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Management of cerebral vasospasm

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Abstract Cerebral vasospasm is delayed narrowing of the large arteries of the circle of Willis occurring 4 to 14 days after aneurysmal subarachnoid hemorrhage (SAH). It is but one cause of delayed deterioration after SAH but, in general, is the most important potentially treatable cause of morbidity and mortality after SAH. Development of vasospasm is best predicted by the volume, location, persistence and density of subarachnoid clot early after SAH. Diagnosis is made by catheter angiography or, with less accuracy, by computed tomographic angiography, transcranial Doppler ultrasound or other methods. Treatment remains problematic because it is expensive, time-consuming, associated with substantial risk and largely ineffective. Treatment includes optimization of factors that affect cerebral blood flow and metabolism, systemic administration of nimodipine, hemodynamic therapy and pharmacologic and mechanical angioplasty.

Keywords Cerebral aneurysm · Cerebral infarction · Cerebral ischemia · Subarachnoid hemorrhage · Vasospasm

Introduction

Ecker and Riemenschneider are usually credited with first describing cerebral vasospasm, on angiograms performed on patients within 26 days of aneurysm rupture [25]. Vasospasm has continued to be a disappointingly frequent and important cause of morbidity and mortality since this description 50 years ago. Understanding of the pathogenesis has been impeded by lack of appropriate animal models and relatively limited research interest in the disease.

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Treatment, at present, consists of neurocritical care measures to prevent or minimize secondary brain injury, calcium channel blockers, hemodynamic management and endovascular therapies. These maneuvers are, however, expensive, time-consuming and only partly effective.

Cerebral vasospasm is a reversible narrowing of the intradural subarachnoid arteries that begins approximately 3 days after subarachnoid hemorrhage (SAH), becomes maximal at 7 to 8 days and then resolves by 14 days. The radiologic detection of vasospasm by digital subtraction angiography is called angiographic vasospasm, and the neurological deficits attributable to it, if present, are termed symptomatic or clinical vasospasm or delayed cerebral ischemia or delayed ischemic neurological deficit.

Epidemiology

Vasospasm is a consequence of SAH and, thus, can occur after any condition that deposits blood in the subarachnoid space. It follows that, since the large, conducting arteries of and in the vicinity of the circle of Willis harbor most intracranial aneurysms and that, since aneurysm rupture tends to produce the thickest, most persistent SAH, it is these arteries that are most often affected clinically by vasospasm [68]. It is likely that any subarachnoid artery that is covered in blood in a high enough dose for long enough will develop vasospasm. Other diseases associated with SAH and vasospasm include hemorrhage from brain vascular malformations, trauma and SAH after surgery in the basal cisterns [68]. Angiographic arterial narrowing has been reported in tuberculous and purulent meningitis, ophthalmoplegic migraine, hypertensive encephalopathy, arteriolar embolization or removal of an embolus from the middle cerebral artery, myelography, electroconvulsive therapy, eclampsia, and in association with unruptured and sometimes unoperated-on aneurysms. In many of these reported cases, the presence of SAH was not definitely excluded. In others where it was, it is likely that the arterial narrowing had a different etiology, pathology and pathogenesis from that occurring after SAH [68].

The time course of vasospasm remains as described by neurosurgeons 35 years ago. It begins to appear 3–4 days, reaches its maximum incidence and severity between 6–8 days and usually resolves 12–14 days after a single SAH [120]. Angiographic vasospasm develops to some extent in almost every patient with substantial SAH, although the traditional teaching that approximately two-thirds of patients develop angiographic vasospasm remains true. Severe angiographic vasospasm (> 50% reduction in arterial diameter) was reported in 23% to 30% of the placebo-treated patients in three clinical trials of aneurysmal SAH [34, 40, 53]. A review of the world literature published after 1960 that provided data regarding angiographic vasospasm found that, when angiography was done during the second week after SAH, 67% of 2,738 patients had vasospasm [21].

Vasospasm is chiefly a hemodynamic problem. Superimposed thromboembolic mechanisms have been postulated to contribute, but their importance remains speculative [106]. Whether or not a patient with angiographic vasospasm develops symptomatic vasospasm depends on the length and severity of the arterial narrowing, other factors that influence cerebral blood flow (CBF), such as blood pressure, intracranial pressure, blood volume, cardiac output, viscosity, collateral and anastomotic blood supply and brain metabolic demand that is influenced by temperature, seizures and drugs. Symptoms and signs probably do not develop unless there is >50% angiographic diameter reduction. The peak day of onset of symptomatic vasospasm is 8 days after SAH or 1 day after the peak of angiographic vasospasm. The incidence of symptomatic vasospasm has remained remarkably consistent over time. The cooperative timing study found that 28% of 3,521 patients treated between 1980 and 1983 developed delayed cerebral ischemia [51]. These patients, for the most part, did not receive nimodipine or hemodynamic therapy. In four tirilazad studies, 30% of 3,567 patients developed clinical vasospasm [39, 40, 58, 59]. All these patients received nimodipine prophylactically, and 62% had some form of prophylactic hemodynamic therapy.

Pathology and pathophysiology

Pathology

The normal red appearance of the cerebral arteries is diminished during vasospasm so that the arteries look grossly whiter, probably secondary to the contraction of the arteries that thickens the relatively avascular arterial wall, which, when devoid of blood, appears whitish. Microscopically, the principal feature of the vasospastic artery is constriction of the smooth muscle cells, which produces a contracted artery. There may be platelet aggregates and/or microthrombi intraluminally, and arterial thrombosis or distal embolization probably are possible, raising the question as to whether antiplatelet agents might be of benefit in this condition [46, 106]. Over the ensuing weeks after SAH there may be some degree of arterial fibrosis and prolif-

eration of myointimal cells and extracellular matrix in the tunica intima, but these changes occur late and progress as angiographic vasospasm reverses [31]. The main arteries affected by vasospasm are the large intradural arteries of the circle of Willis. There is no evidence that veins are affected. Vasospasm of small, intraparenchymal arteries has been postulated to occur after SAH and to be a cause of the delayed neurological deterioration that is sometimes seen in the absence of large artery vasospasm, although evidence for this is based mainly on controversial positron emission tomography and CBF studies [77, 124].

In general, SAH is associated with a global reduction in CBF and cerebral metabolic rate for oxygen, and these reductions are more severe with worsening clinical grade. Vasospasm adds a second, additional reduction in CBF in the territories of the vasospastic arteries. The decreases may be regional and/or global, depending on the distribution of vasospasm [68, 118, 122]. There tends to be some impairment of autoregulation of CBF after SAH, even in good-grade patients. This is not lost in an all-or-none fashion but tends to be progressively impaired with worsening clinical grade and during the time of peak angiographic vasospasm. [109, 118]. The response of CBF to changes in arterial carbon dioxide is usually preserved but may be impaired in patients with severe vasospasm [118].

Pathogenesis

Vasospasm is caused by subarachnoid blood clot. Changes in intracranial pressure and the tear in the aneurysm do not contribute to vasospasm. The most powerful predictor of vasospasm is the volume, density and prolonged presence of subarachnoid blood, usually as observed on computed tomography (CT) scan, around the arteries that develop vasospasm [36, 82, 89, 105]. Animal studies show that vasospasm identical to that occurring in humans can be reproduced by placing autologous blood clot next to the cerebral arteries or by injection of adequate amounts of blood into the cerebrospinal fluid (CSF). Arterial rupture and increased intracranial pressure are not required [28, 65, 68]. Patients with SAH deteriorate in a delayed fashion due to many reasons, some unidentified, and these secondary phenomena, particularly increased intracranial pressure, might contribute in some way, independent of large-artery vasospasm. Fractionation of blood into serum, erythrocytes, plasma, platelet and leukocyte fractions has demonstrated repeatedly that erythrocytes are necessary for vasospasm to develop and that hemoglobin within the erythrocytes is an important spasmogen [70, 84]. Other components of the erythrocyte and the blood also may contribute. Vasospastic arteries become narrowed predominantly by sustained smooth muscle contraction, as demonstrated by the ability of vasodilators to reverse vasospasm, particularly early after SAH [119]. The degree of pharmacological reversibility decreases with time, so other processes must be important [119]. Stimuli for contraction may include free radical reactions and their by-products, alteration in the balance between vasodilator and

vasoconstrictor substances normally produced in the arterial wall, such as prostacyclin, nitric oxide, endothelins and eicosanoids, injury to perivascular nerves and detrimental effects of the inflammatory reaction induced by SAH [24].

Clinical diagnosis

Delayed ischemic neurological deficits due to vasospasm are rare within 3 days of SAH. The peak day of onset is 7 to 8 days post-SAH. Fewer than 4% of deficits occur on or after day 13 [21]. Acute arterial constriction is well described following injection of blood into the subarachnoid space of animals, although it traditionally has been thought not to occur in humans [10]. On the other hand, physicians assessing the 3,478 patients who were entered into randomized trials of tirilazad between 1991 and 1997 diagnosed acute vasospasm on angiography within 48 h of SAH in 339 (10%) cases [8]. Patients with acute vasospasm were significantly more likely than patients without acute spasm to be of poor neurological grade and to have intracerebral hematoma, larger aneurysm, thick SAH on cranial computed tomography, intracerebral hemorrhage and intraventricular hemorrhage. Acute vasospasm was not associated with delayed cerebral vasospasm, although it was a significant predictor of cerebral infarction, neurological worsening and unfavorable outcome.

The onset of symptomatic vasospasm can be sudden or insidious [35]. Symptoms such as increasing headache, neck stiffness and rising temperature are too non-specific to be relied upon. The usual scenario is progressive confusion, delirium and decline in consciousness with or without focal neurological deficit. Careful and frequent neurological assessment remains an important component of the diagnosis of vasospasm, due to the imprecise nature of readily repeatable ancillary diagnostic tests such as transcranial Doppler ultrasound (TCD). There is some controversy as to whether patients who need to be sedated should be allowed to waken at intervals in order for their neurological condition to be assessed. Some investigators believe this may lead to detrimental increases in intracranial pressure. Daily interruption of sedative infusions reduced intensive care length of stay and complications of critical illness among patients in a medical intensive care unit [96]. The author tends to favor this practice, while recognizing that data on neurological patients are unavailable.

The differential diagnosis of delayed neurological deterioration after SAH is broad, and several causes may coexist (Table 1) [83]. If there is a change in the results of the neurological examination after SAH, particularly during the time of risk of vasospasm, the patient usually will require detailed neurological and general examination and repeat cranial CT scan, and to have blood and radiological investigations to detect other causes of deterioration. A diagnostic test for vasospasm will usually be required, such as TCD, CT angiography (CTA) and/or perfusion, magnetic resonance angiography (MRA), and, sometimes, catheter angiography may be indicated.

Table 1 Differential diagnosis of delayed neurological deterioration after SAH (adapted from Peerless, 1979 [83])

Category	Causes
Metabolic/systemic	
Electrolytes	Hyponatremia, hypernatremia
Blood gases	Hypoxia, hypercarbia
Circulation	Hypotension, hypovolemia, hemodilution, low cardiac output, arrhythmia
Infection	Pneumonia, other systemic infections
Iatrogenic	Medication reaction, renal failure
Other	Fever
Neurologic	Aneurysm re-bleeding, epidural hemorrhage, subdural hemorrhage, intraventricular hemorrhage, hydrocephalus, postoperative hemorrhagic complications, edema or infarction, meningitis, ventriculitis, seizures, post-ictal state

Analysis of the 3,567 patients included in the tirilazad studies found that symptomatic vasospasm was more likely in the presence of the following factors: age 40–59 years, history of hypertension, worse neurological grade, thicker clot on admission cranial CT, larger aneurysm size, intraventricular hemorrhage, prophylactic use of induced hypertension and not being in the first European tirilazad study [69]. The most powerful predictor by far was the presence and thickness of subarachnoid clot on the initial CT scan. Another study found that whether or not vasospasm developed depended on the location, volume, density and duration of presence of subarachnoid blood seen on CT scan within the first days of SAH [89]. The most commonly used method to assess the amount of subarachnoid blood is the system reported by Fisher and colleagues (Fig. 1, Table 2) [36]. It is important to recognize that the scale is useful but that the original millimeter measurements reported are not true distances and the scale is at best qualitative at present. The author hypothesizes that vasospasm develops, in part, like a pharmacologic response to spasmogens in subarachnoid blood clot and, thus, will be more severe as there is more clot present for longer times. Other factors noted above may aggravate vasospasm by reducing underlying cerebrovascular reserve or for other unknown reasons. Gender and cigarette smoking have less consistently been shown to predict vasospasm.

Whether vasospasm differs among patients who undergo surgical clipping as opposed to endovascular treatment of the ruptured aneurysm has been addressed. Data from the International Subarachnoid Aneurysm Trial have not been published but could provide a less biased assessment than other retrospective reviews [45, 73, 88]. The two largest reported comparisons included one review of 415 patients of whom 76 underwent treatment with coils and 339 were operated upon [88]. The authors did not adjust for variations between the groups in factors that predict the devel-

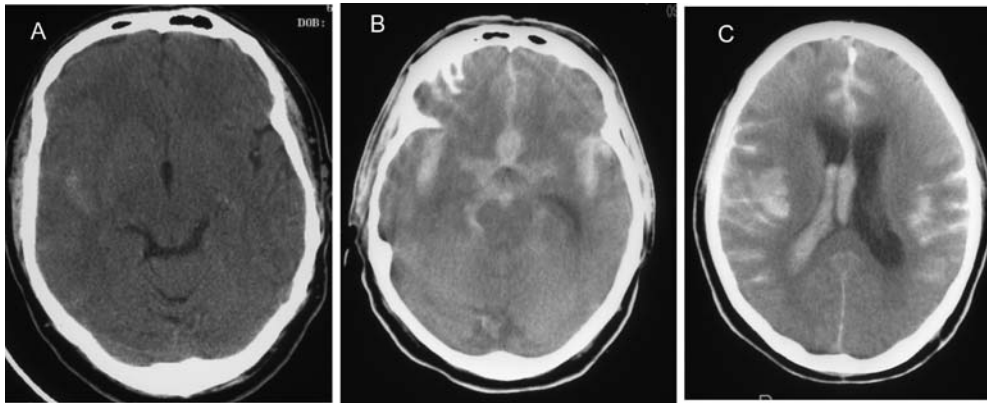


Fig. 1 **a** CT scan showing a focal, thin SAH in the right Sylvian fissure that would be termed a Fisher grade 2 SAH. The patient had a distal middle cerebral artery aneurysm and would be at low risk for vasospasm. **b** CT scan of a diffuse, thick, Fisher grade 3 SAH

secondary to a pericallosal artery aneurysm in a patient who would be at high risk for developing vasospasm. **c** CT scan of the same patient showing intraventricular hemorrhage, which would suggest the patient could be classified as having a Fisher 3+4 hemorrhage

opment of vasospasm, particularly the amount of SAH on admission CT scan. In good-grade patients, vasospasm was more common in patients undergoing surgery. Another review of 515 SAH patients (413 underwent clipping and 79 were treated with coils) that did appear to have a balance in other prognostic factors for vasospasm found symptomatic vasospasm in 28% of clipped and 33% of coiled patients (not statistically significantly different) [45].

Investigations

Catheter-based digital subtraction cerebral angiography remains the gold standard for the diagnosis of vasospasm, although it is being supplanted by less invasive methods such as CTA and MRA. The cerebral arteries may be narrowed by cerebral vasospasm or for other reasons, such as pre-existing arterial hypoplasia, atherosclerosis, stretching and displacement of arteries due to mass effect from

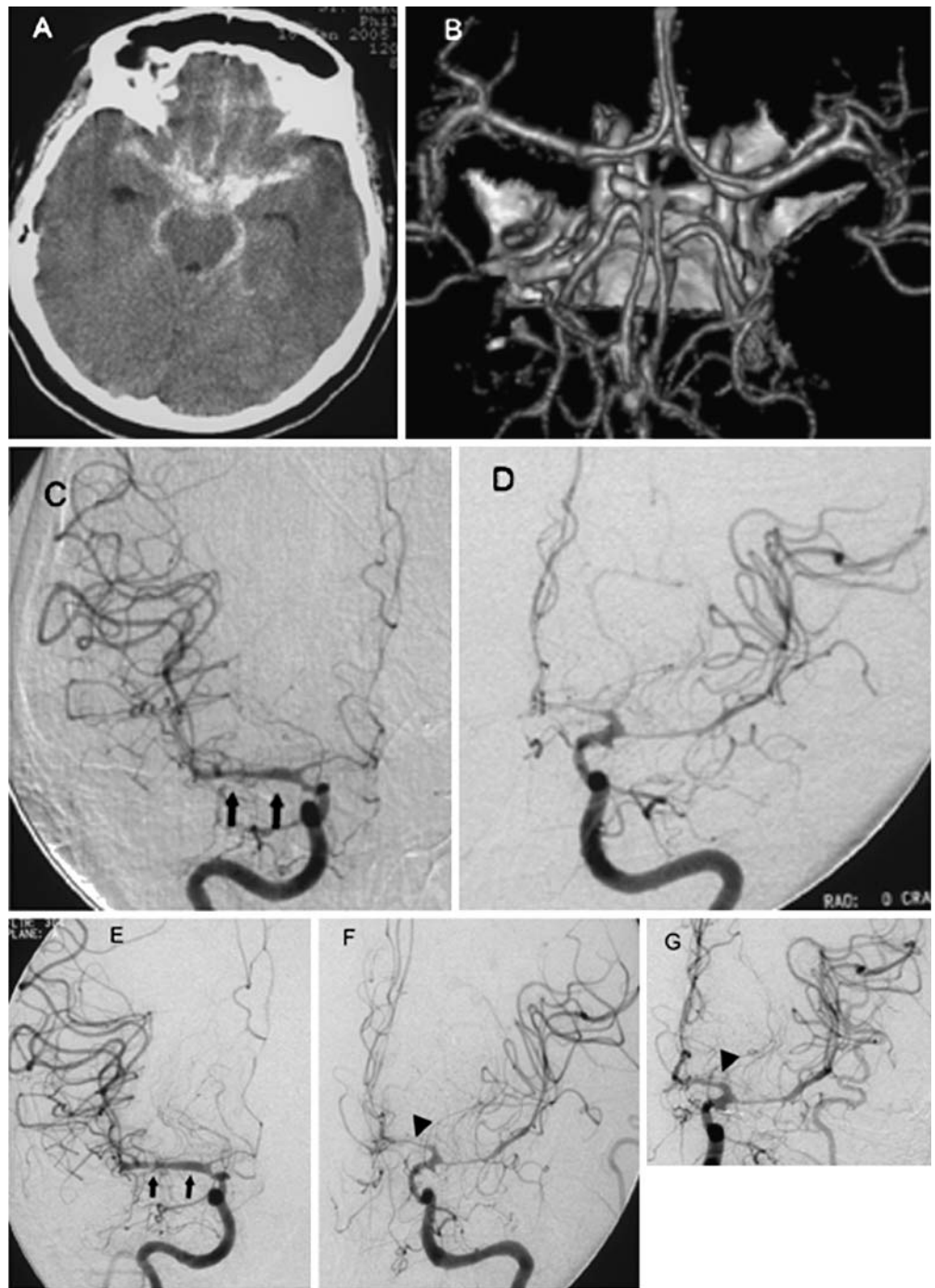
intracerebral hematoma, diffuse arterial narrowing due to intracranial hypertension and variations in angiographic technique (Fig. 2). The author generally reserves catheter angiography for patients who deteriorate neurologically secondary to suspected vasospasm and who do not improve rapidly after hemodynamic optimization and where the diagnosis is uncertain and hemodynamic therapy is difficult or risky, such as the elderly or those with cardiac disease. Catheter angiography carries a 0.5% to 1% risk of permanent morbidity and of mortality, mostly secondary to ischemic stroke, as well as an approximate 5% risk of other transient complications [61].

CT scanning is used liberally in any patient deteriorating after SAH or at scheduled intervals in patients whose condition is difficult to assess neurologically due to sedation or initial severity of the SAH. Intracranial hemorrhage, hypodense areas and hydrocephalus may be detected. An emerging technique is CTA [5, 37, 107]. Anderson and colleagues prospectively compared helical CTA and cath-

Table 2 Fisher scale for grading SAH on CT scan and relationship to vasospasm (adapted from Kistler et al., 1983 [55])

Grade	Description	Patients with angiographic vasospasm	Patients with clinical vasospasm	Total number of patients
1	No blood detectable on CT scan	0	0	33
2	Diffuse blood that did not appear dense enough to represent a large, thick, homogeneous clot	5	2	14
3	Dense collection of blood that appeared to represent thick clot in the vertical plane (interhemispheric fissure, insular cistern or ambient cistern) or in the horizontal plane (stem of the Sylvian fissure, Sylvian cistern, and interpeduncular cistern)	20	19	22
4	Intracerebral or intraventricular clots but with only diffuse blood or no blood in the basal cisterns	0	0	2

Fig. 2 CT scan on the day of SAH in a 38-year-old woman in World Federation of Neurological Surgeons clinical grade 4 [23] shows diffuse, thick, Fisher grade 3 SAH (a). CTA on the day of admission shows the normal caliber of both internal carotid, middle cerebral and anterior cerebral arteries (b). The ruptured left anterior choroidal artery aneurysm is not seen in these views. Nine days later the patient deteriorated neurologically. Anteroposterior right (c) and left (d) internal carotid angiograms on that day show severe vasospasm of the right and left anterior and middle cerebral arteries. One day later angiography was repeated. Anteroposterior right internal carotid angiogram shows that the vasospasm of the right middle cerebral artery (arrows, e) is already reversing. Anteroposterior internal carotid angiogram of the left (f) internal carotid artery shows persistent vasospasm that was partially reversed in the anterior cerebral artery (arrowhead) by infusion of nicardipine, 5 mg, into the supraclinoid internal carotid artery (g)



eter angiography in 17 patients with SAH. CTA was very accurate for diagnosing absence of (92%) or presence of (100%) severe spasm in the proximal arteries (internal carotid, basilar and first segments of the anterior and middle cerebral arteries) but less useful for distal vessels and for differentiating mild and moderate spasm [5]. Advantages of CTA are virtual absence of risk, other than that due to administration of contrast agent, and that it can be done easily, quickly and repeatedly. Magnetic resonance imaging (MRI) and MRA have been less useful in patients with SAH, probably because of time required, difficulties imaging critically ill patients and greater susceptibility to imag-

ing artifacts. Tamatani et al. examined 125 arteries in 32 patients who had undergone catheter angiography and MRA [108]. MRA had a sensitivity of 46% and specificity of 70%. The main limitations were motion artifacts and inability to visualize distal vessels.

TCD remains useful for detecting vasospasm. The flow velocity measured is directly proportional to the volume of blood flowing through the artery in milliliters per minute and inversely proportional to the square of the diameter of the vessel. Assuming constant flow, vasospasm narrows the diameter and increases flow velocity. TCD flow velocities may be altered by alterations in volume flow,

however, and by other factors such as alterations in cerebral perfusion pressure and technical factors [56]. The middle cerebral artery is the easiest vessel to assess, and it is generally accepted that mean flow velocities over 200 cm/s are highly suggestive of severe vasospasm, whereas velocities less than 100 cm/s are rarely associated with substantial vasospasm [1]. In general, the sensitivity of TCD for diagnosis of vasospasm is 50% to 60% for mean flow velocities over 120 cm/s to 150 cm/s and the specificity is over 90% [68, 102]. In addition to the false positive and false negative rates, prediction of vasospasm can be difficult, since TCD velocities may increase coincidentally with the onset of ischemia. Sensitivity may be increased by studying trends in flow velocities over time. Increases in velocity of more than 50 cm/s in 24 h are worrisome for onset of clinical vasospasm. Lindegaard and colleagues attempted to correct for alterations in CBF by calculating the ratio of middle cerebral to extracranial internal carotid artery flow velocity (hemispheric or Lindegaard ratio) [64]. A ratio less than 3 was normal, over 6 was highly suggestive of vasospasm, and intermediate values were indeterminate. The Lindegaard ratio may differentiate vasospasm from a hyperdynamic state due to hemodynamic therapy or hyperemia.

From the above discussion and the fact that vasospasm exerts its effects by reducing CBF enough to cause ischemia, it follows that measuring CBF might permit earlier detection of cases where neurological deterioration is imminent. Clyde et al. reported a retrospective analysis of 50 patients with SAH who underwent TCD and xenon CT within 12 h of each other [18]. If the CBF in the middle cerebral artery territory was <31 ml/100 g/min, then the peak systolic TCD velocity was 119 cm/s, whereas, if CBF was >31 ml/100 g/min, then the corresponding velocity was 169 cm/s. This suggests that high TCD velocities may reflect increased CBF in some cases. Focal neurological deficits were associated with low CBF in the middle cerebral artery territory on xenon CT, whereas peak systolic TCD flow velocities were not.

Other methods of early detection of cerebral ischemia due to vasospasm are reported and have tended to focus on poor-grade patients in whom it is not easy to detect vasospasm by neurological examination. Claassen et al. performed continuous electroencephalography on 34 Hunt and Hess [47] grade 4 or 5 patients [17]. Delayed ischemia developed in 26% of patients. A decrease in the ratio of alpha to delta power had the strongest association with delayed ischemia. Cut points could be set that had good sensitivity but lower specificity for diagnosis. In another study, jugular bulb oximetry detected an increase in venous oxygen saturation on average a day before onset of clinical vasospasm in each of the four patients who developed ischemia and in none of six who did not [43]. Microdialysis probes were inserted into the brain perfused by the artery of origin of the ruptured aneurysm in 42 patients [101]. Delayed cerebral ischemia was associated with increases in the lactate/glucose and lactate/pyruvate ratios that occurred in 17 of 18 cases. Only three of 24 patients without delayed ischemia developed the same ratio changes. The increased

ratios seemed to precede the onset of ischemia. Finally, a thermal-diffusion microprobe was used to measure white matter blood flow in the vascular territory at risk of vasospasm after SAH in 14 poor-grade patients [113]. Xenon-CT was used to measure CBF. A decrease in thermal diffusion CBF below 15 ml/100 g/min reliably predicted onset of ischemia. Each of these methods is promising for early detection of ischemia, although they all have in common complexity of use and need to be studied prospectively by other centers in order to determine how reproducible the methods are.

Treatment of vasospasm

General

Nimodipine is the standard drug administered to patients with aneurysmal SAH. In doses administered orally in North America, it does not significantly dilate vasospastic arteries, leaving open to question the mechanism by which it improves outcome [9]. Brain tissue oxygen monitoring in poor-grade patients showed that brain oxygen concentration decreased for up to an hour after the oral administration of nimodipine in the absence of changes in other parameters such as cerebral perfusion pressure [104].

Management of the treatment of SAH patients relies mainly upon maneuvers to optimize CBF, reduce cerebral metabolic demand and prevent secondary brain injury. These include avoidance of hypotension, hyperthermia, hyperglycemia, hypovolemia, hyponatremia, hypomagnesemia, increased intracranial pressure, seizures, hypercapnia and hypoxia. Hypovolemia and hyponatremia were shown to be particularly dangerous to patients with SAH [42, 121]. Hyponatremia is usually due to natriuresis and volume loss (cerebral salt wasting). Fluid restriction increases the risk of cerebral ischemia. Hyponatremia, even in patients presumably given adequate fluids, is associated with cerebral ischemia [42]. This has led to the recommendations above that patients be maintained at least euvolemic and that hyponatremia be avoided after SAH. Increased intracranial pressure may be treated in several ways. The author uses ventricular drainage frequently and in almost all patients. Important intracerebral hematomas are evacuated surgically. If increased pressure still occurs then additional medical measures are used, including artificial ventilation, sedation and paralysis, short periods of hyperventilation and osmotherapy with mannitol and hypertonic saline. Large decompressive craniectomies are done early in preference to prolonged osmotherapy and/or hyperventilation, when the patient is judged to be able to achieve functional recovery, but there is increased intracranial pressure with midline shift. Craniectomy usually rapidly reduces intracranial pressure and may markedly simplify management and shorten intensive care stay.

Blood transfusions are emerging as being independently associated with unfavorable outcome in several diseases [103]. Smith and colleagues reviewed 441 patients with aneurysmal SAH. After adjusting for some of the prog-

nostic factors for outcome after SAH, they found that intraoperative but not postoperative blood transfusion was associated with increased odds of unfavorable outcome, whereas vasospasm was associated with postoperative transfusion. Other aspects of neurointensive care, such as administration of antiepileptic drugs and steroids, need to be carefully considered in light of similar data showing associations of poor outcome after SAH with antiepileptic drug use [75] and between poor outcome after head injury and use of steroids [91]. The main treatments for vasospasm are induced hypertension (hemodynamic therapy) and dilation of spastic arteries by balloon angioplasty and/or superselective intra-arterial infusion of vasodilators.

Neuroprotection remains a theoretical hope. A randomized, double-blind, placebo-controlled trial of 2,589 patients with ischemic stroke was conducted [74]. Patients received placebo or 16 mmol MgSO₄ intravenously over 15 min followed by 65 mmol over 24 h. No improvement in outcome was noted, although subsets of patients that may have benefitted included those with non-cortical stroke. Several investigators have reported small studies of patients with SAH treated with intravenously administered magnesium [13, 16, 115, 117]. The main conclusion that can be drawn thus far is that doses in the range of those administered to women with toxemia produce acceptable elevations in serum magnesium concentration. These concentrations are towards the low range of vasodilator doses, an observation supported by the lack of effect of acute infusion of a bolus of 5 g MgSO₄ on TCD velocities in patients with SAH [14]. Measurements of blood and CSF magnesium concentrations show a delay in elevation of CSF levels after intravenous administration of magnesium [80]. A randomized, blind trial may be warranted, but large numbers of patients would be needed and care would need to be taken to avoid hypotension, which did occur in an ischemic stroke trial [74].

Clot removal

Animal studies demonstrated that subarachnoid clot placement caused vasospasm and removal of the clot prevented or reduced spasm [76, 125]. The earlier the clot is removed the more completely vasospasm is prevented. Results of surgical clot removal are identical to those using intracisternal fibrinolysis with tissue plasminogen activator (TPA) [32]. These findings argue that there is no process set in motion early after SAH that leads inexorably to vasospasm and that vasospasm is principally a process dependent on the volume, location, density and persistence of subarachnoid clot. On the other hand, the animal models do not replicate the acute aneurysm rupture and intracranial pressure changes that may occur after human SAH. There is, however, evidence in humans that surgical removal of the SAH during aneurysm surgery may reduce vasospasm [72, 79]. Surgical clot removal in humans is technically difficult and often incomplete. This led to the idea to clear the clot away by administration of TPA intracisternally at the time of aneurysm surgery or in the days after surgery by

intracisternal or intraventricular catheters [33, 97]. A double-blind, placebo-controlled trial of TPA was conducted. One-hundred patients were randomly chosen to receive a single intracisternal dose of 10 mg TPA or placebo given after aneurysm clipping [34]. Good outcome occurred in 57% of treated patients at 3 months compared to 43% of placebo patients. This difference was not statistically significant. There was a 56% relative risk reduction in severe vasospasm in the subset of patients with thick subarachnoid clot. TPA did not cause substantial increases in bleeding complications. The trial did not include enough patients to determine effects on overall outcome. Findlay has continued to treat patients with TPA with favorable results in a case series [30]. Investigators in Japan have used urokinase in similar fashion [41, 94]. The author uses intraventricular TPA in 1 mg boluses beginning 24 h after aneurysm surgery. Patients are generally candidates for such treatment if they can have the ruptured vascular lesion excluded from the circulation, have thick SAH on CT scan persisting after treatment of the lesion and can receive TPA within 72 h of SAH.

Hamada and co-workers studied the effect of intrathecal urokinase infusion into the cisterna magna after aneurysm coiling [41]; 110 patients were randomly allocated to undergo urokinase infusion or not after coil embolization of the ruptured aneurysm. No bleeding complications were reported, and symptomatic vasospasm was significantly reduced from 30% in the patients without treatment to 9% in those given urokinase. Permanent morbidity was also reduced. The results require replication by others, which would seem justifiable in view of the surprisingly low risk of precipitating bleeding in the presence of a coiled, ruptured aneurysm.

Hemodynamic therapy

Hemodynamic therapy includes manipulation of blood pressure, volume and viscosity and cardiac output in order to optimize CBF. This may be done prophylactically or therapeutically. A systematic review of the prophylactic hemodynamic therapy for SAH identified four prospective comparative studies [62, 93, 111, 116, 123]. Prophylactic hemodynamic therapy was associated with a reduced risk of symptomatic vasospasm but not of delayed ischemic neurological deficit. The reason symptomatic vasospasm was reduced but not delayed ischemia is strange, since they are usually considered to be different terms for the same problem. Mortality was also reduced. Only one trial was a true randomized, blind study [62]. This study randomly allocated 82 patients with SAH to normovolemia or prophylactic hypervolemia to be administered for 14 days after the SAH. Hypervolemia successfully elevated cardiac filling pressures but had no effect on CBF measurements or the incidence of clinical vasospasm. The authors concluded that, since prophylactic hypervolemia did not increase CBF, any beneficial effects were likely to be due mainly to avoidance of hypovolemia rather than any particular benefit of additional hypervolemia. The conclu-

sion of the systematic review was that there was insufficient evidence from which to derive any information on efficacy of prophylactic hemodynamic therapy nor from which to make any specific recommendations about its use [111]. A Cochrane systematic review [90] excluded two studies included in the review above because one used historical controls [116] and the other study did not specifically study hypervolemia [123]. They did include another trial of 32 patients that randomly allocated patients to normovolemia or hypervolemic, hypertensive hemodilution therapy [26]. It is evident that hemodynamic therapy has only been studied using methods deemed necessary to generate level 1 or 2 evidence in a very small number of patients (73 treated and 73 controls). The lack of evidence of benefit could just be due to inadequate study. Analysis of these trials found that hypervolemia did not improve outcome or reduce the incidence of delayed ischemia. Complications were more common in patients treated with hypervolemia. The limitations of these studies is that each one used different parameters and components of hemodynamic therapy. Target parameters included central venous pressure greater than 5 mmHg to 7 mmHg or greater than 8 mmHg in another study [26, 93]. Pulmonary capillary wedge pressures were recommended to be 12 mmHg to 15 mmHg [93]. Intrathoracic blood volume index may give more accurate assessment of cardiac preload than traditionally used filling pressures, but this measurement has not been assessed after SAH [15]. These filling pressures may be used as endpoints for prophylactic or therapeutic hypervolemia, but I do not use them because each patient is different so universal values are almost useless, the numbers are frequently impossible to obtain and hypervolemia is more likely to cause complications than to be of any benefit. However, this is opinion not based on science and I could be wrong.

Regarding therapy, there is reasonable rationale for raising the blood pressure to treat symptomatic vasospasm. SAH and vasospasm may be accompanied by some degree of loss of pressure autoregulation. When autoregulation is decreased or lost, elevation of blood pressure may increase CBF, at least in regions of brain that have impaired autoregulation. Reversal of neurological deficits in patients with vasospasm after SAH can occur when the blood pressure is elevated [57]. There are no randomized studies of induced hypertension for treatment of symptomatic vasospasm, and almost all investigators have employed some combination of hypertension and hypervolemia. Nevertheless, induced hypertension remains one of the most important measures for alleviating cerebral ischemia due to vasospasm. The author generally does not treat hypertension after the aneurysm has been secured, but we do not use prophylactic induced hypertension. We usually induce hypertension in patients who develop delayed ischemia or in some patients who are judged to be at high risk of developing vasospasm, such as those with rapidly increasing TCD velocities, high mean velocities or substantial vasospasm on, for example, CTA. There is little information upon which to base decisions about which agent to use to increase the blood pressure or what

parameters to use. Recommended values include elevating mean arterial pressure 20 mmHg above the preoperative baseline [26]. As for volume measurements, I do not adhere to any specific numbers for reasons cited above. Also, in the United States of America, the medical legal system makes us reluctant to make dogmatic recommendations for fear of legal action should some adverse event occur and the exact specified parameters not have been met for every femtosecond of the patient's illness.

The use of hypervolemia is based on observations that patients with SAH are volume depleted, that infusions of crystalloid and/or colloid are usually necessary in order to elevate blood pressure, and that experimental studies suggest that hypervolemia itself may augment CBF. Again, there are no scientific studies to support the administration of more fluid to patients who develop symptomatic vasospasm, but, for the above reasons, at least normovolemia should be maintained in SAH patients [62, 111]. The author is not enthusiastic about overly aggressive fluid replacement, however, and we recommend mainly avoiding hypovolemia and maintaining at least normal volume status. If delayed ischemia develops or is judged to be imminent, we may give additional fluids but mainly to ensure that normovolemia is maintained and that hypertension can be induced.

The third component of hemodynamic therapy is hemodilution. Decreasing the hematocrit decreases the arterial oxygen-carrying capacity and increases CBF, but it remains unresolved as to whether the increase in CBF is secondary to regulatory mechanisms attempting to maintain constant oxygen delivery to the brain or to reduced blood viscosity and improved rheology. A Cochrane review of clinical trials of hemodilution for ischemic stroke concluded that there was no evidence that hemodilution was efficacious [6]. There was also no evidence of benefit, even in the subgroup of patients in whom hemodilution was induced within 6 h of stroke onset. The author recommends maintaining the hematocrit over approximately 30%, based on experimental studies showing 30% is the optimal hematocrit for reducing infarction in some animal models [60]. There is little clinical data upon which to base this recommendation. Therapeutic hemodilution also has no data upon which to rationalize its use at this time.

Complications of induced hypertension and hemodynamic therapy were reported in 24% of patients in six publications [67]. They included re-bleeding from the aneurysm if it had not been clipped or coiled, hemorrhagic transformation of infarcts, myocardial ischemia and failure, pulmonary edema, complications of central venous catheterization, renal medullary washout and, rarely, hypertensive encephalopathy [4]. Another common concern is the safety of hemodynamic therapy when the ruptured aneurysm has not been secured or the patient has other untreated, unruptured aneurysms. Re-bleeding is a substantial risk if hemodynamic therapy is instituted in the face of an untreated ruptured aneurysm [50], whereas it is prevented by clipping or coiling [2]. De novo bleeding from an unruptured aneurysm, however, is distinctly rare and I do not treat unruptured aneurysms acutely when the ruptured one is obliterated, unless they are easily clipped through the

same craniotomy as the ruptured aneurysm. Review of 40 patients with 73 unruptured aneurysms who were treated with hemodynamic therapy, including induced hypertension with systolic blood pressures over 180 mmHg in 21 cases for up to 7 days, was not associated with any episode of aneurysm rupture [44].

Pharmacological treatments

Nimodipine is administered prophylactically to most patients with aneurysmal SAH. It is a voltage-gated calcium channel antagonist that inhibits calcium entry into cells that possess these channels, which include vascular smooth muscle and neurons. Evidence for efficacy was derived from eight randomized placebo-controlled trials [3, 9, 29, 71, 78, 85–87]. Several meta-analyses of these studies have been done. Meta-analysis of seven nimodipine trials found that nimodipine improved the odds of good outcome by 1.86 and reduced the odds of deficit and/or mortality due to vasospasm and infarction on CT scan by 0.46 to 0.58 [9]. There was no statistically significant reduction in mortality with nimodipine treatment. A Cochrane review included eight trials of nimodipine (1,574 patients), two trials of nicardipine (954 patients) and one trial of fasudil (AT877, 276 patients) [29]. Nicardipine is another dihydropyridine that has the same pharmacological mechanism of action as nimodipine, whereas fasudil is a protein kinase inhibitor with a different mechanism of action. The findings were similar to those of Barker and Ogilvy in that orally administered nimodipine reduced the odds of poor outcome by 0.69 without significantly reducing mortality. The review commented that, while the effect of nimodipine on outcome was statistically robust, it depended mainly on the oral nimodipine trials. We hypothesize that voltage-gated calcium channel antagonists are effective at preventing and even reversing vasospasm but that the dose that can be administered systemically is too low to exert a maximal pharmacologic effect. Systemic hypotension is the main side effect that prevents administration of higher systemic doses. This theory is supported by several observations. Kasuya and colleagues treated 20 patients with thick SAH by subarachnoid placement of pellets containing 8 mg to 40 mg nicardipine [54]. In this small, non-randomized, cohort study nicardipine effectively prevented vasospasm. Selective intra-arterial infusions of nimodipine or nicardipine also show promising efficacy [7, 12]. Experimental evidence also strongly supports a role for influx of calcium through voltage-gated calcium channels as a primary underlying mechanism responsible for vasospasm [48]. In the nicardipine trials higher doses were used, and these reduced vasospasm [38]. The nimodipine studies provided no convincing evidence that the drug reduced angiographic arterial spasm. Other postulated mechanisms include neuroprotection, improving collateral blood flow and/or by favorably affecting blood rheology. Duration of treatment with nimodipine originally was 21 days. It seems reasonable to discontinue nimodipine earlier in selected

good-grade patients who are beyond the period of risk of vasospasm [110].

Tirilazad (U74006F) is a 21-amino steroid that was developed to optimize beneficial effects of steroids, such as antioxidant properties, and to eliminate glucocorticoid side effects. There were four randomized, placebo-controlled, double-blind studies including approximately 3,500 patients conducted around the world between 1991 and 1997 [39, 53, 58, 59]. The drug is approved for use in some countries but not in the United States of America. A meta-analysis of these studies suggested that there was some efficacy in poor-grade men [22].

Fasudil (AT877 or HA1077) is used in Japan in patients with aneurysmal SAH. It is a protein kinase inhibitor that inhibits multiple kinases, principally rho kinase. Rho kinase increases the sensitivity of the smooth muscle contractile apparatus to calcium, thereby enhancing the contractile response to a given stimulus [95]. Inhibition of rho kinase is associated with smooth muscle relaxation. The main randomized trial of fasudil was conducted in Japan on 276 patients with SAH [99]. Fasudil significantly reduced clinical vasospasm from 50% in the placebo group to 35% in the treatment group. There was no statistically significant effect on outcome. Further clinical trials would be needed in order to determine efficacy of this drug in SAH.

The other major development in the treatment of vasospasm involves endothelin antagonists. Evidence from experimental models of SAH and clinical studies of endothelin concentrations in humans with SAH suggest that alterations in the vasoconstricting endothelin system might contribute to vasospasm [126]. TAK-044, an endothelin receptor antagonist, was compared with placebo in a randomized, blind trial of 420 patients treated within 96 h of the SAH [98]. There was a trend towards reduced ischemic events in the treated patients (23% with placebo, 21% with TAK-044, not significant) but no significant differences in outcome or mortality overall. Patients receiving TAK-044 had significantly more hypotensive episodes (16% versus 7% in the placebo group), necessitating increased use of pressors. TAK-044 is an antagonist of both the A and B types of endothelin receptors. There are theoretical reasons why antagonists that are selective for the A receptor may be more effective against vasospasm, and, indeed, results of a small clinical trial of clazosentan, an A receptor-specific antagonist, were recently reported [114]. Thirty-two patients with thick aneurysmal SAH were randomly allocated to receive placebo or clazosentan. Angiographic vasospasm occurred in 88% of the placebo-treated patients but in only 40% of the clazosentan-treated patients ($P=0.008$). Furthermore, the severity of vasospasm was reduced by clazosentan, reversal of established vasospasm was documented angiographically after selective intra-arterial infusions, and there was a trend towards reduction in the incidence of cerebral infarction in treated patients. Those promising results are being investigated in a larger clinical trial. A potential problem common to the endothelin antagonists, calcium channel antagonists and, essentially, all vasodilators is that they are insufficiently selective to dilate

the cerebral arteries at doses that do not dilate the systemic circulation and cause potentially detrimental hypotension.

Other agents undergoing clinical trials at present include magnesium and hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). There are two small studies that randomly allocated patients with SAH to receive a statin [simvastatin ($n=19$) or pravastatin ($n=40$)] or placebo ($n=60$) [66, 112]. Statin therapy was associated in both studies with a significant reduction in transcranial Doppler ultrasound evidence of vasospasm and, in the larger study, with reduced duration of severe vasospasm and reduced overall mortality [112]. Those very promising results were corroborated by a retrospective cohort study of 20 SAH patients who were admitted to hospital on statins and 40 SAH controls [81]. The investigators found that patients on statins had better functional outcome and were less likely to develop delayed cerebral ischemia, although there was no effect on mortality. Singhal et al., however, noted in a similar retrospective, observational study that patients with SAH who were admitted on statins had an increased risk of vasospasm, and they speculated that this might be due to abrupt discontinuation of the drug upon admission to hospital for SAH [100].

Endovascular treatment

Twenty-one years ago Zubkov and colleagues reported using balloon catheters to dilate 105 vasospastic cerebral arteries in 33 patients with SAH [127]. Those investigators noted that vasospasm did not recur after vasospastic arteries were dilated with balloons, a finding that has been confirmed repeatedly. Balloon angioplasty has not been subjected to randomized, controlled studies, but a review of reported case series suggests that neurologic improvement occurs in 31% to 80% of treated patients, which is greater than what would occur without the procedure [11, 19, 27, 67]. CBF improves and TCD velocities fall in treated arteries. The major limitation of balloon angioplasty is that complications are reported in 5% of cases and include rupture of the artery that has undergone angioplasty, which is almost invariably fatal, and stroke due to arterial occlusion. Balloon angioplasty, therefore, is generally reserved for patients who have had their ruptured aneurysms obliterated by clipping or coiling, are deteriorating neurologically and have failed other treatments for vasospasm, including endovascular vasodilator drug infusion. For patients who present with vasospasm, simultaneous balloon or pharmacologic angioplasty and endovascular treatment of the aneurysm with coils is a possible treatment option. If the vasospasm is treated and the aneurysm cannot be treated with coils, it generally should be secured immediately by surgical clipping. In such cases surgery to clip the aneurysm, followed by immediate postoperative angioplasty, may also be performed [63].

In 1992 two groups reported that angiographic vasospasm could be reversed by superselective intra-arterial infusion of papaverine into the vasospastic arteries [49, 52]. The vasodilation generally is less marked than with

balloon angioplasty, and the effect is transient, lasting only hours. Clinical improvement, if present, is transient, and repeated treatments may be necessary. Complications include cerebral infarction, blindness, increased intracranial pressure and neurological deterioration. Furthermore, there are reports of permanent gray matter damage after intra-arterial infusion of papaverine [103]. Papaverine generally is used only in patients with vasospasm inaccessible to treatment with balloon angioplasty in whom the aneurysm is secured and intracranial pressure is being directly monitored [68]. It is being replaced by other drugs, such as verapamil, nimodipine and nicardipine [7, 12, 68]. In addition, because of the risks of balloon angioplasty and the relative, albeit based on limited data, safety profile of calcium channel antagonists, these agents are being used in preference to balloon angioplasty in some centers. Biondi and colleagues retrospectively analyzed the effects of 30 infusions of nimodipine into the internal carotid or vertebral arteries of 25 patients with vasospasm [12]. There was clinical improvement in 19 patients (76%) overall, although angiographically visible arterial dilation was observed in only 12 (63%) patients [12]. Another study reported the effects of intra-arterial infusion of nicardipine into 44 arteries in 18 patients with vasospasm after SAH [7]. There was angiographic dilation of all infused arteries, and the systemic blood pressure was not reduced. Intracranial pressure was elevated in six patients (33%). Mean TCD velocities were significantly reduced and there was neurologic improvement in eight patients (42%).

Treatment algorithm

The following is one approach to management of treatment for patients with aneurysmal SAH. As can be deduced from the above discussion, this algorithm is largely an empiric approach and not based for the most part on scientifically derived data. The vast majority of patients is admitted within 24 h of their SAH. The ruptured aneurysm is identified by computed tomographic angiography and surgically clipped. Endovascular treatment is used preferentially for poor-grade patients, posterior circulation aneurysms and aneurysms with favorable geometry in older patients. We do not use antifibrinolytics, as recommended by a recent Cochrane review that found no benefit for even a short course of treatment before aneurysm obliteration [92]. Ventricular drainage is employed in almost all surgically treated patients and in those endovascularly treated patients with hydrocephalus that is judged to be impairing consciousness. If there is persistent, thick, subarachnoid clot visible on the CT scan the day after the aneurysm has been obliterated, TPA, 1 mg, is injected into the ventricular drain; the drain is closed for an hour, and then CSF is allowed to drain against a pressure of 5 cm H₂O. CT is repeated every 12–24 h, and TPA is injected after each scan until most of the SAH is gone. The author suspects that surgery and ventricular drainage aggravate vasospasm by impairing clot clearance. All patients receive nimodipine, 60 mg, orally every 4 h, for approximately 14 days. Blood pressure is

controlled before the aneurysm is obliterated, but, afterwards, no antihypertensive medications are administered unless the blood pressure is persistently extremely high. Monitoring includes an arterial line, urinary bladder catheter and daily transcranial Doppler ultrasound. Central venous pressure monitoring is not routine. Approximately 4 l fluid are administered per day, and the patient is weighed daily. We do not try to maintain any specific blood pressure or central venous pressure. Hyponatremia is treated with 3% saline infusion or NaCl, taken orally; body temperature is kept normal with acetaminophen, cold intravenous fluids and cooling blankets, as necessary, and serum magnesium and glucose are maintained in the normal range. Sedated patients are wakened every few hours to be assessed neurologically. The hematocrit is kept over 30% with transfusions of packed erythrocytes.

Neurological deterioration at any time is investigated immediately and exhaustively with CT, blood tests and such to determine the cause. If this occurs during the vasospasm time (approximately 3 days to 14 days after SAH) and vasospasm is suspected because there is no other cause and/or the transcranial Doppler velocities have increased and/or are elevated, then a CT or catheter angiogram is done right away. If there is any question of hydrocephalus contributing to the deterioration, a ventricular drain is placed if not already done. Cerebral perfusion is optimized by lowering intracranial pressure with CSF drainage and intermittent doses of mannitol and hypertonic saline. Decompressive craniectomy is usually preferred to aggressive osmotherapy and hyperventilation. We generally induce hypertension with α agonists and usually place a central venous catheter, if not a Swan–Ganz catheter, under such circumstances to see if the patient improves and to determine if there are adequate cardiac filling pressures. The endpoint is clinical improvement or maximal doses of inotropes; pressures above what we would be comfortable with (such as a systolic pressure over 220 mmHg) are seldom reached or of additional benefit. A Swan–Ganz catheter is used, and catheter angiography done sooner in patients with suspected heart disease or stunned myocardium, because we would use chemical or mechanical angioplasty in such cases in preference to hemodynamic therapy. If the patient improves we tend to do a CT angiogram to document vasospasm and judge whether or not angioplasty will be needed. If there is no improvement or deterioration occurs again then catheter angiography is performed with balloon angioplasty of the vasospastic arteries supplying symptomatic territories. Nicardipine infusions are used for distal vasospasm inaccessible to balloon dilation. This may be repeated every day if needed.

Prognosis and outcome from vasospasm

Vasospasm is a significant independent risk factor for poor outcome in patients with aneurysmal SAH [51]. The cooperative study on timing of aneurysm surgery included 3,521 patients, of whom 26% died or were disabled. In this 26%, vasospasm was thought to be the primary cause of

death in 28% and of disability in 39%. In the entire study population the incidences of death and disability due to vasospasm were 7% and 6%, respectively. Multivariate analysis of factors predicting poor outcome identified lower level of consciousness on admission, older age, higher admission blood pressure, more SAH on admission CT scan, pre-existing medical conditions, posterior circulation aneurysm, vasospasm and presence of intracerebral or intraventricular hemorrhage as factors. Dorsch and King reviewed the world literature on vasospasm [20]. Vasospasm significantly increased mortality from 17% to 31% and reduced the frequency of good outcome from 70% to 44%.

In the timing study no patients received nimodipine, only 22% had prophylactic hemodynamic management and 9% had therapeutic hemodynamic therapy [51]. The 3,578 patients in the tirilazad studies all received nimodipine, 62% had prophylactic and 23% had therapeutic hemodynamic therapy [40, 53, 58, 59]. The patients in the tirilazad studies tended to be better grade overall than in the timing study. Death occurred in 16% of patients and was attributed to vasospasm in 16% or in only 2.5% of the overall population. Symptomatic vasospasm, however, occurred in approximately a third of patients and was thought to cause morbidity in half of these. It remains a reasonable approximation that 67% of patients develop more than mild vasospasm after aneurysmal SAH, 33% develop delayed ischemia and half of these die or suffer permanent morbidity from the vasospasm.

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Comments

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Cerebral vasospasm is one of the most serious complications of aneurysmal SAH. Angiographic vasospasm is detected in 50% to 70% of patients with SAH, but symptomatic vasospasm leading to a DIND occurs in 19% to 46% of SAH patients, and 64% of the DIND patients will develop infarction. The hemodynamically relevant or symptomatic vasospasm remains a leading cause of morbidity and mortality after SAH.

In the present manuscript, Dr. Macdonald reviews the current knowledge and literature on the epidemiology, pathophysiology, diagnosis, investigations, treatment, and prognosis of cerebral vasospasm. This manuscript provides an excellent expert and in depth review of the contemporary management of cerebral vasospasm. The timing of this review is certainly perfect since several novel aspects in the diagnosis and treatment of this disease have recently occurred. Based on these recent developments it is fair enough to speculate that the future in treating cerebral vasospasm is bright and that our patients will soon profit from the past investments in a better understanding of the pathophysiological and molecular mechanisms underlying the disease. This review will certainly serve as a key reference in the future.