to the point where some centers use it as the primary test to identify an aneurysm (38, 39). Magnetic resonance imaging techniques are rapidly advancing to this point as well.

Table 1. Clinical grading scales following subarachnoid hemorrhage

Grade	Hunt and Hess Scale (28) Symptoms	World Federation of Neurological Surgeons Scale (29)	
		Glasgow Coma Scale	Motor Deficits
I	Asymptomatic or mild headache	15	Absent
II	Moderate to severe headache, nuchal rigidity, with or without cranial nerve deficits	14–13	Absent
III	Confusion, lethargy, or mild focal symptoms	14–13	Present
IV	Stupor and/or hemiparesis	12–7	Present or absent
V	Comatose and/or extensor posturing	6–3	Present or absent

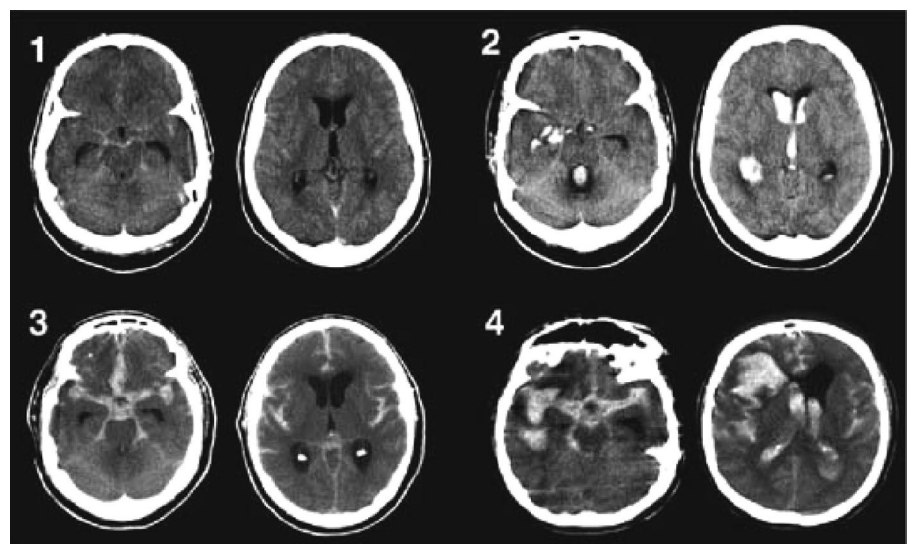


Figure 1. The modified Fisher computed tomography rating scale: grade 1 (minimal or diffuse thin subarachnoid hemorrhage without intraventricular hemorrhage [IVH]), indicating low risk for symptomatic vasospasm; grade 2 (minimal or thin subarachnoid hemorrhage with IVH); grade 3 (thick cisternal clot without IVH), indicating intermediate risk for symptomatic vasospasm; and grade 4 (cisternal clot with IVH), indicating high risk for symptomatic vasospasm. Reproduced with permission from Claassen J, Bernardini GL, Kreiter K, et al: Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: The Fisher scale revisited. *Stroke* 2001; 32:2012–2020, 2001. From: Frontera et al (31).

Angiography fails to demonstrate the cause of nontraumatic SAH in ~15% to 20% of cases (40). Repeat angiography should be performed within a few days to weeks. Patients with a high-quality complete angiogram that does not identify a source of bleeding have a very low incidence of rebleeding, especially if the blood is limited to the perimesencephalic and ambient cisterns (8, 9).

If the patient is lethargic or agitated, management of the airway should be addressed. Consideration should be given to elective intubation of agitated patients to facilitate performing safe and rapid angiography.

Blood pressure is often elevated following SAH because of pain and anxiety and generalized sympathetic activation (41). To prevent aneurysmal re-rupture, hypertension requires prompt treatment. Analgesics alone may be effective, otherwise rapidly acting antihypertensives are needed. The preferred agents include labetalol, β -blockers, hydralazine, and nicardipine (42–44). A notable exception to vigorous treatment of hypertension is when hydrocephalus is present. In that situation blood pressure should be addressed after the hydrocephalus is treated.

Cardiac abnormalities are common in the first 48 hours after SAH. Electrocardiographic changes including tall peaked T-waves or cerebral T-waves, ST segment depression, and prolonged QT segments are frequent (45–47). Cardiac enzymes are often mildly elevated (48, 49). Arrhythmias are very common but typically benign.

In rare cases, the cardiac abnormalities are much more severe. Myocardial contractility may be markedly impaired, leading to a fall in cardiac output (CO) and blood pressure and pulmonary edema (50–52). This condition has been referred to as “stunned myocardium,” and may also include an element of neurogenic pulmonary edema (53). The typical pattern on echocardiography is that of Takotsubo cardiomyopathy (54), and the management is similar to other causes of acute pump failure with inotropic agents, diuretics, high concentrations of oxygen, and positive end-expiratory pressure (50, 55, 56). Troponin levels are frequently elevated and variably associated with echocardiographic abnormalities (57). The condition is surprisingly transient and completely reversed in a few days (48, 49). In patients with known coronary artery disease, the pattern of echocardiographic

changes is often helpful in determining the etiology (41, 58). The most important predictors of cardiac dysfunction are those that reflect the severity of the hemorrhage (55, 59).

Early Critical Care Management

The routine monitoring of all patients with acute SAH should include serial neurologic examinations, continuous electrocardiogram monitoring, and frequent determinations of blood pressure, electrolytes, body weight, fluid balance, and, in many centers, transcranial Doppler (TCD) (60–62). Volume status should be closely monitored and adequate hydration with isotonic saline provided to avoid volume contraction (63–65). Strict attention to other aspects of critical care management is important as well. Although beyond the scope of this review, aspects of oxygenation, management fever, glucose control, and nutrition are covered elsewhere (66–69).

Anticonvulsants

The risk and implications of seizures associated with SAH are not well defined, and the need and efficacy for routinely administered anticonvulsants following SAH are not well established. It is unclear whether abnormal movements at the time of aneurysm rupture are epileptic in origin. Patients with parenchymal hematoma may be at higher risk (70–72).

Recently, the routine use of anticonvulsants has been associated with cognitive impairment in patients with SAH (73, 74) and heralded the growing acceptance of reduced use of anticonvulsants. It appears that short term (3 day) use during the perioperative period does not increase risk of seizures (75).

Steroids

Dexamethasone is widely used to reduce meningeal irritation and intra- and postoperative edema, but there is no convincing evidence documenting its efficacy. A recent Cochrane review concluded that there is no evidence of a beneficial or adverse effect of corticosteroids in patients with SAH (76).

Rebleeding

The risk of rebleeding is highest immediately following hemorrhage (4% to 6% over the first 24 hours) and declines over the next few days (2, 77). Rates are

highest in women and those with a poor clinical grade, in poor medical condition, and with elevated systolic blood pressure. More than half of the patients who rebleed, die.

In the days of delayed surgery, antifibrinolytic agents were routinely administered to prevent re-bleeding (78). Although they reduced the incidence of rebleeding, this benefit was offset by an increase in ischemic infarctions so there was no overall effect on outcome (79, 80). Short term (3-day) use of antifibrinolytics may prevent rebleeding without increased risk of vasospasm (81, 82).

Before aneurysm repair, factors associated with rebleeding (cough, valsalva) should be minimized. Rapid drainage of a large volume of cerebrospinal fluid during lumbar puncture or ventriculostomy should be avoided. Excessive stimulation should be minimized. Headache should be controlled. Agitated patients should be sedated with short-acting agents to the point of drowsiness, but should remain responsive for assessment of neurologic status. Care must be taken to avoid oversedation that could mask clinical deterioration.

Definitive prevention of rebleeding is done by repair of the aneurysm, either by a surgical or an endovascular approach (Fig. 2). Outcome in a large prospective-controlled trial found that for patients appropriate for either modality, 4-year outcome was better with endovascular coiling (83, 84). The study has generated considerable controversy. Follow up of patients enrolled in this study revealed that patients treated with endovascular coiling were 6.9 times more likely to undergo retreatment over a mean interval of 21 months because of aneurysm recurrence or rebleeding (85). Long-term rebleeding rates remain an unresolved concern (86–90); and the technology continues to evolve rapidly.

Hydrocephalus

Early (within 3 days) hydrocephalus (Fig. 3) occurs in 20% to 30% of patients and is often accompanied by intraventricular blood. Hydrocephalus is more frequent in patients with poor clinical grade and more subarachnoid blood (91–93). Clinical improvement is seen in the majority after external ventricular drainage.

Delayed (up to several weeks) hydrocephalus develops in about one fourth of surviving patients and is associated with older age, early ventriculomegaly, ventric-

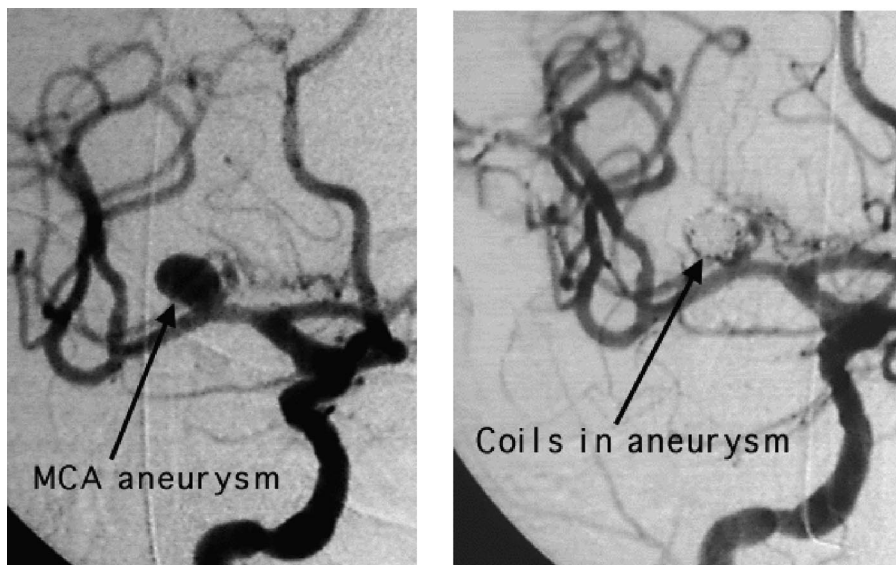


Figure 2. Middle cerebral artery aneurysm before and after endovascular coiling. *MCA*, middle cerebral artery.

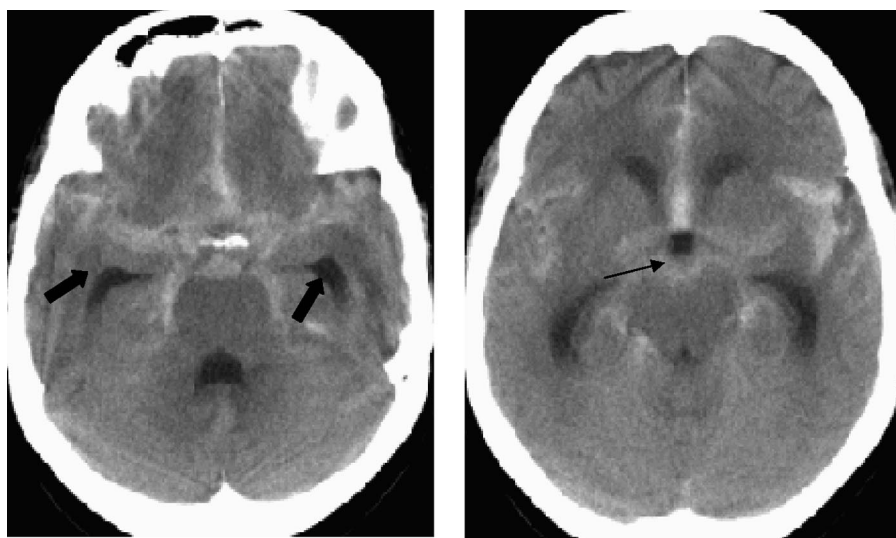


Figure 3. Computed tomography scan of patient with subarachnoid hemorrhage showing early hydrocephalus. Note the enlargement of the temporal horns of the lateral ventricle (*thick arrows*) and ballooning of the third ventricle (*thin arrow*).

ular hemorrhage, poor clinical condition on presentation, and female gender (94). Hydrocephalus rates are not different in patients undergoing clipping or endovascular treatment of their aneurysms.

Late Complications

Hyponatremia and Intravascular Volume Contraction. Hyponatremia occurs in up to one third of patients following SAH. Although originally attributed to the syndrome of inappropriate secretion of antidiuretic hormone, the picture is more complex (65, 95–98). There are disturbances of humoral and neural regulation of sodium, intravascular volume, and

water in SAH that lead to intravascular volume depletion and hyponatremia, sometimes referred to as cerebral salt wasting (96, 99). Reduced intravascular volume has been associated with clinical symptoms in patients with angiographic vasospasm. Hypervolemic therapy appears to ameliorate the tendency toward intravascular volume contraction (65).

Hyponatremia can frequently be managed with restriction of free water by giving only isotonic intravenous fluids, minimizing oral liquids, and using concentrated enteral feedings. Persistent hyponatremia can be treated by utilizing mildly hypertonic solutions (1.25%–3.0% saline) as the sole intra-

venous fluid. Two randomized, controlled trials of fludrocortisone failed to show any important benefit (100–103).

Vasospasm. In the context of SAH, the term “vasospasm” refers to a condition that is more complex than simple constriction of blood vessels. Pathologic changes occur in intracranial arteries following SAH that thicken the wall, narrow the lumen, and impair relaxation (104). This, along with impaired autoregulatory function of the arterioles and intravascular volume depletion can lead to a fall in cerebral blood flow. If the reduction in flow is severe enough, ischemia and infarction follow (105). The term delayed ischemic neurologic deficit describes the clinical situation where these multiple factors conspire to produce ischemia (63, 106, 107).

Monitoring for vasospasm typically consists of serial neurologic exams, serial measurement of blood flow velocities by TCD (61, 62, 108–110), and catheter angiography. Neurologic signs may be vague, such as a global decline in responsiveness, or consist of focal deficits such as hemiparesis, hemiplegia, abulia, or language disturbance that may wax and wane (111). TCD is a noninvasive method that detects elevation in linear blood flow velocities, mainly in the middle and internal cerebral arteries (62, 110, 112). Although it is almost as sensitive as angiography in detecting symptomatic vasospasm, its use has limitations, such as inadequate insonation windows and poor specificity (113). Additionally, improving cerebral blood flow with induced hypertension leads to increased linear blood flow velocities that can be misinterpreted as worsening vasospasm (114).

When making a clinical diagnosis of vasospasm, alternative causes of neurologic changes such as sedatives, rebleeding, hydrocephalus, cerebral edema, metabolic derangements, and infections should be promptly excluded using radiographic, clinical, and laboratory assessments. Detection of clinical signs of vasospasm is particularly difficult in poor grade patients because of the limited exam that is possible.

The utility of other imaging modalities, like perfusion computed tomography, Xenon computed tomography, diffusion weighted magnetic resonance imaging, and single photon emission computed tomography in detecting vasospasm is under investigation. Cerebral microdialysis, which involves measuring extracellular cerebral fluid levels of glu-

cose, glutamate, lactate, and pyruvate, and brain tissue oxygen tension monitoring may offer promise (115–117).

Management of Vasospasm. The management of vasospasm involves both routine “prophylactic” measures and more aggressive intervention reserved for situations where there are signs or symptoms of active vasospasm.

Nimodipine is safe, cost-effective, and reduces the risk of poor outcome and secondary ischemia (44, 118–120). It is thus used prophylactically in all patients with SAH. Hypotension is infrequent, especially if patients are well hydrated. In those being treated with vasopressors for symptomatic vasospasm, dips in blood pressure following nimodipine administration may be more of a problem, and administering small, more frequent dose is helpful.

While there is general agreement that hypovolemia must be avoided, the use of prophylactic hypervolemia is more controversial (107, 121, 122). In a prospective controlled study, prophylactic volume expansion with albumin failed to reduce the incidence of clinical or TCD-defined vasospasm, did not improve cerebral blood flow (CBF), and had no effect on outcome (123). Costs and complications may be higher with the use of prophylactic hypervolemia.

The amount of blood in the subarachnoid space is a strong predictor of vasospasm, and several methods have been proposed to facilitate its clearance. A meta-analysis found a clinically relevant and beneficial effect of intracisternal thrombolysis, but the findings were limited by the predominance of nonrandomized studies (124). Another technique uses lumbar cerebrospinal fluid drainage (125).

Other approaches under investigation include insertion of prolonged release implants impregnated with vasodilators (papaverine and nicardipine), enoxaparin (126), and prophylactic transluminal balloon angioplasty (127).

The threshold for instituting more aggressive interventions varies widely across centers. Some actively intervene in the setting of rising TCD velocities (114) or angiographic vasospasm in asymptomatic patients (128), whereas others institute aggressive measures in the setting of neurologic deterioration.

Aggressive measures include both hemodynamic and endovascular manipulations (63, 129, 130). The goal is to improve CBF in ischemic regions. Because

SAH patients tend to become hypovolemic and lose pressure autoregulation (131–133), it has been inferred that hypervolemia, induced hypertension, and augmentation of CO would accomplish that goal.

The use of triple-H therapy (hypervolemia, hypertension, and hemodilution) stems from numerous clinical observations noting improvement in patients’ clinical symptoms following induced hypertension and volume expansion (134–136). The relative contribution of each component is debated.

Despite being widely advocated, data supporting the use of hypervolemia are scant. A prospective randomized trial found no impact of prophylactic hypervolemia on CBF, vasospasm, or outcome (123). Other studies question whether hypervolemia adds further benefit beyond correction of hypovolemia (122) and report that the impact of volume expansion on CBF is modest compared with induced hypertension (137).

Hemodilution is perhaps the least understood component of triple-H therapy. The rationale is to reduce blood viscosity to augment CBF. The trade-off is that oxygen-carrying capacity is reduced, potentially diminishing cerebral oxygen delivery. It is argued that a hematocrit of 30% provides the optimal balance between oxygen-carrying capacity and vis-

cosity. One study found that despite a rise in CBF, oxygen delivery fell with hemodilution to this level, suggesting that it produced more harm than good (121).

Blood pressure augmentation by raising pressure by a percent of baseline or to an arbitrary goal may be the most effective hemodynamic intervention. Studies have found a consistent rise in CBF in response to blood pressure elevation with dopamine and phenylephrine, although they have not yet identified the optimal target (138).

Under normal conditions, changes in CO do not influence CBF. There is growing evidence, however, that with cerebral ischemia or impaired autoregulation, changes in CO can alter CBF. Administration of dobutamine or milrinone may be effective in improving CO and CBF in some patients (138–140).

Endovascular techniques frequently play a role in the aggressive treatment of vasospasm. They include transluminal angioplasty (Fig. 4) and intra-arterial infusion of vasodilators. Both methods have their unique associated risks and benefits and are usually undertaken after a trial of medical therapy, except in patients with severe cardiac disease.

Transluminal balloon angioplasty is very effective at reversing angiographic spasm of large proximal vessels and produces a sustained reversal of arterial nar-

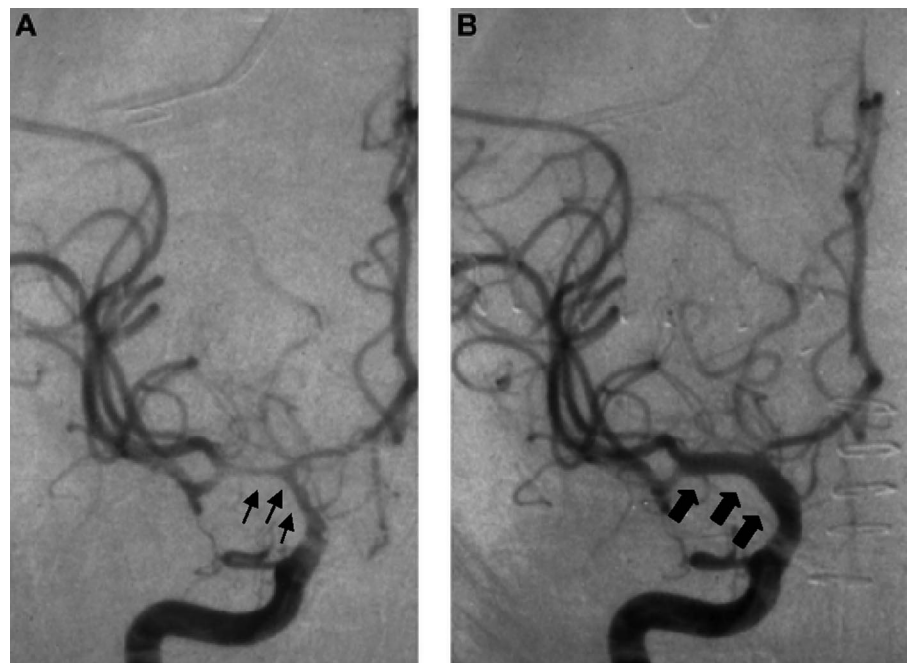


Figure 4. Vasospasm before and after angioplasty. *A*, angiogram with vasospasm in the middle cerebral artery territory (*thin arrows*); *B*, angiogram after angioplasty with improvement in vasospasm (*thick arrows*).

rowing (141–143). The optimal timing of angioplasty in relation to medical therapy is uncertain. Major complications occur in ~5% of procedures and include vessel rupture, occlusion, dissection, hemorrhagic infarction, and hemorrhage from unsecured aneurysms (144). A recent prospective controlled trial of prophylactic angioplasty in patients at high risk for vasospasm did not show any improvement in outcome.

Intra-arterial papaverine has an immediate and dramatic effect on blood vessels, but reversal of clinical deficits is variable (145–147). In most centers, use of papaverine has been abandoned because of its short-lived effect and complications including increased intracranial pressure, apnea, worsening of vasospasm, neurologic deterioration, and seizures. This has led to the growing use of intra-arterial nicardipine, verapamil, nimodipine, and milrinone as alternatives to papaverine (148–150).

Emerging Therapies

A number of potential new therapies are currently under active investigation, including an endothelin antagonist, magnesium, and statins.

Two small prospective controlled trials have found a reduction in delayed ischemia neurologic deficits and symptomatic vasospasm with statin therapy. In contrast, a much larger case-control study failed to identify any benefit of statin use. A prospective, randomized controlled trial of intravenous magnesium found a nonsignificant trend toward better outcome. Clazosentan, a selective endothelin A receptor antagonist, was evaluated in a randomized, double-blind, placebo-controlled, multicenter phase IIa study, and it was found that it reduced the frequency and severity of angiographic vasospasm (109). A phase III study is underway.

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