Continuing Medical Educational Article
Concise Definitive Review — **Jonathan Sevransky, MD, MHS, Section Editor**

Management of aneurysmal subarachnoid hemorrhage

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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 aneurysm (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-

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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 enlargement 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

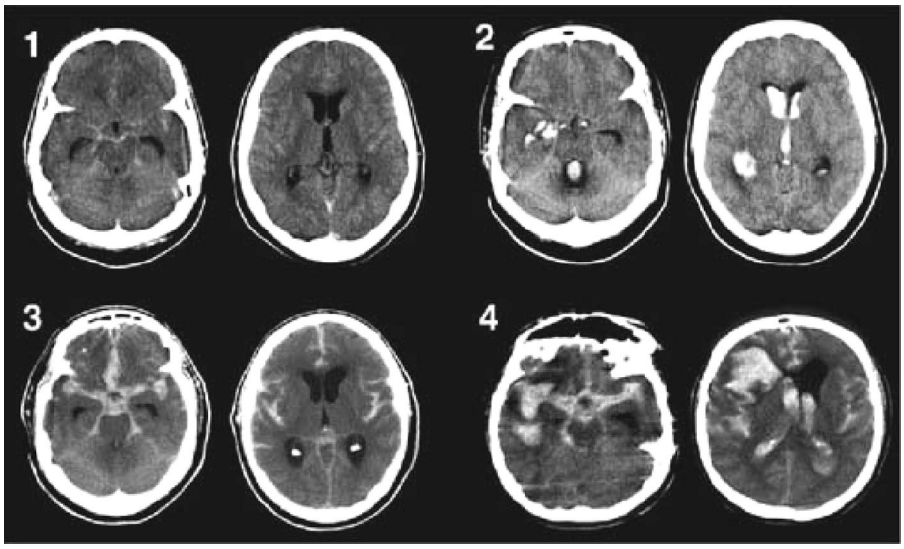

Figure 1. The modified Fisher computed tomography rating scale: grade 1 (minimal or diffuse thin subarachnoid hemorrhage without intraventricular hemorrage [IVH]), indicating low risk for symptomatic vasospasm; grade 2 (minimal or thin subarachnoid hemorrhage with IVH); grade 3 (thick cisternal clot 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 abnormities 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-

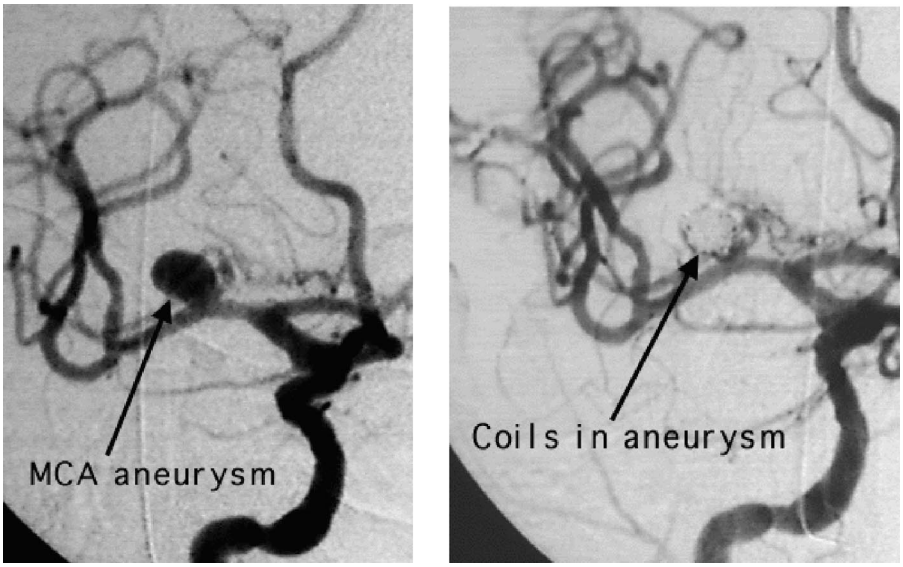

Figure 2. Middle cerebral artery aneurysm before and after endovascular coiling. *MCA*, middle cerebral artery.

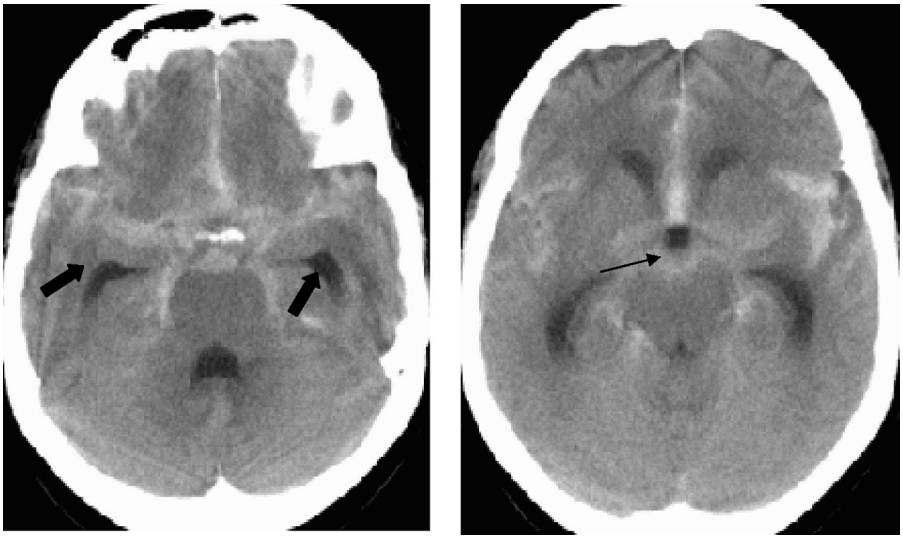

Figure 3. Computed tomography scan of patient with subarachnoid hemorrhage showing early hydrocephalus. Note the enlargement of the temporal horns of the lateral ventricle (*thick arrows*) and ballooning of the third ventricle (*thin arrow*).

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 intravenous 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 viscosity. 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-

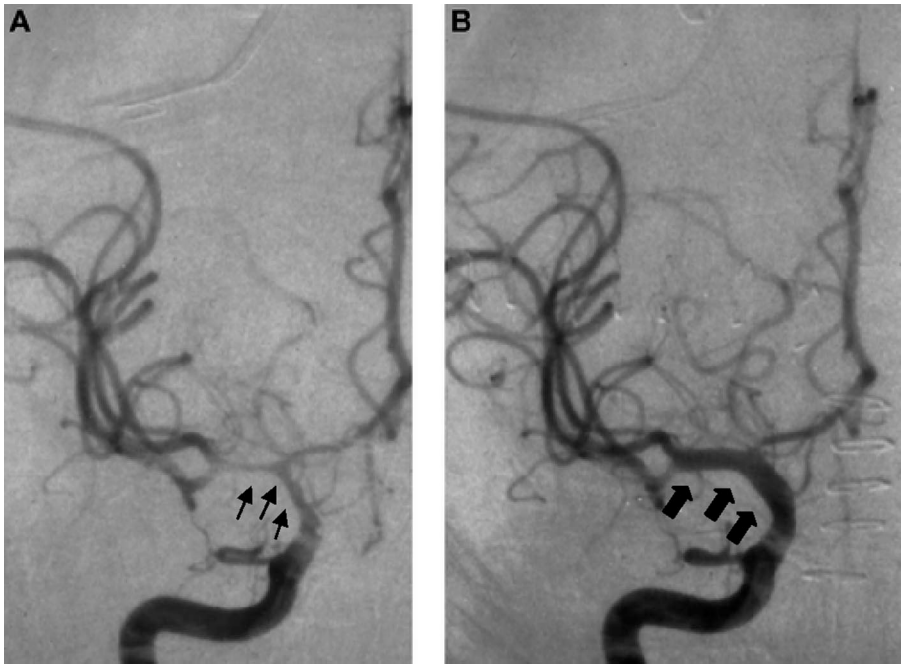

Figure 4. Vasospasm before and after angioplasty. *A,* angiogram with vasospasm in the middle cerebral artery territory (*thin arrows*); *B,* angiogram after angioplasty with improvement in vasospasm (*thick arrows*).

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.

REFERENCES

1. Heros RC, Kistler JP: Intracranial arterial aneurysm—An update. *Stroke* 1983; 14: 628–631
2. Winn HR, Richardson AE, Jane JA: The long-term prognosis in untreated cerebral aneurysms. I. The incidence of late hemorrhage in cerebral aneurysm: A 10-year evaluation of 364 patients. *Ann Neurol* 1977; 1:358–370
3. Ohkuma H, Tsurutani H, Suzuki S: Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. *Stroke* 2001; 32: 1176–1180
4. Mohr JP, Kistler JP: Intracranial aneurysms. *In:* Stroke: Pathophysiology, Diagnosis and Management. Mohr JP, Choi D, Grotta J, et al (Eds). London, Churchill Livingstone, 1985, pp 643–677
5. Rabinstein AA, Weigand S, Atkinson JL, et al: Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke* 2005; 36:992–997
6. Hijdra A, van Gijn J, Stefanko S, et al: Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: Clinicoanatomic correlations. *Neurology* 1986; 36: 329–333
7. van Gijn J, Kerr RS, Rinkel GJ: Subarachnoid haemorrhage. *Lancet* 2007; 369: 306–318
8. van Gijn J, van Dongen KJ, Vermeulen M, et al: Perimesencephalic hemorrhage. *J Neurosurg* 1986; 65:727–728
9. Ruigrok YM, Rinkel GJ, Buskens E, et al: Perimesencephalic hemorrhage and CT angiography: A decision analysis. *Stroke* 2000; 31:2976–2983
10. Ingall T, Asplund K, Mahonen M, et al: A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. *Stroke* 2000; 31: 1054–1061
11. Epidemiology of aneurysmal subarachnoid hemorrhage in Australia and New Zealand: Incidence and case fatality from the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). *Stroke* 2000; 31:1843–1850
12. Ohkuma H, Fujita S, Suzuki S: Incidence of aneurysmal subarachnoid hemorrhage in Shimokita, Japan, from 1989 to 1998. *Stroke* 2002; 33:195–199
13. Kawachi I, Colditz GA, Stampfer MJ, et al: Smoking cessation and decreased risk of stroke in women. *JAMA* 1993; 269:232–236
14. Qureshi AI, Suarez JI, Parekh PD, et al: Risk factors for multiple intracranial aneurysms. *Neurosurgery* 1998; 43:22–26
15. Juvela S: Risk factors for multiple intracranial aneurysms. *Stroke* 2000; 31:392–397
16. Ellamushi HE, Grieve JP, Jager HR, et al: Risk factors for the formation of multiple intracranial aneurysms. *J Neurosurg* 2001; 94:728–732
17. Taylor CL, Yuan Z, Selman WR, et al: Cerebral arterial aneurysm formation and rupture in 20,767 elderly patients: Hypertension and other risk factors. *J Neurosurg* 1995; 83:812–819
18. Qureshi AI, Suri MF, Yahia AM, et al: Risk factors for subarachnoid hemorrhage. *Neurosurgery* 2001; 49:607–612
19. Raaymakers TW: Aneurysms in relatives of patients with subarachnoid hemorrhage: Frequency and risk factors. MARS Study Group. Magnetic resonance angiography in relatives of patients with subarachnoid hemorrhage. *Neurology* 1999; 53:982–988
20. Kissela BM, Sauerbeck L, Woo D, et al: Subarachnoid hemorrhage: A preventable disease with a heritable component. *Stroke* 2002; 33:1321–1326
21. Kojima M, Nagasawa S, Lee YE, et al: Asymptomatic familial cerebral aneurysms. *Neurosurgery* 1998; 43:776–781
22. Sekhar LN, Heros RC: Origin, growth, and rupture of saccular aneurysms: A review. *Neurosurgery* 1981; 8:248–260
23. Crawford PM, West CR, Chadwick DW, et al: Arteriovenous malformations of the brain: Natural history in unoperated patients. *J Neurol Neurosurg Psychiatry* 1986; 49: 1–10
24. Nehls DG, Flom RA, Carter LP, et al: Multiple intracranial aneurysms: Determining the site of rupture. *J Neurosurg* 1985; 63: 342–348
25. Linn FH, Rinkel GJ, Algra A, et al: Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998; 65: 791–793
26. Waga S, Otsubo K, Handa H: Warning signs in intracranial aneurysms. *Surg Neurol* 1975; 3:15–20
27. Hart RG, Byer JA, Slaughter JR, et al: Occurrence and implications of seizures in subarachnoid hemorrhage due to ruptured intracranial aneurysms. *Neurosurgery* 1981; 8:417–421
28. Hunt WE, Hess RM: Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; 28:14–20
29. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. *J Neurosurg* 1988; 68:985–986
30. Boesiger BM, Shiber JR: Subarachnoid hemorrhage diagnosis by computed tomography and lumbar puncture: Are fifth generation CT scanners better at identifying subarachnoid hemorrhage? *J Emerg Med* 2005; 29:23–27
31. Frontera JA, Claassen J, Schmidt JM, et al: Prediction of symptomatic vasospasm after subarachnoid hemorrhage: The modified fisher scale. *Neurosurgery* 2006; 59:21–27
32. Smith ML, Abrahams JM, Chandela S, et al: Subarachnoid hemorrhage on computed tomography scanning and the development of cerebral vasospasm: The Fisher grade revisited. *Surg Neurol* 2005; 63:229–234
33. Klimo P Jr, Schmidt RH: Computed tomography grading schemes used to predict cerebral vasospasm after aneurysmal subarachnoid hemorrhage: A historical review. *Neurosurg Focus* 2006; 21:E5
34. van der WN, Rinkel GJ, Hasan D, et al: Detection of subarachnoid haemorrhage on early CT: Is lumbar puncture still needed after a negative scan? *J Neurol Neurosurg Psychiatry* 1995; 58:357–359
35. Beetham R: Recommendations for CSF analysis in subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 2004; 75: 528

36. Cruickshank AM: ACP Best Practice No 166: CSF spectrophotometry in the diagnosis of subarachnoid haemorrhage. *J Clin Pathol* 2001; 54:827–830
37. Beetham R, Fahie-Wilson MN, Holbrook I, et al: CSF spectrophotometry in the diagnosis of subarachnoid haemorrhage. *J Clin Pathol* 2002; 55:479–480
38. Villablanca JP, Martin N, Jahan R, et al: Volume-rendered helical computerized tomography angiography in the detection and characterization of intracranial aneurysms. *J Neurosurg* 2000; 93:254–264
39. Velthuis BK, Van Leeuwen MS, Witkamp TD, et al: Computerized tomography angiography in patients with subarachnoid hemorrhage: From aneurysm detection to treatment without conventional angiography. *J Neurosurg* 1999; 91:761–767
40. Qu F, Aiyagari V, Cross DT III, et al: Untreated subarachnoid hemorrhage: Who, why, and when? *J Neurosurg* 2004; 100: 244–249
41. Tung P, Kopelnik A, Banki N, et al: Predictors of neurocardiogenic injury after subarachnoid hemorrhage. *Stroke* 2004; 35: 548–551
42. Liu-Deryke X, Janisse J, Coplin WM, et al: A comparison of nicardipine and labetalol for acute hypertension management following stroke. *Neurocrit Care* 2008; 9:167–176
43. Rose JC, Mayer SA: Optimizing blood pressure in neurological emergencies. *Neurocrit Care* 2004; 1:287–299
44. Mee E, Dorrance D, Lowe D, et al: Controlled study of nimodipine in aneurysm patients treated early after subarachnoid hemorrhage. *Neurosurgery* 1988; 22: 484–491
45. Galloon S, Rees GA, Briscoe CE, et al: Prospective study of electrocardiographic changes associated with subarachnoid haemorrhage. *Br J Anaesth* 1972; 44: 511–516
46. Grad A, Kiauta T, Osredkar J: Effect of elevated plasma norepinephrine on electrocardiographic changes in subarachnoid hemorrhage. *Stroke* 1991; 22:746–749
47. Yamaguchi T, Shimizu Y, Ono N, et al: A case of subarachnoid hemorrhage with electrocardiographic and echocardiographic changes simulating transmural myocardial infarction. *Jpn J Med* 1991; 30:142–145
48. Deibert E, Barzilai B, Braverman AC, et al: Clinical significance of elevated troponin I levels in patients with nontraumatic subarachnoid hemorrhage. *J Neurosurg* 2003; 98:741–746
49. Deibert E, Aiyagari V, Diringer MN: Reversible left ventricular dysfunction associated with raised troponin I after subarachnoid haemorrhage does not preclude successful heart transplantation. *Heart* 2000; 84: 205–207
50. Wartenberg KE, Mayer SA: Medical complications after subarachnoid hemorrhage: New strategies for prevention and management. *Curr Opin Crit Care* 2006; 12:78–84
51. Jain R, Deveikis J, Thompson BG: Management of patients with stunned myocardium associated with subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 2004; 25:126–129
52. Hammermeister KE, Reichenbach DD: QRS changes, pulmonary edema, and myocardial necrosis associated with subarachnoid hemorrhage. *Am Heart J* 1969; 78:94–100
53. Takahashi M, Mitsuhashi T, Katsuki T, et al: Neurogenic pulmonary edema and large negative T waves associated with subarachnoid hemorrhage. *Intern Med* 2001; 40: 826–828
54. Das M, Gonsalves S, Saha A, et al: Acute subarachnoid haemorrhage as a precipitant for takotsubo cardiomyopathy: A case report and discussion. *Int J Cardiol* 2007 [epub ahead of print]
55. Stevens RD, Nyquist PA: The systemic implications of aneurysmal subarachnoid hemorrhage. *J Neurol Sci* 2007; 261: 143–156
56. Sugimoto K, Watanabe E, Yamada A, et al: Prognostic implications of left ventricular wall motion abnormalities associated with subarachnoid hemorrhage. *Int Heart J* 2008; 49:75–85
57. Banki NM, Kopelnik A, Dae MW, et al: Acute neurocardiogenic injury after subarachnoid hemorrhage. *Circulation* 2005; 112: 3314–3319
58. Davies KR, Gelb AW, Manninen PH, et al: Cardiac function in aneurysmal subarachnoid haemorrhage: A study of electrocardiographic and echocardiographic abnormalities. *Br J Anaesth* 1991; 67:58–63
59. Kopelnik A, Fisher L, Miss JC, et al: Prevalence and implications of diastolic dysfunction after subarachnoid hemorrhage. *Neurocrit Care* 2005; 3:132–138
60. Newell DW, Grady MS, Eskridge JM, et al: Distribution of angiographic vasospasm after subarachnoid hemorrhage: Implications for diagnosis by transcranial Doppler ultrasonography. *Neurosurgery* 1990; 27: 574–577
61. Sloan MA, Haley EC Jr, Kassell NF, et al: Sensitivity and specificity of transcranial doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. *Neurology* 1989; 39:1514–1518
62. Sekhar LN, Wechsler LR, Yonas H, et al: Value of transcranial Doppler examination in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery* 1988; 22:813–821
63. Keyrouz SG, Diringer MN: Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. *Crit Care* 2007; 11:220
64. Diringer MN, Axelrod Y: Hemodynamic manipulation in the neuro-intensive care unit: Cerebral perfusion pressure therapy in head injury and hemodynamic augmentation for cerebral vasospasm. *Curr Opin Crit Care* 2007; 13:156–162
65. Diringer MN, Wu KC, Verbalis JG, et al: Hypervolemic therapy prevents volume contraction but not hyponatremia following subarachnoid hemorrhage. *Ann Neurol* 1992; 31:543–550
66. Smith M: Intensive care management of patients with subarachnoid haemorrhage. *Curr Opin Anaesthesiol* 2007; 20:400–407
67. Treggiari-Venzi MM, Suter PM, Romand JA: Review of medical prevention of vasospasm after aneurysmal subarachnoid hemorrhage: A problem of neurointensive care. *Neurosurgery* 2001; 48:249–261
68. Bilotta F, Spinelli A, Giovannini F, et al: The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: A randomized prospective pilot trial. *J Neurosurg Anesthesiol* 2007; 19:156–160
69. Axelrod YK, Diringer MN: Temperature management in acute neurologic disorders. *Crit Care Clin* 2006; 22:767–785
70. Kvam DA, Loftus CM, Copeland B, et al: Seizures during the immediate post operative period. *Neurosurgery* 1983; 12:14–17
71. Rose FC, Sarner M: Epilepsy after ruptured intracranial aneurysm. *Brit Med J* 1965; 1:18–21
72. Cabral RJ, King TT, Scott DF: Epilepsy after two different neurosurgical approaches to treatment of ruptured intracranial aneurysm. *J Neurol Neurosurg Psychol* 1976; 39:1052–1056
73. Rosengart AJ, Huo JD, Tolentino J, et al: Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. *J Neurosurg* 2007; 107:253–260
74. Naidech AM, Kreiter KT, Janjua N, et al: Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. *Stroke* 2005; 36: 583–587
75. Chumnanvej S, Dunn IF, Kim DH: Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. *Neurosurgery* 2007; 60:99–102
76. Feigin VL, Anderson N, Rinkel GJ, et al: Corticosteroids for aneurysmal subarachnoid haemorrhage and primary intracerebral haemorrhage. *Cochrane Database Syst Rev* 2005; 20:CD004583
77. Winn HR, Almaani WS, Berga SL, et al: The long-term outcome in patients with multiple aneurysms. Incidence of late hemorrhage and implications for treatment of incidental aneurysms. *J Neurosurg* 1983; 59: 642–651
78. Torner JC, Kassell NF, Wallace RB, et al: Preoperative prognostic factors for rebleeding and survuval in aneurysm patients receiving antifibrinolytic therapy: Report of the cooperatvie aneruysm study. *Neurosurg* 1981; 9:506–511
79. Roos YB, Rinkel GJ, Vermeulen M, et al: Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2003; 2:CD001245
80. Roos Y, Rinkel G, Vermeulen M, et al: An-

tifibrinolytic therapy for aneurysmal subarachnoid hemorrhage: A major update of a cochrane review. *Stroke* 2003; 34: 2308–2309
81. Hillman J, Fridriksson S, Nilsson O, et al: Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: A prospective randomized study. *J Neurosurg* 2002; 97:771–778
82. Chwajol M, Starke RM, Kim GH, et al: Antifibrinolytic therapy to prevent early rebleeding after subarachnoid hemorrhage. *Neurocrit Care* 2008; 8:418–426
83. de Oliveira JG, Beck J, Ulrich C, et al: Comparison between clipping and coiling on the incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Neurosurg Rev* 2007; 30:22–30
84. Diringer MN: To clip or to coil acutely ruptured intracranial aneurysms: Update on the debate. *Curr Opin Crit Care* 2005; 11: 121–125
85. Campi A, Ramzi N, Molyneux AJ, et al: Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). *Stroke* 2007; 38: 1538–1544
86. Molyneux AJ, Kerr RS, Yu LM, et al: International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005; 366:809–817
87. Molyneux A, Kerr R, Stratton I, et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised trial. *Lancet* 2002; 360:1267–1274
88. Reeves BC, Langham J, Lindsay KW, et al: Findings of the International Subarachnoid Aneurysm Trial and the National Study of Subarachnoid Haemorrhage in context. *Br J Neurosurg* 2007; 21:318–323
89. Wolstenholme J, Rivero-Arias O, Gray A, et al: Treatment pathways, resource use, and costs of endovascular coiling versus surgical clipping after aSAH. *Stroke* 2008; 39: 111–119
90. Mitchell P, Kerr R, Mendelow AD, et al: Could late rebleeding overturn the superiority of cranial aneurysm coil embolization over clip ligation seen in the International Subarachnoid Aneurysm Trial? *J Neurosurg* 2008; 108:437–442
91. Dorai Z, Hynan LS, Kopitnik TA, et al: Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2003; 52:763–769
92. Brisman JL, Berenstein A: Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2004; 54: 1031
93. Tian HL, Xu T, Hu J, et al: Risk factors related to hydrocephalus after traumatic subarachnoid hemorrhage. *Surg Neurol* 2008; 69:241–246
94. Hirashima Y, Hamada H, Hayashi N, et al: Independent predictors of late hydrocephalus in patients with aneurysmal subarachnoid hemorrhage—Analysis by multivariate logistic regression model. *Cerebrovasc Dis* 2003; 16:205–210
95. Diringer MN: Sodium disturbances frequently encountered in a neurologic intensive care unit. *Neurol India* 2001; 49(Suppl 1):S19–S30
96. Diringer MN: Neuroendocrine regulation of sodium and volume following subarachnoid hemorrhage. *Clin Neuropharmacol* 1995; 18:114–126
97. Wijdicks EFM, Vermeulen M, Hijdra A, et al: Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: Is fluid restriction harmful. *Annals Neurol* 1985; 17:137–140
98. Wijdicks EFM, Vermeulen M, ten Haaf JA, et al: Volume depletion and natriuresis in patients with a ruptured intracranial aneurysm. *Annals Neurol* 1985; 18:211–216
99. Diringer MN: Management of sodium abnormalities in patients with CNS disease. *Clin Neuropharmacol* 1992; 15:427–447
100. Hasan D, Lindsay KW, Wijdicks EF, et al: Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. *Stroke* 1989; 20:1156–1161
101. Mori T, Katayama Y, Kawamata T, et al: Improved efficiency of hypervolemic therapy with inhibition of natriuresis by fludrocortisone in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg* 1999; 91:947–952
102. Wijdicks EF, Vermeulen M, van Brummelen P, et al: The effect of fludrocortisone acetate on plasma volume and natriuresis in patients with aneurysmal subarachnoid hemorrhage. *Clin Neurol Neurosurg* 1988; 90: 209–214
103. Woo MH, Kale-Pradhan PB: Fludrocortisone in the treatment of subarachnoid hemorrhage-induced hyponatremia. *Ann Pharmacother* 1997; 31:637–639
104. Seifert V, Stolke D, Reale E: Ultrastructural changes of the basilar artery following experimental subarachnoid haemorrhage. A morphological study on the pathogenesis of delayed cerebral vasospasm. *Acta Neurochir (Wien)* 1989; 100:164–171
105. Powers WJ, Grubb RL Jr, Baker RP, et al. Regional cerebral blood flow and metabolism in reversible ischemia due to vasospasm. Determination by positron emission tomography. *J Neurosurg* 1985; 62: 539–546
106. Kirsch JR, Diringer MN, Borel CO, et al: Cerebral aneurysms: Mechanisms of injury and critical care interventions. *Crit Care Clin* 1989; 5:755–772
107. Miller J, Diringer M: Management of aneurysmal subarachnoid hemorrhage. *Neurol Clin* 1995; 13:451–478
108. Romner B, Ljunggren B, Brandt L, et al: Transcranial Doppler sonography within 12 hours after subarachnoid hemorrhage. *J Neurosurg* 1989; 70:732–736
109. Vajkoczy P, Horn P, Thome C, et al: Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2003; 98:1227–1234
110. Verlooy J, Heytens L, Van den Brande E, et al: Transcranial Doppler sonography in subarachnoid hemorrhage. *Acta Neurol Belg* 1989; 89:346–351
111. Kassell NF, Sasaki T, Colohan AR, et al: Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Stroke* 1985; 16: 562–572
112. Romner B, Ljunggren B, Brandt L, et al: Correlation of transcranial Doppler sonography findings with timing of aneurysm surgery. *J Neurosurg* 1990; 73:72–76
113. Suarez JI, Qureshi AI, Yahia AB, et al: Symptomatic vasospasm diagnosis after subarachnoid hemorrhage: Evaluation of transcranial Doppler ultrasound and cerebral angiography as related to compromised vascular distribution. *Crit Care Med* 2002; 30:1348–1355
114. Manno EM, Gress DR, Schwamm LH, et al: Effects of induced hypertension on transcranial Doppler ultrasound velocities in patients after subarachnoid hemorrhage. *Stroke* 1998; 29:422–428
115. Skjoth-Rasmussen J, Schulz M, Kristensen SR, et al: Delayed neurological deficits detected by an ischemic pattern in the extracellular cerebral metabolites in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2004; 100:8–15
116. Sarrafzadeh AS, Sakowitz OW, Kiening KL, et al: Bedside microdialysis: A tool to monitor cerebral metabolism in subarachnoid hemorrhage patients? *Crit Care Med* 2002; 30:1062–1070
117. Schulz MK, Wang LP, Tange M, et al: Cerebral microdialysis monitoring: Determination of normal and ischemic cerebral metabolisms in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2000; 93:808–814
118. Kostron H, Twerdy K, Grunert V: The calcium entry blocker nimodipine improves the quality of life of patients operated on for cerebral aneurysms. A 5-year follow-up analysis. *Neurochirurgia (Stuttg)* 1988; 31: 150–153
119. Neil Dwyer G, Mee E, Dorrance D, et al: Early intervention with nimodipine in subarachnoid haemorrhage. *Eur Heart J* 1987; 8:41–47
120. Welty TE: Use of nimodipine for prevention and treatment of cerebral arterial spasm in patients with subarachnoid hemorrhage. *Clin Pharm* 1987; 6:940–946
121. Ekelund A, Reinstrup P, Ryding E, et al:

Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)* 2002; 144: 703–712
122. Raabe A, Zimmermann M, Setzer M, et al: Effect of intraventricular sodium nitroprusside on cerebral hemodynamics and oxygenation in poor-grade aneurysm patients with severe, medically refractory vasospasm. *Neurosurgery* 2002; 50:1006–1013
123. Lennihan L, Mayer SA, Fink ME, et al: Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial. *Stroke* 2000; 31:383–391
124. Amin-Hanjani S, Ogilvy CS, Barker FG: Does intracisternal thrombolysis prevent vasospasm after aneurysmal subarachnoid hemorrhage? A meta-analysis. *Neurosurgery* 2004; 54:326–334
125. Klimo P Jr, Kestle JR, MacDonald JD, et al: Marked reduction of cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage. *J Neurosurg* 2004; 100:215–224
126. Wurm G, Tomancok B, Nussbaumer K, et al: Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: A double-blind, randomized comparison of enoxaparin versus placebo. *Clin Neurol Neurosurg* 2004; 106:97–103
127. Muizelaar JP, Zwienenberg M, Rudisill NA, et al: The prophylactic use of transluminal balloon angioplasty in patients with Fisher Grade 3 subarachnoid hemorrhage: A pilot study. *J Neurosurg* 1999; 91:51–58
128. Nolan CP, Macdonald RL: Can angiographic vasospasm be used as a surrogate marker in evaluating therapeutic interventions for cerebral vasospasm? *Neurosurg Focus* 2006; 21:E1
129. Koebbe CJ, Veznedaroglu E, Jabbour P, et al: Endovascular management of intracranial aneurysms: Current experience and future advances. *Neurosurgery* 2006; 59(Suppl 3):S93–S102
130. Kirmani JF, Alkawi A, Ahmed S, et al: Endovascular treatment of subarachnoid hemorrhage. *Neurol Res* 2005; 27(Suppl 1): S103–S107
131. Lam JM, Smielewski P, Czosnyka M, et al: Predicting delayed ischemic deficits after aneurysmal subarachnoid hemorrhage using a transient hyperemic response test of cerebral autoregulation. *Neurosurgery* 2000; 47:819–825
132. Czosnyka M, Smielewski P, Czosnyka Z, et al: Continuous assessment of cerebral autoregulation: Clinical and laboratory experience. *Acta Neurochir Suppl* 2003; 86: 581–585
133. Jaeger M, Schuhmann MU, Soehle M, et al: Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke* 2007; 38:981–986
134. Kosnik EJ, Hunt WE: Postoperative hypertension in the management of patients with intracranial arterial aneurysms. *J Neurosurg* 1976; 45:148–154
135. Kassell NF, Peerless SJ, Durward QJ, et al: Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. *Neurosurgery* 1982; 11:337–343
136. Denny-Brown D: The treatment of recurrent cerebrovascular symptoms and the question of "vasospasm." *Med Clin North Am* 1951; 35:1457–1474
137. Muench E, Horn P, Bauhuf C, et al: Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. *Crit Care Med* 2007; 35:1844–1851
138. Joseph M, Ziadi S, Nates J, et al: Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: A study using xenon computed tomographic measurement of cerebral blood flow. *Neurosurgery* 2003; 53:1044–1051
139. Naidech A, Du Y, Kreiter KT, et al: Dobutamine versus milrinone after subarachnoid hemorrhage. *Neurosurgery* 2005; 56:21–6l
140. Romero CM, Morales D, Reccius A, et al: Milrinone as a rescue therapy for symptomatic refractory cerebral vasospasm in aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2008 [E-pub ahead of print]
141. Suzuki S, Jahan R, Duckwiler GR, et al: Contribution of endovascular therapy to the management of poor-grade aneurysmal subarachnoid hemorrhage: Clinical and angiographic outcomes. *J Neurosurg* 2006; 105:664–670
142. Mueller-Kronast N, Jahromi BS: Endovascular treatment of ruptured aneurysms and vasospasm. *Curr Treat Options Neurol* 2007; 9:146–157
143. Jestaedt L, Pham M, Bartsch AJ, et al: The impact of balloon angioplasty on the evolution of vasospasm-related infarction after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2008; 62:610–617
144. Zwienenberg-Lee M, Hartman J, Rudisill N, et al: Endovascular management of cerebral vasospasm. *Neurosurgery* 2006; 59(Suppl 3):S139–S147
145. Cross DT III, Moran CJ, Angtuaco EE, et al: Intracranial pressure monitoring during intraarterial papaverine infusion for cerebral vasospasm. *AJNR Am J Neuroradiol* 1998; 19:1319–1323
146. Milburn JM, Moran CJ, Cross DT III, et al: Effect of intraarterial papaverine on cerebral circulation time. *AJNR Am J Neuroradiol* 1997; 18:1081–1085
147. Sayama CM, Liu JK, Couldwell WT: Update on endovascular therapies for cerebral vasospasm induced by aneurysmal subarachnoid hemorrhage. *Neurosurg Focus* 2006; 21:E12
148. Brisman JL, Eskridge JM, Newell DW: Neurointerventional treatment of vasospasm. *Neurol Res* 2006; 28:769–776
149. Fraticelli AT, Cholley BP, Losser MR, et al: Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke* 2008; 39:893–898
150. Hirsh LF: Intra-arterial nitroprusside treatment of acute experimental vasospasm. *Stroke* 1980; 11:601–605

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REFERENCES

1. Gentry CA, Gross KB, Sud B, et al: Adverse outcomes associated with the use of drotrecogin alfa (activated) in patients with severe sepsis and baseline bleeding precautions. *Crit Care Med* 2009; 37:19–25
2. Sweeney DA, Natanson C, Eichacker PQ: Recombinant human activated protein C, package labeling, and hemorrhage risks. *Crit Care Med* 2009; 37:327–329
3. Code of Federal Regulations. 21 CFR § 201.57 (c) (5)
4. Code of Federal Regulations. 21 CFR § 201.57 (c) (6)

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The author replies:

We appreciate the opportunity to comment on these letters to the editor from US Food and Drug Administration officials and a representative from Eli Lilly, Inc. Dr. Lorenz and colleagues offer a constructive explanation of the considerations that Food and Drug Administration personnel must carefully address to determine appropriate precaution, warning, and contraindication labeling for any prescription drug. They conclude by summarizing the Warning and Precautions section of Xigris product labeling, cautioning that treating physicians consider the increased bleeding risk for patients with any bleeding precautions listed in the section. Our study was an initial assessment of that risk, which, in part, led the Food and Drug Administration to recently release an "Early Communication about an Ongoing Safety Review" for Xigris, specifically warning clinicians of the potential risks of using the drug in these patients (1). The Food and Drug Administration indicated that a review of serious bleeding events and mortality is ongoing, and that it will communicate the conclusions and recommendations when the review is completed.

Dr. Williams acknowledges that industry-sponsored trials for Xigris excluded patients with baseline bleeding precautions. Thus, the data he provides on the bleeding risk and mortality of patients from the recent safety analysis and from the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis trial patients with disseminated intravascular coagulation do not directly pertain to our study. Dr. Williams states that most deaths in patients with serious bleeding events were attributed to sepsis-related organ failure. However, this fails to acknowledge the often subjective nature of attributing a cause of death in these patients, and the fact that the consequences of a serious bleeding event in a patient with sepsis may well contribute to the end-organ failure that results in death.

Our study concerned serious drug-related complications in patients that were not included in key registration trials, but were revealed by use of the drug in clinical practice. It is unfortunate that since the release of Xigris onto the market in 2001, little, if any, data have been provided to help clinicians to assess the risk/benefit relationship of bleeding-related precautions as noted in the product labeling. Dr. Williams concludes that his colleagues at Eli Lilly Inc. believe that some patients with baseline bleeding precautions are appropriate candidates for Xigris; however, no tools are presented to assist physicians in identifying these patients. Our study, likewise, found no existing tools to identify any patients with baseline bleeding precautions who might benefit from the drug. However, we did identify that these patients seem to be at substantial risk.

The authors have not disclosed any potential conflicts of interest.

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REFERENCE

1. Early Communication about an Ongoing Safety Review: Xigris (Drotrecogin alfa [activated]). United States Food and Drug Administration. Rockville, MD. 2009. Available at: http://www.fda.gov/cder/drug/early_comm/drotrecogin_alfa.html. Accessed 2 March 2009

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Intensive care treatment of aneurysmal subarachnoid hemorrhage

To the Editor:

In a recent review, the management of aneurysmal subarachnoid hemorrhage (SAH) was discussed (1). This review is intended for the general intensivist and for this reason I would like to make some additional comments.

First, the author advises to treat hypertension promptly as long as endovascular or surgical occlusion of the ruptured intracranial aneurysm has not taken place to prevent aneurysmal rerupture. Although this statement may seem appealing, the author neither provides a target blood pressure to aim for, nor does he provide references to support this advice. The reason is that there is no evidence to support aggressive treatment of hypertension to prevent rerupture. On the other hand, overenthusiastic treatment of hypertension in a previously hypertensive patient with (partially) impaired (because of SAH) and rightward shifted (because of preexisting hypertension) cerebral arterial autoregulatory response curve may lead to acute cerebral blood flow impairment resulting in cerebral ischemia.

Second, perception about conventional catheter subtraction angiography as the gold standard for the diagnosis and treatment of acutely ruptured intracranial aneurysms is shifting, because CT angiography has been shown to be sufficient to decide on further treatment, either endovascularly or surgically in most, if not all, patients (2). Further, in some cases, CT angiography may even superiorly depict anatomy around ruptured aneurysms when compared with conventional angiography (2). Therefore, the advice to perform conventional angiography as soon as possible is not true in all circumstances, depending on local experience with CT angiography and degree of implementation into clinical practice.

Third, pump failure which may be caused by "stunned" myocardium after SAH should be treated identically as other causes of acute pump failure including diuretics, according to the author. However, as the author states himself, hypovolemia is best avoided to prevent cerebral ischemia, whereas for hypervolemia, either prophylactically or as treatment of cerebral ischemia, proof for any beneficial effects is still lacking. Therefore, aiming for normovolemia is probably the most rational (3). However, bedside assessment of volume status has been shown to be unreliable (4). Therefore, when confronted with a patient with cardiac stunning as assessed by echocardiography, with or without pulmonary edema, treatment should be aimed at normovolemia and diuretics should be used cautiously and only when directed by some form of advanced hemodynamic monitoring.

Fourth, treatment with mineralocorticoids is discouraged based on several

small prospective studies. On the other hand, the author encourages prophylactic hypervolemic therapy because this may prevent volume contraction, which may be harmful. The author fails to recognize that these same studies and a more recent randomized trial (5) supported the administration of either hydrocortisone or fludrocortisone to maintain volume status by inhibiting excessive diuresis that exceeded fluid intake.

In conclusion, for intensivists treating patients with SAH one should be reserved in the treatment of acute hypertension, diagnosis may be more straightforward nowadays with the advent of CT angiography, cardiac failure, and pulmonary edema has a different pathophysiology in SAH compared with primary cardiac disease and volume contraction because of excessive diuresis may be treated with mineralocorticoids.

The author has not disclosed any potential conflicts of interest.

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REFERENCES

1. Diringer MN: Management of aneurysmal subarachnoid hemorrhage. *Crit Care Med* 2009; 37:432–440
2. Van der Jagt M, Flach HZ, Tanghe HL, et al: Assessment of feasibility of endovascular treatment of ruptured intracranial aneurysms with 16-detector row CT angiography. *Cerebrovasc Dis* 2008; 26:482–488
3. Muench E, Horn P, Bauhuf C, et al: Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. *Crit Care Med* 2007; 35: 1844–1851
4. Hoff RG, Rinkel GJE, Verweij BH, et al: Nurses' prediction of volume status after aneurysmal subarachnoid hemorrhage: A prospective cohort study. *Crit Care* 2008; 12:R153
5. Katayama Y, Haraoka J, Hirabayashi H, et al: A randomized controlled trial of hydrocortisone against hyponatremia in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 2007; 38:2373–2375

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The author replies:

Dr. van der Jagt takes exception with a number of points made in my review of subarachnoid hemorrhage. Each point relates to an area for which definitive data are not available. In such situations, my recommendations were based on the review of available data and weighing the potential risks and benefits of the intervention. In such situations, disagreement is common.

His first criticism is about the management of hypertension at initial presentation. Dr. van der Jagt is rightfully concerned about overaggressive treatment of blood pressure in chronically hypertensive patients. The goal of treatment should be to maintain the usual blood pressure of the patient. Because this will vary from patient to patient, a specific target is not provided. With adequate clinical assessment, high-risk patients can be identified through a review of fundoscopy (hypertensive retinopathy), electrocardiogram (left ventricular hypertrophy), medications (multiple antihypertensives), and computed tomography (hydrocephalus), and a goal should be chosen accordingly. After excluding the high-risk patients, the theoretical benefits of treating hypertension to prevent re-rupture during the period of highest risk (which carries a 50% to 80% mortality) outweigh the theoretical risks.

I must also differ with Dr. van der Jagt's statements about the effects of hypertension and subarachnoid hemorrhage on autoregulation. Although the lower limit of autoregulation is shifted to higher pressures in untreated severe chronic hypertension, this is not necessarily the case with lesser degrees of hypertension (1). Similarly, although autoregulation may be impaired in subarachnoid hemorrhage, it is the case in only about half of the patients during vasospasm (2) and has never been studied at presentation.

Second, Dr. van der Jagt does not consider my recommendation for catheter angiography appropriate. I do not dispute his experience with computed tomography angiography nor do I disagree with its growing use. Because its use depends on local interest and expertise, however, it can hardly be a general recommendation but may become one in the future.

Third, Dr. van der Jagt disagrees with the use of diuretics in the management of stunned myocardium and congestive heart failure because of the risk of hypovolemia. Diuretics are a mainstay in the management of congestive heart failure (3). Hypovolemia should be avoided during the period of risk for vasospasm, beginning several days after the hemorrhage, and not at the time of rupture. Given these potential risks and benefits, clinical judgment would argue for diuretic use; if hypovolemia develops, the fluid can be replaced because cardiac function usually improves before the period of vasospasm risk.

Fourth, he objects to my interpretation of the studies on the use of mineralocorticoids and hypervolemic therapy. In my discussion of hyponatremia, I stated that trials of fludrocortisone failed to show any important benefit. The study cited by Dr. van der Jagt as showing benefit failed to support its primary end point, and found only a reduced need for sodium and water replacement. This was at the expense of hyperglycemia, hypokalemia, hypoproteinemia, two gastrointestinal hemorrhages, and one case of congestive heart failure (4).

Finally, I must also differ with Dr. van der Jagt's conclusions because he presented no information on the pathophysiology of cardiac failure in subarachnoid hemorrhage nor on treating volume contraction with mineralocorticoids.

The author has not disclosed any potential conflicts of interest.

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REFERENCES

1. Claassen JA, Levine BD, Zhang R: Cerebral vasomotor reactivity before and after blood pressure reduction in hypertensive patients. *Am J Hypertens* 2009; 22:384–391
2. Manno EM, Gress DR, Schwamm LH, et al: Effects of induced hypertension on transcranial Doppler ultrasound velocities in patients after subarachnoid hemorrhage. *Stroke* 1998; 29:422–428
3. Gheorghiade M, Pang PS: Acute heart failure syndromes. *J Am Coll Cardiol* 2009; 53: 557–573
4. Katayama Y, Haraoka J, Hirabayashi H, et al: A randomized controlled trial of hydrocortisone against hyponatremia in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 2007; 38:2373–2375

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Pediatric septic shock guidelines and extracorporeal membrane oxygenation management

To the Editor:

The recently updated guidelines for the hemodynamic support of pediatric septic