Therapeutic approaches to vasospasm in subarachnoid hemorrhage
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Delayed vasospasm as a result of subarachnoid blood after rupture of a cerebral aneurysm is a major complication. It is seen in over half of patients and causes symptomatic ischemia in about one third. If left untreated, it leads to death or permanent deficits in over 20% of patients. The essential cause and the relative contribution of true muscle spasm and other changes in the vessel wall remain uncertain. The mainstays of treatment are careful maintenance of fluid balance, induced hypervolemia and hypertension, calcium antagonists, balloon or chemical angioplasty, and, in some centers, cisternal fibrinolytic drugs. Promising future lines of treatment include gene therapy, nitric oxide donors, magnesium, sustained release cisternal drugs, and several other drugs that are under experimental or clinical trial. Current Opinion in Critical Care 2002, 8:128–133 © 2002 Lippincott Williams & Wilkins, Inc.

Delayed cerebral ischemia as a result of arterial spasm is the most common cause of death and disability due to aneurysmal subarachnoid hemorrhage (SAH) after recurrent hemorrhage. The reported incidence of this complication varies widely, but angiographic vasospasm is seen in over 67% of untreated patients with angiography at the time of maximum spasm around the end of the first week [1]. Symptomatic vasospasm, or delayed ischemic deficit (DID), affects nearly one third. Without specific treatment, the outcome of DID is devastating—it results in death in 30% and permanent disability in 34% of patients (Table 1).

Until recently, despite many reports that aroused initial optimism but the results of which could not be duplicated, there was no effective treatment. In the 1980s, two large reviews by Wilkins [2,3] discussed well over 100 different drugs and other treatments—a sure sign that none were effective. This was not quite the case by the time of the second article, because the use of variations of hypervolemia, hypertension, and hemodilution (HHH) therapy was well under way by then.

Prediction of vasospasm
No treatment for vasospasm is entirely safe or without side effects, and it would be useful if an accurate predictor of which patients are most at risk were available. Although cerebral angiography is accepted as the most accurate diagnostic standard, it is an invasive procedure with occasional complications, and also can miss vasospasm altogether if the spasm is restricted to small vessels that are not seen angiographically. In some centers, postoperative angiography after early aneurysm clipping is scheduled for 5 to 7 days after SAH when vasospasm is most likely [4].

It is well known that vasospasm is more likely in patients classified in a poor clinical grade (in whom it is, incidentally, more difficult to detect subtle early deterioration) or with a thicker subarachnoid clot. In addition, a sudden increase in flow velocity or a high velocity measured by transcranial Doppler (TCD) sonography may warn of spasm development. TCD itself is not entirely accurate; the technique is quite operator dependent, and increased velocity due to hyperemia can be misleading [5].

Attempts have been made from time to time to improve prediction, largely without success. In a recent example, 283 control subjects from a drug trial were analyzed [6].
An index based on four significant variables—thickness of subarachnoid clot, early increase in TCD velocity, initial Glasgow Coma Scale score under 14, and carotid or anterior cerebral artery aneurysms—was still only 68% sensitive in identifying those who would develop DID, limiting the utility of this index. Other studies have used TCD assessment of impaired autoregulation [7,8], cerebral microdialysis [9,10], and measurement of tissue oxygen and other parameters [11,12] with some success to improve the accuracy of prediction of vasospasm or of ischemia.

Hypervolemia, hypertension, and hemodilution therapy

The first report on the use of induced systemic hypertension was published in 1976 [13]. This was strictly for the treatment of established DID and was followed by other open studies with similar, apparently successful results. Later, HHH (triple-H) treatment became widespread.

It was not until several years later that the vital importance of at least maintaining a normal fluid intake was realized. Following evidence that patients with SAH had reduced blood volume, plasma volume, erythrocyte mass, and many other metabolic and electrolyte disturbances [14], HHH or its variations began to be used also for the prophylaxis or prevention of vasospasm. In a review of the management of vasospasm, the incidence of DID with HHH prophylaxis was reduced by almost half compared with the natural history (Table 1) [15], but further comparison is not statistically valid. Similarly, in reports of HHH therapy for the treatment of established DID, outcome was apparently better than would be expected in untreated cases and, in particular, was characterized by a lower death rate (Table 1).

The usefulness of HHH treatment is generally accepted, but it has never been unequivocally demonstrated by a randomized controlled trial to be superior to simple moderate fluid loading. An early controlled study showed less DID and a better outcome with volume expansion, but control patients received daily diuretics as part of their hypertension treatment and were probably kept relatively dehydrated [16]. In a more recent trial with 82 patients, no effect of hypervolemia on either cerebral blood flow or DID incidence was found; daily fluid intake averaged 530 mL more in the hypervolemia group, but patients in both groups received over 3000 mL per day for much of the study period [17]. Another controlled trial with 1-year outcome as a primary endpoint showed no difference in TCD-determined or clinical vasospasm or in outcome and noted higher costs and more complications in the “hyperdynamic” group; again, although that group received considerably more fluids over the 12-day study period, the control group still averaged 3000 mL or more daily [18].

It seems likely, then, that in recent studies “control” patients have, in fact, been receiving at least hypervolemia. certainly in comparison with the situation with SAH 25 years ago, when most patients were kept quite dehydrated, and delayed ischemia was much more common. In my view, adequate fluid loading is the most important aspect of early treatment and vasospasm prophylaxis. It is reasonable to reserve the more vigorous loading and induced hypertension for when DID occurs.

It is common with hypervolemic treatment to find it difficult to maintain the desired blood pressure, venous pressure, pulmonary capillary pressure, or whatever one is monitoring. This is particularly the case in young, fit people with normal renal function, and large volumes of

| TABLE 1. Summary of the natural history of vasospasm; hypervolemia, hypertension, and hemodilution therapy; and nimodipine and nicardipine |
|---|---|---|---|
| **Incidence of DID** |  |
|  | No. patients | % DID |
| Natural history | 32,188 | 32.45 |
| HHH prophylaxis | 2516 | 17.6 |
| Nimodipine prophylaxis |  |
| Oral | 1271 | 21.7 |
| Intravenous | 4555 | 14.3 |
| Nicardipine prophylaxis | 1643 | 24.6 |
| **Outcome of DID** |  |
|  | No. patients | % Dead | % Permanent deficit | % Recovery |
| Natural history | 3327 | 30.3 | 34.0 | 35.7 |
| HHH treatment | 2111 | 17.5 | 28.5 | 54.0 |
| Nimodipine treatment |  |
| Continued from prophylaxis | 445 | 18 | 32 | 50 |
| De novo for DID | 343 | 13 | 20 | 67 |
| Nicardipine treatment | 191 | 12 | 17 | 71 |

DID, delayed ischemic deficits; HHH, hypervolemia, hypertension, and hemodilution. Data from [1,15].
fluid can lead to electrolyte disturbance (particularly hyponatremia), pulmonary edema, and other complications. Suggested measures to counteract this include fludrocortisone [19] or albumin solution [20] to minimize sodium and fluid loss.

**Calcium antagonists**

Calcium antagonists have been in use since the mid-1980s, and, by far, the most experience has been with the dihydropyridine analogue nimodipine, which was tested in several controlled trials. These studies were reviewed by Barker and Ogilvie [21] in a well-organized meta-analysis, which showed notable improvements in good and good-plus-fair outcomes and reductions in death due to vasospasm and computed tomography–detected infarcts with nimodipine. Although it has never been tested formally, in a review of several thousand reported cases, the overall incidence of DID (15.9%) was somewhat lower when intravenous rather than oral nimodipine was used. When used de novo for the treatment of established DID, outcome was better than the expected natural history—13% of patients died and 20% experienced permanent deficits (Table 1).

Controlled trials have also been performed on nicardipine. Although the largest trial showed a considerably lower rate of DID, the overall outcome was not improved [22]. It was noteworthy that therapeutic or “rescue” HHH was used much more often in the control group, which may explain the lack of difference in outcome. This problem did not occur in the trials of nimodipine, which were performed earlier when HHH treatment was not so widely used.

Other calcium antagonists have also been used from time to time. An interesting recent series showed a 20% incidence of DID when oral diltiazem was used and favorable outcome in 75% of 123 consecutive cases [23••]. Also noteworthy in this series was the limited use of intensive care monitoring and aggressive HHH treatment.

**Angioplasty**

First described for vasospasm in 1984, transluminal angioplasty was initially performed with the use of specially designed balloons that could be passed into a spastic vessel and then inflated [24]. This technique requires special equipment and a highly skilled and experienced interventionist neuroradiology team. An alternative is “chemical angioplasty,” in which the angiography catheter is used to instill a vasodilator, usually papaverine. Each technique has its proponents and advantages and disadvantages. In general, angioplasty is recommended for angiographic vasospasm or at an early stage in DID (ie, if there has been no improvement after a trial of vigorous HHH). It is possibly more effective if used within 2 hours of DID onset [25].

Balloon angioplasty is generally more effective at reversing spasm, and the dilatation is also much more prolonged. However, it can only be used for fairly proximal arteries, and there is a risk of rupturing an artery (this can be reduced if the patient is kept intubated and paralyzed to prevent movement [26]) or an unclipped aneurysm. Chemical angioplasty often has to be repeated within hours or days [4] and carries complications including pupillary changes, seizures, and respiratory arrest with vertebral artery injection. In many centers, both forms are used, often in combination, depending on the size of vessel affected. In a recent review of 41 publications on angioplasty (unpublished data), immediate clinical improvement was seen in 55% of nearly 400 reported patients who underwent balloon angioplasty (occasionally combined with chemical angioplasty) as compared with 40% of those undergoing drug angioplasty.

An interesting trial of prophylactic balloon angioplasty is underway: patients with thick layers of subarachnoid clot undergo early aneurysm surgery, which is followed immediately by another angiogram and angioplasty on all the major arteries regardless of their state at the time. This is based on evidence of the involvement of endothelium in the development of vasospasm and the endothelial disruption caused by angioplasty. So far, in 18 patients there has been no symptomatic vasospasm, but there were three deaths—one resulted from arterial rupture during angioplasty. In a nonrandomized control group of nine cases, there were four deaths [26].

**Cisternal therapy**

There has been great interest over the last decade in the cisternal injection or infusion of fibrinolytic agents, which are most commonly recombinant tissue plasminogen activator or urokinase. In an early multicenter trial of tissue plasminogen activator in 100 patients, there were trends toward reduced angiographic spasm (significant in those with thick subarachnoid clot), a lower incidence of DID, and improved outcome in the treated group, with no increase in bleeding complications [27]. Studies of these treatments were discussed at length at a recent conference (Seventh International Conference on Cerebral Vasospasm, Interlaken, Switzerland, 2000), by V. Seifert and others; it was concluded that more study is needed regarding the best agent, dosage and timing of treatment, complications, efficacy, and the situation after coiling versus clipping of aneurysms.

One recent report concerned patients with coiled aneurysms, with urokinase infused via a cisternal catheter after coiling treatment for several doses until CT scanning showed clearance of blood [28]. One of 15 patients developed a transient DID, and all made a good recovery. None of 16 aneurysms bled again, and no patient developed significant hydrocephalus.
A much larger group was treated with cisternal irrigation with urokinase and ascorbic acid (to accelerate the breakdown of oxyhemoglobin); this was administered to patients with thick subarachnoid clot after early operation via bilateral cisternal catheters (with a third catheter for drainage) for up to 10 days [29]. This obviously requires intensive medical and nursing management because of the associated risks of raised intracranial pressure, infection, and hemorrhage. Of the 217 patients treated, six developed DID, which was reversible in four. Complications included meningitis in two and bleeding in four, with no permanent sequelae. Outcome was excellent or good in 175, and only six (3%) patients died. Interestingly, 39% needed shunts for hydrocephalus.

Other treatments

Space does not allow for adequate discussion of many other treatments (e.g., the phosphodiesterase inhibitor milrinone [30], the platelet-activating factor receptor antagonist E5880 [31], or the protein kinase inhibitor fadsudil hydrochloride [32]) that are under continuing investigation. Of considerable initial interest was the modified steroid free radical scavenger tirilazad mesylate, which was used in four large, controlled trials in the 1990s [33]. In the first, it appeared likely to be effective in reducing spasm, but later metaanalysis showed only a trend, whereas outcome was improved only in patients categorized in clinical grades IV and V [34].

Clinical therapies

(1) In early reports, the use of intrathecal sodium nitroprusside as a nitric oxide donor had impressive results, with little or no hypotension (as occurs with systemic administration) [41,42]. Of 10 patients with thick subarachnoid clots who received prophylactic intraventricular sodium nitroprusside, none developed vasospasm. In other patients with severe DID and failed HHH therapy, sodium nitroprusside, sometimes combined with balloon angioplasty, showed reversal of angiographic spasm and symptomatic improvement.

(2) With cisternal placement of controlled-release pellets containing papaverine, treated patients had significantly less vasospasm and better outcomes than nonrandomized control subjects [43].

(3) An interesting case report described two patients in whom symptoms persisted despite HHH therapy and angioplasty, and cardiac ischemia was limiting the possible intensity of HHH [44]. Aortic balloon counterpulsation was started, with improvement in cardiac function and in the neurologic state. Eventual recovery was better than expected.

(4) Based on experimental data showing relief of vasospasm and neuroprotection, two small series were reported in which, in addition to the usual treatment, intravenous magnesium sulfate was also given, a bolus followed by continuous infusion to

Experimental therapies

(1) The capsaicin-derived glyceryl nonivamide has a vasodilating effect via the release of calcitonin gene-related peptide (CGRP). In a rabbit study, cisternal instillation after SAH reduced or prevented basilar artery narrowing in a dose-dependent manner [36].
raise serum magnesium to twice baseline (or to 2.0 to 2.4 mMol/L) in one study [45], and infusion to maintain plasma levels of 1.0 to 1.5 mMol/L in the other [46]. Five of 10 patients in the first study developed spasm on TCD and three had symptomatic spasm, but, eventually, eight made a good recovery. In the study conducted by Chia et al. [46], the infusion was started as early as possible; the 13 treated patients had less angiographic vasospasm than 10 historical controls. Importantly, there were no adverse effects from magnesium in either study. Randomized trials were recommended.

Cervical spinal cord electrical stimulation [47] and mild hypothermia [48] have also been recommended after SAH for prophylaxis and treatment, respectively.

Conclusions
Although major advances have been made in the management of what is now probably the most significant complication of cerebral aneurysm rupture, the problem is by no means solved. Much research is continuing to be devoted to elucidating the complex pathophysiology of vasospasm itself and of the consequent, but less common ischemia. Because vasospasm is such a multifactorial problem, it is likely that prevention and treatment will continue to require application along several different lines, as is done at present with clearance of blood, hypervolemia, calcium antagonists, and, if necessary, intensive HHH and balloon or chemical angioplasty.

Another recent review by Treggiari-Venzi, Suter, and Romand [49••] is well worth reading. It includes a wide-ranging discussion of the diagnosis of vasospasm and the problems with various diagnostic modalities including TCD, as well as the common difficulty with distal artery spasm. The early trials of HHH are reviewed, and the continuing lack of definite evidence from large trials, along with the lack of standardization of blood pressure or wedge pressure goals, and complications of HHH are discussed. The different calcium antagonists are also discussed, along with fibrinolysis, antioxidants, immunosuppression, and other experimental and clinical treatments not mentioned here.

The current, generally accepted recommendations for prevention and treatment of delayed vasospasm include careful fluid management and maintenance of hypervolemia, use of a calcium antagonist, and, in some centers, cisternal therapy. For more difficult situations, full HHH treatment and angioplasty are standard.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest

** Of outstanding interest


A large, consecutive series of patients with aneurysms most treated outside the intensive care situation and without invasive monitoring, but who received fluids and oral diltiazem, and therapeutic HHH if DID developed. This occurred in only 24 of 123 patients, with poor outcome due to DID in 5.7%. Overall, 75% of patients had a good outcome or moderate disability on the Glasgow Outcome Scale. This study shows that good results can be obtained in a standard neurosurgical ward setting with ICU backup when needed.


A good analysis of the complex molecular biology of the changes leading to vasospasm.


A comprehensive review of the pathogenesis, diagnosis, and management of vasospasm. The authors point out the problems of extrapolating experimental results to the clinical situation. The rationale of the present mainstays of treatment and possible future developments are discussed. Comments are provided (pp 261–262).