Controversies in the management of aneurysmal subarachnoid hemorrhage*

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**Background:** The care of patients with aneurysmal subarachnoid hemorrhage has evolved significantly with the advent of new diagnostic and therapeutic modalities. Although it is believed that these advances have contributed to improved outcomes, considerable uncertainty persists regarding key areas of management.

**Objective:** To review selected controversies in the management of aneurysmal subarachnoid hemorrhage, with a special emphasis on endovascular vs. surgical techniques for securing aneurysms, the diagnosis and therapy of cerebral vasospasm, neuroprotection, antithrombotic and anticonvulsant agents, cerebral salt wasting, and myocardial dysfunction, and to suggest venues for further clinical investigation.

The rupture of an intracranial aneurysm may be associated with an array of severe disturbances in intracranial and systemic physiology that represent a unique challenge to the clinician. Surgical management has traditionally emphasized the prevention of renewed intracranial bleeding by clipping or wrapping the responsible aneurysm. Medical management is based on the detection and treatment of cerebral and extracerebral complications of aneurysmal subarachnoid hemorrhage (aSAH). Cerebral complications of aSAH include recurrent intracranial hemorrhage, vasospasm, cerebral infarction, hydrocephalus, cerebral edema, and intracranial hypertension; extracerebral complications include respiratory failure, derangements of water and electrolyte homeostasis, myocardial dysfunction, sepsis, and thromboembolism. As many of these complications are life-threatening but reversible, it is widely believed that patients with aSAH can benefit from management in an intensive care setting.

Recent years have seen a considerable expansion in the use of image-guided endovascular therapies for aSAH, including coiling of aneurysms and balloon angioplasty or intraarterial drug delivery for cerebral vasospasm (1–4). These advances have occurred in a general setting of increasing knowledge of aSAH epidemiology, pathophysiology, diagnosis, and prevention and of significant refinements in microsurgical technique and in medical therapy. There is a widespread perception that this broader understanding and expertise is yielding benefits in the form of improved outcome after aSAH. Indeed, a progressive increase in aSAH survival over the past three decades has been reported in several studies (5–7). However, evidence of a direct relationship between aSAH outcomes and a specific strategy or intervention is limited (2, 3, 8, 9). In several key areas of management, supporting data are lacking or equivocal in nature, generating uncertainty and controversy among clinicians.

This review focuses on controversies that are central to the acute management of aSAH. These include surgical vs. endovascular aneurysm repair, the diagnosis and management of cerebral vasospasm, neuroprotective strategies, use of antithrombotic agents (thrombolytic agents, heparin, and platelet inhibitors), prophylaxis of seizures, and the approach to cerebral salt wasting and to cardiac dysfunction after aSAH. For each controversy, a critical evaluation of the available evidence is coupled with recommendations for further clinical investigation. The review is selective, focusing on the principal debates at the expense of other equally important but arguably less controversial issues (e.g., post-aSAH hydrocephalus and ventricular drainage).

**Controversy 1: Surgical vs. Endovascular Aneurysm Repair**

Endovascular coiling emerged as an alternative to surgery in patients with intracranial aneurysms who were deemed poor surgical candidates due to significant neurologic injury, the presence of severe medical co-morbidities, or difficult surgical access to the aneurysm (1). More recent work has sought to extend the indications of endovascular coiling to other patient categories. In a small randomized trial of 109 patients with aSAH, 3- and 12-month clinical and neuropsychological outcomes were the same between the surgical group and the endovascular group (10). This was followed by...
the International Subarachnoid Aneurysm Trial (ISAT), a multiple-center, randomized study of endovascular coiling vs. surgical clipping conducted in 2,143 patients with aSAH who were deemed suitable for either therapy. Posterior circulation aneurysms accounted for only 58 of 2,143 patients (as many of these patients were not enrolled because coiling was considered the preferred modality of treatment). At 1 yr, endovascular coiling was associated with dependency or death in 23.5% of patients compared with 30.9% in the surgical group, a relative risk reduction of 22.6% (p < .001). Of concern, however, nonprocedural re-bleeding within 1 yr was higher in patients randomized to endovascular treatment (40 recurrent aSAHs, with 22 deaths) compared with patients allocated to neurosurgical treatment (33 patients with aSAHs, 30-day mortality in 21 patients) (2, 3).

Although widely regarded as a landmark trial, the ISAT has been criticized with regard to biases in patient selection, low rates of randomization of eligible patients, the definition of clinical equipoise, expertise of the neurosurgeons and interventionalists, the failure to use an operative microscope, the higher than expected morbidity in the surgically treated group, the absence of angiographic data after the initial treatment, the lack of long-term (>1 yr) follow-up, and the appropriateness of the reported outcome assessment scale (11, 12). An expert panel suggested that 1-yr outcome as reported in the ISAT is not an appropriate end point for the comparison of therapies, given that endovascular coiling is believed to carry a risk of aneurysmal re-bleeding that extends beyond 1 yr. In defense of ISAT, its authors observed that outcomes of surgically treated patients in ISAT were comparable with those in a prospective, multiple-center North American trial (13). They acknowledge that the rate of randomization of eligible patients was low (22.4%); however, they point out that this rate was comparable with other large randomized trials of vascular therapy such as the North American Symptomatic Carotid Endarterectomy Trial (14) or the Asymptomatic Carotid Atherosclerosis Study (15), studies that have significantly influenced the treatment of patients with carotid artery stenosis.

A recent report from the ISAT trial group provides further crucial information regarding long-term outcomes (3). Based on 3,258 patient years of follow-up after the first year for the endovascular group and 3,107 patient years of follow-up for the neurosurgical group, with a mean follow-up of 4 yrs, risk of recurrent aSAH was higher in patients randomized to coiling (seven patients) compared with clipping (two patients), but mortality related to recurrent aSAH was equal in both groups. A higher risk for seizures and poor cognitive outcomes was seen in the surgical group, and cumulative 7-yr mortality curves showed more deaths in the surgical group compared with coiling. The increased risk of re-bleeding in the coiling group did not seem to reverse the early benefit seen with this modality. Notwithstanding its limitations, ISAT represents level I evidence that in this patient population, endovascular coiling is associated with better 1-yr outcomes, with trends toward superior long-term outcomes, when compared with surgical clipping.

Apart from the recently published information stemming from the ISAT trial, randomized trials comparing long-term outcomes after coiling vs. clipping of ruptured aneurysms are not available. However, in an analysis of patients who underwent coiling of unruptured aneurysms and were followed for a median of 22.3 months, annual re-bleeding rates were 0.8% in the first year, 0.6% in the second year, and 2.4% in the third year after embolization, with no re-bleeding in subsequent years (16). In a study of 29 patients with giant aneurysms treated with endovascular coiling and followed up for a median of 50 months, long-term clinical outcomes were good in 79% of patients; however, the stability of the coil over time was poor, requiring repeat coiling, surgery, or parent-vessel occlusion in more than half of the aneurysms initially treated with coils (17). Finally, Friedman et al. (18) reported clinical (mean, 19.1 months) and angiographic (mean, 11.6 months) data in 83 patients with aSAHs treated with endovascular coils. Neurologic outcome was good in 77% of patients; however, 26% had a “dog-ear” remnant, 35% had a residual neck, and 3% had residual aneurysm filling. Two or more coiling procedures were required in 34% of patients.

An important question concerns the influence of surgical or endovascular treatment on the prevalence of cerebral ischemic complications. In several non-randomized comparisons of surgery and endovascular therapy of ruptured aneurysms, the rate of symptomatic vasospasm was either not significantly different (19–21) or slightly higher (22, 23) among surgically treated patients. An early nonrandomized study of 156 patients had suggested a higher rate of cerebral infarction in patients receiving endovascular vs. surgical therapy; however, the proportion of patients with poor initial neurologic presentation was higher in the endovascular group (24).

Comment. The available data indicate that in patients with good neurologic grade aSAH who undergo treatment for aneurysms in the anterior circulation, 1-yr outcomes are clearly superior after endovascular coiling when compared with surgical clipping. Follow-up of patients receiving endovascular treatment in some studies suggests that despite good clinical results, a significant proportion of patients may require repeat endovascular or surgical therapy for residual or recurrent aneurysmal lesions. However, long-term (>1 yr) clinical trends in patients enrolled in ISAT do seem to suggest that endovascular coiling is likely to retain its advantage over clipping as a superior procedure, and further follow-up of these patients is likely to add insight to this debate. Preliminary results from various studies have failed to consistently show an association between treatment modality and the rate of delayed cerebral ischemia. For posterior circulation aneurysms and for large, anatomically complex or wide-necked aneurysms, further studies are needed to define the best therapeutic approach.

Controversy 2: Diagnosis of Delayed Cerebral Ischemia

A critical concern in the management of patients with aSAH is the prediction and accurate diagnosis of delayed cerebral ischemia because timely institution of therapeutic interventions may prevent the occurrence of tissue infarction. Spasm of large arteries in the circle of Willis is a significant determinant of cerebral ischemia after aSAH and carries a 15–20% risk of stroke or death (25). Four-vessel cerebral digital subtraction angiography is the gold standard for diagnosing vasospasm, but given the inherent risks and allocation of time and resources required for this procedure, alternative and complementary diagnostic tools have been proposed (26). These include transcranial Doppler (TCD), computed tomographic angiography (CTA), magnetic resonance imaging, radionu-
TCD is an ultrasound-based monitor that uses the principle that the velocity of blood flow in an artery is proportional to the ratio of flow to the luminal surface area of that vessel (27). TCD is a noninvasive, low-risk procedure that can be readily performed at the bedside and lends itself to repeated (e.g., daily) observations, enabling trend analysis. However, there is debate about the correlation between increased TCD flow velocities and a) angiographic vasospasm and b) clinically significant or “symptomatic” vasospasm. Although mean middle cerebral artery (MCA) cerebral blood flow (CBF) velocities of >200 cm/sec accurately predict angiographic vasospasm, velocities in the 120–200 cm/sec range have a far lower predictive value (28). Moreover, it has been observed that TCD is not as reliable in estimating distal MCA vasospasm compared with the more proximal portions of the MCA (29). Studies showing a significant moment-to-moment variability during continuous measurement of CBF velocities have heightened concern about the accuracy of this technique (30).

To address these limitations, several refinements have been proposed. Investigators have suggested that incremental increases in CBF velocities over time are more helpful than velocities taken in isolation. One study indicated that an increase of >50 cm/sec in 24 hrs was closely associated with angiographic and clinical vasospasm (31). To overcome the numerical dependence of flow velocities in the measurement of CBF, Lindegaard et al. (32) developed a “hemispheric index” that normalizes flow velocity in the MCA to that in the ipsilateral extracranial internal carotid artery (an index of >3 is strongly predictive of angiographic vasospasm). Torbey et al. (33), observing that angiographic vasospasm occurs at lower TCD velocities in older patients, suggested that the accuracy of TCD can be enhanced by using an age-adjusted nomogram based on a quadratic relationship between age and CBF velocities. Some investigators have proposed that the diagnostic capability of TCD may be enhanced by transcranial color-coded sonography. Transcranial color-coded sonography is an ultrasound-based neuroimaging technique that allows real-time visualization of intracranial vascular structures in addition to measurement of CBF velocities. In a prospective study comparing transcranial color-coded sonography and conventional TCD in the prediction of angiographic spasm, sensitivity and specificity of transcranial color-coded sonography for MCA and internal carotid artery vasospasm were higher than those for TCD (34). The validity of TCD in diagnosing angiographic vasospasm was summarized in a recent systematic review (35). For the MCA, sensitivity of TCD was 67% and specificity was 99%, with a positive predictive value of 97% and negative predictive value of 78%. The accuracy of TCD was considerably less for detecting spasm in vessels other than the MCA.

Interest has developed in CTA as a diagnostic modality for detecting cerebral vasospasm. CTA may be combined with perfusion computed tomography (CT), allowing characterization of both vascular anatomy and associated cerebral perfusion abnormalities. Using CTA, a positive predictive value of 100% for angiographic vasospasm was reported in a recent small series (36). Another group reported that CTA was highly accurate in detecting severe cerebral vasospasm in proximal arterial locations but was less accurate for detecting mild and moderate spasm in distal locations (37). A third group noted an excellent concordance between the severity of vasospasm as determined by CTA and conventional angiography in both proximal and distal arterial segments (38). Of note, none of these studies included >20 patients.

Although the phenomenon of cerebral vasospasm has historically elicited much scientific interest, recent investigations have turned to the related question of brain ischemia and infarction in patients with aSAH. The predictors of CT-defined cerebral infarction after aSAH were analyzed in a recent study. Multivariate analysis revealed that both TCD and angiographic vasospasm were independently associated with cerebral infarction, however there was agreement between the two tests only in 73% of cases, and the validity of the two tests alone or in combination was disappointing (combined sensitivity, 0.72; specificity, 0.68; positive predictive value, 0.67; negative predictive value, 0.72) (39). These results are consistent with data suggesting that the pathophysiologic model of cerebral ischemia after aSAH may need to consider factors other than large artery spasm.

Magnetic resonance diffusion-weighted imaging accurately identifies brain tissue that is at high risk of infarction, whereas perfusion-weighted imaging reveals asymmetries in regional perfusion. In a study of 14 patients with aSAH, diffusion-weighted imaging abnormalities were noted in all patients with vasospasm suggested by TCD, whereas no such abnormalities were observed in patients without abnormal TCD findings (40). A study of aSAH patients using perfusion-weighted imaging revealed areas of hypoperfusion that correlated well with delayed ischemic neurologic deficits (DIND) and were larger than the areas of diffusion-weighted imaging abnormality performed at the same time. Of note, whereas all 15 patients with DIND showed alterations in perfusion-weighted imaging, TCD evidence of vasospasm was noted in only seven of these patients (41).

Radionuclide-based studies of CBF and metabolism include single-photon emission computed tomography (SPECT) and positron emission tomography. In a series of 129 patients with aSAH, Rajendran et al. (42) found that 89 had SPECT evidence of hypoperfusion, and this correlated with TCD evidence of vasospasm in only 64% of cases. In another study, Jabre et al. (43) observed that the sensitivity of SPECT for symptomatic vasospasm was inferior to TCD; however, SPECT was more specific. Studies using positron emission tomography in patients with aSAH suggest this technique can help differentiate neurologic deficits due to reversible ischemia or to irreversible infarction (44); however, the accuracy of positron emission tomography (45) in the diagnosis of vasospasm is unknown.

Monitoring of neurochemical markers of ischemia with cerebral microdialysis has been proposed as a technique for detecting vasospasm and delayed cerebral ischemia. In a study of 97 patients with aSAH, neurochemical changes indicative of ischemia were observed before the onset of symptoms in 83% of patients with DIND (46). In another report, an ischemic pattern of cerebral metabolites preceded the occurrence of DIND by a mean interval of 11 hrs (47). In a comparison with TCD and angiography, microdialysis was found to have the highest specificity and likelihood ratio, but lower sensitivity, as a diagnostic tool for DIND (48). In a study of 13 patients combining cerebral microdialysis and positron emission tomography, it was noted that transient reductions in regional CBF correlated with elevations in extracellular glutamate and glycerol, whereas the lactate/pyruvate ratio was enhanced by TCD.
vate ratio was sensitive only after longer periods of hypoperfusion (49). Although these results are encouraging, several inherent limitations of cerebral microdialysis have been recognized, including the difficulty of extrapolating from measurements made in a very restricted volume of tissue, the development of reactive gliosis around the catheter tip decreasing the accuracy of measurements, the intersubject variability in basal neurochemical values, and the tissue trauma after probe implantation (50). The use of this technique as a routine diagnostic method in patients with aSAH was not supported in a recent systematic review (51).

Several groups have assessed the role of electroencephalography in the diagnosis of cerebral ischemia after aSAH. In a study of 151 patients, Rivierez et al. (52) noted that that focal areas of slowing correlated with angiographic vasospasm in 96% of cases. Vespa et al. (53), using continuous electroencephalography, found that relative alpha variability was decreased in 19 patients with angiographically proven vasospasm; in ten of these patients, the relative alpha variability change preceded clinical symptoms by nearly 3 days. Finally, Claassen et al. (54), in comparative-analysis quantitative electroencephalographic variables in 34 patients with Hunt and Hess grade IV or V aSAH, determined that a decrease in alpha to delta ratio (ADR) was strongly associated with delayed cerebral ischemia defined by clinical or CT criteria. In this report, a 50% decrement in alpha to delta ratio has a sensitivity of 89% and a specificity of 84% for delayed cerebral ischemia.

Comment. The prediction and accurate diagnosis of cerebral ischemia is a cardinal goal in the critical care of patients with aSAH. Using serial TCD and transcranial color-coded sonography, incremental changes in flow velocities and calculation of the hemispheric index may provide valuable information with regard to underlying angiographic vasospasm, in particular, vasospasm involving the MCA. The diagnostic capability of CTA is unclear and needs investigation in a prospective study. Recent studies have shifted away from the characterization of vessel lumen diameter to the detection of changes in CBF and of cerebral ischemia. Perfusion CT, diffusion- and perfusion-weighted magnetic resonance imaging, radionuclide-based perfusion studies, cerebral microdialysis, and electroencephalography hold promise as techniques that might expand the therapeutic window for treating ischemia in patients with aSAH; however, their introduction into clinical practice needs further confirmation in clinical trials.

Controversy 3: Management of Delayed Cerebral Ischemia

The principal options for treating delayed cerebral ischemia are hemodynamic augmentation and endovascular therapy. Alternative therapies include intraaortic balloon counterpulsation (IABC), therapeutic hypothermia, and barbiturate coma.

The concept of hemodynamic augmentation—also referred to as hypertension, hypervolemia, hemodilution or triple-H therapy—in patients with aSAH evolved out of two important and related observations. The first, suggested in studies from the 1950s and 1960s, was the strong association between cardiovascular variables, such as intravascular volume status, cardiac output, and blood pressure in the days and weeks ensuing aSAH, and clinical outcomes, such as symptomatic vasospasm and long-term neurologic function. The second observation was that cerebral vasospasm is characterized by a shift in cerebrovascular resistance away from the penetrating arterioles to the major branches of the circle of Willis and their proximal branches, vessels that are incapable of effective autoregulation. As a result, CBF becomes passively dependent on systemic blood pressure, greatly increasing the risk of cerebral ischemia. Using the Poiseuille relationship, it can be predicted that efforts to increase systemic blood pressure or to decrease blood viscosity will ameliorate cerebral perfusion and reverse ischemia (55).

In an early case series of patients with DIND, Kosnik and Hunt noted significant improvements in neurologic function after initiating therapy with phenylephrine and colloid fluid expansion (56). This was followed by several other uncontrolled studies further substantiating the clinical efficacy of hemodynamic augmentation (57–60). Randomized studies evaluating the efficacy of hemodynamic augmentation therapy in aSAH are limited in number. In 30 aSAH patients who were being studied before they underwent aneurysm clipping, Rosenwasser et al. (61) noted that a strategy of blood pressure control with vasodilators in addition to volume expansion with packed red blood cell transfusion and albumin was associated with a significantly lower rate of symptomatic vasospasm and death when compared with a strategy of blood pressure control with diuretics. Lennihan et al. (62) randomly assigned 82 aSAH patients on the day after aneurysm clipping to receive albumin fluid boluses titrated to normal or high cardiac filling pressures (central venous and pulmonary artery diastolic pressures). They discovered that higher filling pressures were not associated with any significant change in CBF (as measured by xenon CT) or blood volume, nor were there any differences in the rate of symptomatic vasospasm, cerebral infarction, or 3-month Glasgow Outcome Scale. Finally, in a study of 32 aSAH patients randomized to hypertensive/hypervolemic vs. normotensive/normovolemic management protocols, Eggé et al. (63) reported no difference in vasospasm rates, CBF as measured by SPECT, or 1-yr Glasgow Outcome Scale, whereas a higher rate of complications (hemorrhage, coagulopathy, congestive heart failure) was noted in the hypertensive/hypervolemic group. When the results of these three trials were pooled in a systematic review, no significant effect of prophylactic triple-H therapy on the rate of symptomatic vasospasm, DIND, or death was noted (64). A Cochrane meta-analysis reached a similar conclusion (9).

Triple-H therapy has many inherent limitations, notably a) the association of hemodynamic augmentation with severe complications such as congestive heart failure, noncardiogenic pulmonary edema, myocardial ischemia, intracranial hemorrhage, global cerebral edema, and death; b) failure to reverse neurologic deterioration in certain patients; and c) contraindications to its use such as the presence of significant preexisting or acquired cardiopulmonary dysfunction. Alternative approaches to treating vasospasm have emerged, including a) a strategy targeting cardiac output rather than mean arterial pressure as a physiologic end point, b) the endovascular therapies, including balloon angioplasty and intraarterial vasodilator administration, and c) the use of IABC.

To augment cardiac output, the inotropic agent dobutamine was administered in combination with hypervolemic preload enhancement to 23 patients with vasospasm whose neurologic examination failed to improve after preload enhancement alone. The authors noted a 52% increase in cardiac index, and cli-
cal reversal of ischemic symptoms was evident in 18 of the 23 patients (65). In a more recent study, xenon CT was used to evaluate CBF in 16 patients with symptomatic vasospasm who underwent volume expansion combined with either mean arterial pressure augmentation with phenylephrine or cardiac output augmentation with dobutamine. The increase in mean CBF was similar in both groups (66). The mechanism whereby increases in cardiac output without changes in mean arterial pressure affect CBF is unclear, and this phenomenon may be unique to the setting of vasospasm, as a relationship between cardiac output and CBF was not observed in patients with traumatic brain injury (67). It has been postulated that the wider pulse pressure and enhanced pulsatile flow associated with the administration of inotropic agents may ameliorate flow through collateral vessels and through the microvasculature (68).

Recent years have seen a significant development in the use of endovascular therapies for patients with, or at risk of, cerebral vasospasm (69). Endovascular treatments include transluminal balloon angioplasty (TBA) and the intraarterial delivery of vasodilating compounds. These techniques are most commonly used in patients with symptomatic vasospasm that has been resistant to triple-H therapy. TBA is highly effective in relieving focal spasm involving proximal segments of the circle of Willis; however, when vasospasm is diffuse or more distal, the selective intraarterial infusion of vasodilators may be helpful. Clinical improvement after angioplasty is well documented and is generally durable, whereas the response to intraarterial vasodilators is transitory. Complications of TBA include trauma to the arterial wall leading to dissection, rupture, and thrombosis, with consequent cerebral infarction or hemorrhage; in addition, perfusion of cerebral tissue in which infarction has already occurred may induce edema and hemorrhage. The most commonly administered cerebral intraarterial vasodilator is papaverine. However, papaverine is neurotoxic and has been linked to seizures, coma, blindness, and irreversible cortical injury (70). Verapamil (71), nimodipine (72), and nicardipine (73) have been used as alternative intraarterial cerebral vasodilators; however, data on their efficacy and safety is largely anecdotal.

Although the efficacy of TBA in treating vasospasm is well documented, interest has developed on the preventive use of this technique in high-risk patients. Based on results from an animal model showing that TBA performed on the day of the hemorrhage prevented the development of angiographic spasm on day 7 after aSAH, Muizelaar et al. (74) evaluated prophylactic TBA in 13 patients with Fisher grade III aSAH who had a high probability of developing vasospasm. Of these patients, none developed DIND or more than mild TCD-defined vasospasm. At 3 months posttreatment, eight patients had a good recovery, two were moderately disabled, and three had died (one because of a vessel rupture during TBA). These authors are conducting a randomized trial (Balloon Prophylaxis of Aneurysmal Vasospasm trial; see http://www.strokecenter.org/trials for details) to determine whether the efficacy of prophylactic TBA is sufficient to justify the risks and to clarify which vessels need to be dilated prophylactically.

In recent years, several groups have reported on the use of IABC in patients with delayed cerebral ischemia (75–79). IABC has been associated with reversal of neurologic deficits and significant increases in CBF in patients who did not respond to conventional triple-H therapy (79) or who had cardiopulmonary dysfunction contraindicating it (75, 76). Of note, despite the invasive nature of this technique, the prevalence of severe adverse effects was remarkably low, and a recent series evaluated the prophylactic placement use of IABC in six patients who were considered at high risk for cerebral vasospasm (77). As with pharmacologic cardiac output augmentation, the beneficial effects of IABC are not well understood and might reflect augmentation of diastolic perfusion through the carotid and vertebral arteries and heightened pulsatility, which has been associated with improved microvascular blood flow (78).

Comment. Hypovolemia and hypotension after aSAH are strongly linked to adverse outcome and should be avoided in all patients. The existing data do not support the prophylactic use of triple-H therapy in patients with aSAH who do not have clinical evidence of vasospasm. In patients with symptomatic vasospasm, hemodynamic augmentation may reverse neurologic deterioration; however, an adequately powered randomized trial is needed to test the hypothesis that triple-H therapy has a favorable effect on neurologic outcomes or survival and is safe when compared with a strategy of normovolemia and normotension. Further study is needed to better understand the effects of increased cardiac output, as opposed to hypertensive therapy, on CBF and on the reversal of symptomatic vasospasm. At this time, TBA and intraarterial vasodilators administration are reasonable options in treating vasospasm refractory to medical management. However, the relative efficacy and harm of TBA vs. medical management needs further substantiation. This might take the form of a randomized trial comparing immediate angioplasty vs. triple-H therapy in patients who have developed symptomatic vasospasm. In patients with symptomatic vasospasm in whom triple-H therapy and endovascular options have either failed or are contraindicated, consideration should be given to IABC or to neuroprotective interventions such therapeutic hypothermia and pentobarbital coma (see below).

Controversy 4: Cerebral Protection

The development of cerebral ischemic complications in a significant proportion of patients after aSAH has prompted great interest in the possibility of preventing or limiting irreversible brain injury. The risk of a cerebral ischemic event is particularly high during specific events associated with aSAH, namely a) the initial aneurysmal rupture (risk of global cerebral ischemia secondary to increased intracranial pressure, hypertension, and hypoxemia), b) the procedure undertaken for securing the aneurysm (risk of stroke in relation to surgical clipping or endovascular coiling), and c) delayed cerebral ischemia and vasospasm. Cerebral protective strategies that have been studied in these settings include a) pharmacologic agents with cytoprotective or vasodilatory properties, b) therapeutic hypothermia, and c) hemodynamic augmentation or endovascular therapies, which are discussed above. Pharmacologic cerebral protectants that have been tested in clinical studies of aSAH include calcium channel antagonists, tirilazad mesylate, glucocorticoids, magnesium, endothelin receptor antagonists, and hydroxymethylglutaryl coenzyme A reductase inhibitors.

A meta-analysis of trials using calcium channel antagonists after aSAH was reported by the Cochrane group (8). Of 11
studies (2,804 patients), eight involved nimodipine (1,574 patients), two involved nicardipine (954 patients), and one involved AT877 (276 patients). When compared with placebo, calcium channel antagonists were associated with a significantly reduced risk of poor outcome, with a relative risk (RR) of 0.82 (95% confidence interval [CI], 0.72–0.93), an absolute risk reduction of 5.1%, and numbers needed to treat of 20. The results were most robust for oral nimodipine (RR of poor outcome, 0.70; 95% CI, 0.58–0.84). The RR of death in patients treated with calcium antagonists was 0.94 (95% CI, 0.80–1.10), that of ischemic neurologic deficits was 0.67 (95% CI, 0.59–0.76), and that of CT or MR documented cerebral infarction was 0.80 (95% CI, 0.71–0.89). Of note, the prevalence of angiographic vasospasm was not influenced by treatment allocation, suggesting that the benefit of nimodipine was linked to its cytoprotective rather than its cerebral vasodilatory properties. The effects of nimodipine on aSAH outcome are fairly consistent across published trials. However, it is plausible that the results were confounded because nimodipine-treated patients may have received greater amounts of intravenous fluids to counteract the effect of the drug on systemic blood pressure, surreptitiously exposing them to a more aggressive regimen of triple-H therapy.

Tirilazad mesylate, a non–glucocorticoid 21-aminosteroid that inhibits lipid peroxidation, has been evaluated in four randomized, placebo-controlled trials of patients with aSAH. The first trial, conducted in Europe and Australasia, demonstrated an improvement in symptomatic (but not angiographic) vasospasm, 3-month survival, and Glasgow Outcome Scale in patients receiving 6 mg/kg tirilazad for 10 days (80). These results were not reproduced in a second study undertaken in North America in which tirilazad administration had no significant effect on symptomatic vasospasm, 3-month mortality, or Glasgow Outcome Scale (13). The divergence in these results was believed to reflect differences in management protocols, including the widespread use of anticonvulsants (e.g., phenytoin) in the American trial, which may have diminished the bioavailability of tirilazad. Further analysis of these two studies indicated that any detected improvement in outcome seemed limited to men. This led to two other studies conducted in women only. The first of these demonstrated a rate of symptomatic vasospasm that was significantly lower in women who received tirilazad, 15 mg/kg, without any effect on mortality (81). In the other trial, the rate of symptomatic vasospasm was not affected by tirilazad therapy; however, mortality was significantly lower in treated patients with Hunt and Hess grades IV and V (82). When results of the four trials were combined in a meta-analysis, it was concluded that overall mortality was decreased in patients who received tirilazad, with an effect that seemed most pronounced in patients with poor neurologic grade (83).

Animal studies have shown that glucocorticoids may effectively prevent delayed cerebral ischemia after aSAH (84–86). The potential benefit of glucocorticoids in humans was suggested in a nonrandomized comparative study of 21 patients by Chyatte et al. in which patients receiving high-dose methylprednisolone had a significantly lower rate of DIND (87). However, these results have not been reproduced in any other clinical trial.

The neuroprotective effects of magnesium have been reported in experimental models of traumatic brain injury, cerebral ischemia, and aSAH. Magnesium sulfate therapy is both safe and effective in preventing neurologic complications in obstetric patients with preeclampsia. A randomized trial of 40 patients demonstrated that high-dose intravenous magnesium sulfate is safe in patients with aSAH (88). In a more recent randomized, placebo-controlled trial of 283 patients, an infusion of magnesium started within 4 days of aSAH and continued up to 14 days postaneurysm occlusion was associated with a 34% RR reduction for the primary outcome of delayed cerebral ischemia, however, this result did not achieve statistical significance (89). Of note, significantly more patients treated with magnesium had excellent outcome (defined as a Rankin score of 0) at 3 months (RR, 0.91; 95% CI, 0.84–0.98).

Following experimental evidence implicating the vasoconstrictor endothelin peptides and their receptors in the pathophysiology of cerebral vasospasm, a randomized, placebo-controlled trial of an endothelin receptor antagonist, TAK-044, was conducted in 412 patients with aSAH (90). A nonsignificant decrease in the rate of delayed cerebral ischemia was noted in the treated group. A more recent observational study suggested that increased CSF levels of endothelin did not correlate with vasospasm but were a more general marker of neuronal damage (91).

Initially developed as cholesterol-lowering agents, the hydroxymethylglutaryl coenzyme A reductase inhibitors or statins are capable of modulating endothelial function by reducing vascular inflammation, inhibiting vascular smooth muscle cell proliferation, decreasing platelet aggregation, and promoting NO-mediated cerebral vasodilation (92). In a murine model of aSAH, pretreatment with simvastatin was associated with a reduction in vasospasm and with increased expression of NO synthetase (93). A retrospective review of 60 aSAH patients suggested that patients who were taking statins, when compared with a control group who were not, had a significantly lower rate of DIND and cerebral infarctions of any type, but no impact on mortality or global outcome (modified Rankin scale) was detected (94). Another retrospective study showed an increased risk of vasospasm associated with use of statins (95). The effects of statins have been further explored in two recent randomized, placebo-controlled trials. In the first, therapy with simvastatin (19 patients) initiated within 48 hrs of aSAH was linked to reduced serum levels of brain injury biomarkers and a decrease in the prevalence of DIND confirmed by TCD or angiography when compared with placebo (20 patients) (96). In the second, treatment with pravastatin started within 72 hrs of aSAH ameliorated cerebral vasospasm, improved cerebral autoregulation, and reduced vasospasm-related DIND by 83% and mortality by 75% (97). Additional agents that have generated interest as cerebral protectants after aSAH include erythropoietin (98), nitric oxide donors (99), and potassium channel activators (100); to our knowledge, there are no published clinical trials of these compounds in patients with aSAH.

The neuroprotective effect of hypothermia is supported by a large body of experimental and clinical evidence. This effect may result from decreased excitatory amino acid release and free-radical production, reduced intracellular calcium accumulation, stabilization of the blood–brain barrier, and decreased cerebral edema (101). Hypothermia also has serious deleterious consequences, including cardiovascular depression, immune suppression, coagulopathy, and electrolyte abnormality. The use of moderate hypothermia (28–32°C) to protect the brain during cerebral aneurysm surgery
was first described in the 1950s; however, interest in this technique declined in light of very poor clinical outcomes. More recently, several studies have evaluated mild hypothermia (38–35°C) as a protective strategy during aneurysm surgery. In an early randomized trial, 114 patients with ruptured and unruptured intracranial aneurysms who received mild intraoperative hypothermia had a lower rate of neurologic deterioration at 24 and 72 hrs after surgery, a greater frequency of discharge to home, and a greater rate of good long-term outcomes (102). However, a subsequent multiple-center study of 1,001 patients with aSAH who had World Federation of Neurologic Surgeons scores of I, II, or III failed to detect any beneficial effect of intraoperative cooling on 3-month neurologic outcomes or on any perioperative outcomes (103). Moving beyond the perioperative setting, small-scale investigations indicate that mild hypothermia may be helpful in cases in which vasospasm is refractory to conventional treatment (104, 105). The effects of hypothermia on the relationship between CBF and cerebral metabolic oxygen demand in patients with aSAH are poorly understood. Hypothermia was associated with evidence of brain ischemia in one study (106), but another study did not confirm this finding (107).

Comment. Although considerable research has focused on the possibility of neuroprotection in patients with aSAH, only oral nimodipine has been clearly associated with improved outcome. Meta-analysis suggests a survival benefit with high-dose tirilazad mesylate in patients with poor neurologic grade. Preliminary results with magnesium and statins need substantiation in larger randomized placebo-controlled trials. Finally, no benefit was seen for intraoperative mild hypothermia in aSAH patients with good neurologic grade; however, further studies are needed to explore other methodologies and applications of therapeutic hypothermia, for example, more prolonged cooling protocols and its effects on patients with poor neurologic grade or refractory vasospasm.

Controversy 5: Antithrombotic Agents

Although the conventional view of aneurysmal rupture emphasizes the pathophysiologic role of hemorrhage and the need to prevent recurrent intracranial bleeding, data have accrued to suggest that clot formation, both in the intravascular and extravascular compartments, is a key determinant of cerebral injury after aSAH. The presence of a thick clot in the subarachnoid space is consistently reported as one of the strongest predictors of vasospasm after aSAH (108). The poor neuroanatomic correlation between radiologically defined vasospasm and cerebral infarction suggests alternate or complementary hypotheses of DIND, among which intravascular thrombosis is a postulated mechanism.

Thrombolytics. Experimental and clinical evidence indicate that a subarachnoid clot may be removed with the help of thrombolytic agents. Cisternal irritation with recombinant tissue plasminogen activator was found to be safe (109), and intrathecal urokinase infusion has been associated with a decreased rate of vasospasm and permanent neurologic deficits (110). A systematic review of nine studies (only one of which was randomized) noted that cisternal thrombolysis was associated with an absolute risk reduction of 14.4% for DIND (p < .001), 9.5% for poor Glasgow Outcome Scale scores (p < .01), and 4.5% for death (p < .05) (111). Treatment effects did not significantly differ among the studies on the basis of the type of thrombolytic agent used (recombinant tissue plasminogen activator vs. urokinase) or the method of administration (intraoperative vs. postoperative). Studies that enrolled only patients at high risk for vasospasm seemed to demonstrate greater treatment effects (109). In an intriguing recent trial, Hamada et al. (110) randomized 110 patients to endovascular coating with or without infusion of urokinase into the subarachnoid space via a microcatheter inserted in the lumbar space. The rate of symptomatic vasospasm was 8.8% in the urokinase-treated group vs. 30.2% in the untreated group (p = .012).

Anticoagulants. Heparin, an antithrombin III agonist, has biological properties that include anticoagulation, modulation of inflammation, neuroprotection, and antiproliferative effects. In an animal model of aSAH, administration of heparin has been associated with smooth muscle relaxation, increased CBF, and a reduction in proliferative angiopathy (112). A recent randomized, placebo-controlled trial that enrolled 120 patients indicated that low-molecular-weight heparin significantly reduced the rate of vasospasm-related cerebral infarction (3.5% of enoxaparin-treated patients and 28.3% of placebo-treated patients, p < .001), without any increase in the rate of intracranial bleeding (113).

Antithrombotic Agents. Platelet aggregation and release of thromboxanes have been demonstrated after aSAH, and these changes are more pronounced in patients who develop DIND (115). These data, in combination with the identification of microembolic signals by TCD in patients with aSAH (116), have prompted several small clinical trials examining the therapeutic potential of antithrombolytic agents. Meta-analysis of these results indicated that in patients treated with aspirin or antithrombolytic agents, the RR of DIND was significantly reduced (RR, 0.65; 95% CI, 0.47–0.89), without a concomitant increase in the risk of intracranial hemorrhage. There was also a trend toward a reduced risk of poor outcome in patients receiving antithrombotic agents (RR, 0.87; 95% CI, 0.65–1.17) (117).

Comment. Preliminary data indicate that placement of thrombolytic agents in the subarachnoid space may improve outcome after aSAH, but adequately powered, randomized, controlled studies are needed to substantiate these findings. The two randomized trials assessing the association between low-molecular-weight heparin and aSAH outcome are contradictory. Regarding antithrombotic therapy, although a beneficial effect is suggested, the evidence does not support the routine use of these agents in aSAH at the present time. Randomized trials with greater power would be needed to clarify the role of these therapies.

Controversy 6: Seizure Prophylaxis

Aneurysmal SAH has been linked to an increased risk of seizures, yet the role of seizure prophylaxis is controversial. In a retrospective analysis of 217 surgically treated patients with aSAH over a 2-yr period, 20% experienced one or more seizures, with more than half of these occurring in the perioperative period; of note, the occurrence of perioperative seizures did not predict epilepsy in this study (118). Another investigation revealed that 24 of 121 aSAH patients with
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ISAT, International Subarachnoid Aneurysm Trial; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; PPV, positive predictive value; MCA, middle cerebral artery; CT, computerized tomography; triple-H, hypertension/hypervolemia/hemodilution therapy; DIND, delayed ischemic neurologic deficits.  
<sup>a</sup>Intervention decreased DIND and improved neurologic outcomes but not mortality rates; <sup>b</sup>intervention decreased DIND but did not improve neurologic outcome.
clipped aneurysms had at least one seizure and that ten patients had two or more seizures after hospital discharge (119). Seizure risk has been linked to the thickness of the aSAH clot (120), to location of the aneurysm on the MCA (121), to the presence of a subdural hematoma, and to cerebral infarction (122). In one study, variables associated with the development of epilepsy were, in order of importance, a history of hypertension, cerebral infarction, and duration of impaired consciousness after the seizure (123).

Although empirical prophylaxis of seizures after aSAH might seem reasonable, the benefit of preventive anticonvulsant administration has yet to be demonstrated in a prospective randomized trial. A cohort study of 123 aSAH patients followed up at 4 to 7 yrs found no evidence for the effectiveness of prophylactic anticonvulsants (119). A recent retrospective evaluation of 527 patients with aSAH indicated a strong association between phenytoin exposure in the setting and functional and cognitive disability (122). In a study of 101 patients with aSAH who had unexplained coma or neurologic deterioration, eight (all of whom were receiving prophylactic anticonvulsants) were found to be in nonconvulsive status epilepticus. Despite successful termination of seizures in five of eight patients, all eight patients eventually died after a period of prolonged coma (125).

Comment. The available evidence suggests that prophylaxis of seizures may be useful in aSAH patients with stroke or other distinct focal pathology. Indiscriminate administration of anticonvulsants to patients with aSAH has been linked with unfavorable functional and cognitive outcomes. A randomized, placebo-controlled trial is warranted to assess the effect of anticonvulsant prophylaxis on the prevalence of early and late seizures in patients with aSAH. Such a trial would ideally incorporate predefined stratification based on focal parenchymal pathology, aneurysm location, aSAH grade, age, and history of hypertension.

Controversy 7: Cerebral Salt Wasting Syndrome

Hyponatremia occurs in up to 30% of patients after aSAH and has been associated with several disorders, most notably cerebral salt wasting (CSW) syndrome and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion (126). CSW involves renal salt loss leading to a negative sodium balance, hyponatremia, and intravascular volume depletion, whereas SIADH is characterized by an inability to appropriately excrete free water, resulting in a euolemic or hypervolemic state. Because therapeutic interventions for CSW and SIADH are radically opposed, clinical differentiation between the two entities is essential. It has been suggested that hypouricemia and an increased fractional excretion of uric acid are more consistent with a diagnosis of CSW (127). However, physiologic indicators of intravascular volume are generally viewed as the most reliable way to distinguish between these conditions (128).

The pathogenesis of CSW is poorly understood (129). The main pathologic processes that have been linked with this derangement are a) decreased sympathetic input to the kidney leading to a deficient regulation of proximal tubule sodium resorption and to an inadequate rise in renin and aldosterone in response to hypovolemia, and b) increased levels of circulating natriuretic peptides. The natriuretic peptides are produced in the heart, brain, and endothelium and promote vasodilation, sodium excretion, and diuresis. Several groups have demonstrated an association between aSAH, hyponatremia, volume depletion, and increased blood natriuretic peptide levels, in particular B-type natriuretic peptide (BNP) (130–133). Others have observed a link between increased levels of BNP and the development of cerebral vasospasm (134, 135). Recent work suggests that cardiac dysfunction (136) and triple-H therapy (137) are factors that might stimulate BNP release after aSAH. When these results are considered collectively, it remains unclear whether the relationship between increased BNP levels and the development of CSW or vasospasm is causative or merely circumstantial.

Therapeutic options for CSW are limited. It has been argued that increasing salt intake during CSW only further enhances sodium excretion. The mineralocorticoid fludrocortisone, which acts directly on the kidney tubules to enhance sodium resorption, has been shown to prevent intravascular volume depletion in patients with aSAH (138). In a related study, Hasan et al. (139) found that 0.2 mg of fludrocortisone given intravenously or orally twice a day in 46 patients with aSAH significantly reduced the frequency of a negative sodium balance and led to smaller decreases in plasma volume and, consequently, less risk of cerebral ischemia. More recently, Moro et al. (140) demonstrated that hydrocortisone attenuated excessive natriuresis in the setting of aSAH with development of hyponatremia in 43% of treated patients vs. 0% in the untreated group.

Comment. Although the pathogenesis of CSW needs clarification, its consequences of hyponatremia and intravascular volume depletion can be deleterious in the setting of aSAH. Preliminary data support the careful use of salt-conserving medications such as fludrocortisone or hydrocortisone in patients with aSAH.

Controversy 8: Management of Cardiac Dysfunction After aSAH

A spectrum of cardiac sequelae have been described in patients after aSAH,
Many aspects of care in patients with aneurysmal subarachnoid hemorrhage remain highly controversial and warrant further resolution with hypothesis-driven clinical or translational research.

including electrocardiographic changes, reversible cardiomyopathy (stunned myocardium), and release of cardiac-specific markers (141, 142). Aneurysmal SAH has also been linked to hypoxic respiratory failure, which may take the form of congestive heart failure, neurogenic pulmonary edema, or acute lung injury (143). Extracerebral organ dysfunction in aSAH has been associated with a greater risk of poor neurologic outcome and death (144). Although there is general agreement regarding the importance of cardiac complications after aSAH, many aspects of their pathophysiology, diagnosis, and treatment remain undefined.

A widely held view postulates a sequence of events involving acute cerebral injury, derangements in autonomic function, release of endogenous catecholamines, and activation of adrenergic receptors, culminating in target organ damage (145). The severity of neurologic compromise as measured by the Hunt and Hess grade is highly predictive of myocardial necrosis after aSAH, supporting the hypothesis that cardiac injury after aSAH is a neurally mediated process (146). Significantly, impaired left ventricular function and low cardiac output elevate the risk of cerebral ischemia and have been identified as independent predictors of symptomatic vasospasm (147).

Regarding diagnosis, several investigators have evaluated the significance of cardiac-specific markers such as cardiac troponin I in patients after aSAH. In a 7-day observation of 39 patients with aSAH, measurements of cardiac troponin I revealed a higher incidence of myocardial injury (21%) than predicted by CK-MB (13%), and elevations of cardiac troponin I were associated with a higher incidence of congestive heart failure (148). Another group found that the sensitivity of cardiac troponin I in the detection of echocardiographically demonstrated left ventricular dysfunction was significantly higher than CK-MB (100% compared with 29%) (149). In a third study, mild elevations in cardiac troponin I (<2.8 ng/mL) associated with depressed left ventricular function in the absence of significant electrocardiographic changes were proposed as characteristics that might aid in the differentiation of neurogenic stunned myocardium from myocardial infarction (150). Recently, there has been increasing recognition of the importance of BNP as a diagnostic and prognostic marker in patients with cardiac dysfunction. Increased serum levels of BNP are highly predictive of the short- and long-term risk of cardiac death across the entire spectrum of acute coronary syndromes and in patients with decompensated congestive heart failure (151). A correlation between increased levels of BNP and myocardial necrosis, pulmonary edema, and both systolic and diastolic left ventricular dysfunction after aSAH was demonstrated in a recent study (136). However, there is debate as to the source—cardiac or cerebral—of BNP in patients with aSAH (152). A recent study evaluated serum and CSF levels of atrial natriuretic peptide, BNP, and troponin T in patients with aSAH. Of note, increased levels of atrial natriuretic peptide and BNP were detected in the serum but not CSF, leading to the conclusion that these peptides were exclusively of cardiac origin (153). This contradicted previous results in which a selective increase of BNP, but not atrial natriuretic peptide, suggested that the hormone was secreted in the brain (134).

The therapeutic approach to patients with cardiac dysfunction acquired in the setting of aSAH is a matter of further controversy. In light of the postulated role of catecholamines in the development of this disorder, early randomized trials evaluated the effect of pharmacologic α and β adrenergic receptor blockade (e.g., phentolamine and propanolol) in patients with aSAH, noting a favorable effect on the rate of myocardial necrosis, survival, and neurologic outcome (154, 155). These data are at variance with more recent studies that suggest that neurogenically induced ventricular dysfunction and its associated low cardiac output/pulmonary edema may exacerbate cerebral ischemia and should be treated with the use of inotropic agents such as dobutamine (65, 147, 156). Finally, patients presenting with severe neurocardiomyopathy or cardiogenic shock and vasospasm may benefit from temporary support with IABC (108, 110).

Comment. Cardiac dysfunction complicating aSAH is common and has been linked to poor neurologic outcomes. These complications may contraindicate, or be exacerbated by, brain-targeted therapies such as hemodynamic augmentation. Studies are needed to elucidate risk factors, pathogeneses, natural history, diagnostic markers, management strategies, and prognostic impact of these complications.

CONCLUSIONS

This review highlights some of the controversies that exist in the clinical management of patients with aSAH, a summary of which is presented in Table 1, along with a classification of levels of evidence (157, 158) in Table 2.

It is anticipated that these areas of uncertainty will generate hypothesis-driven experimental and translational research, prospective observational studies, and clinical trials, with the goal of improving outcomes in these complex and challenging patients.

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