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CHAPTER

14

Endovascular Therapy for Vasospasm

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INTRODUCTION

The incidence of angiographic vasospasm following subarachnoid hemorrhage is reported to be as high as 60%-80% and the incidence of symptomatic vasospasm as high as 30% (1-3). The morbidity and mortality associated with vasospasm have had a significant negative impact on the outcome of patients with aneurysmal subarachnoid hemorrhage (3, 4). Over the past two decades, a variety of modalities have been used for the prevention of ischemia secondary to vasospasm. These include treatment with the calcium-channel blocker nimodipine, which may improve outcome both by a direct neuroprotective effect and by action on cerebral blood vessels (5, 6), and hypervolemic-hypertensive-hemodilutional (HHH) therapy (7). Despite this, a subgroup of patients may progress to develop delayed ischemic neurological deficits (DIND); endovascular therapy may be employed to reverse these deficits.

DIAGNOSIS

Subarachnoid hemorrhage may lead to a sustained contraction of smooth muscle cells of the large cerebral vessels generally between 4 and 10 days after the hemorrhage, followed by collagen deposition in the adventitia and thickening of the intima, which may persist for weeks following the resolution of clinical vasospasm (8). These morphological changes may result in a reduction in cerebral blood flow (CBF); however, although most patients may develop some degree of narrowing, the majority does not develop DINDs (9). It is only when CBF is greatly reduced, and compensatory mechanisms such as autoregulation, collateral flow, and increased oxygen extraction are exhausted, that ischemic deficits result.

The diagnosis of clinical vasospasm is made on the basis of the clinical examination and ancillary studies. The development of a new fo-

cal neurologic deficit or a deterioration in the level of consciousness may herald the onset of vasospasm (1). Other causes for clinical deterioration, such as hydrocephalus, intracranial hemorrhage or edema, seizures, and infection need also be considered; however, these may aggravate the ischemia secondary to vasospasm and should not exclude vasospasm if the index of clinical suspicion is high.

We routinely used transcranial Doppler (TCD) to detect vessel narrowing and to follow the course of vasospasm with time and treatment (10) (Fig. 14-1). In the middle cerebral artery (MCA), a velocity of >120 cm/sec is considered mild vasospasm, >160 cm/sec moderate vasospasm, and >200 cm/sec severe vasospasm (11). In the vertebrobasilar distri-

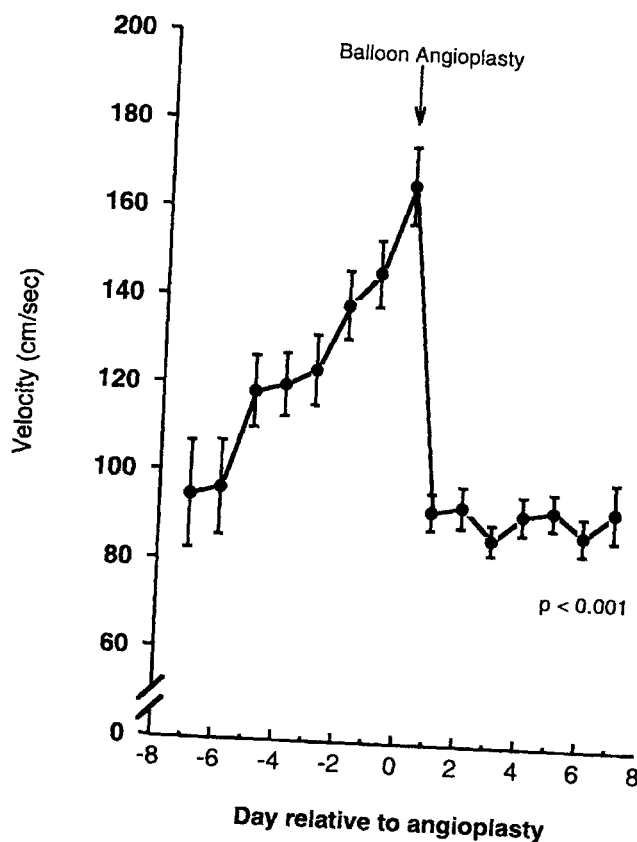


FIG. 14.1 Graph illustrating the use of transcranial Doppler (TCD) to measure velocity in the distal internal carotid or middle cerebral vessels in 39 patients to document development of vasospasm and sustained response to angioplasty. From Elliott JP, Newell DW, Lam DJ, et al.: Comparison of balloon angioplasty and papaverine infusion for treatment of vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 88:277-284, 1998, with permission.

bution, >65 cm/sec is consistent with vasospasm and >95 cm/sec consistent with severe vasospasm (12). Although TCD can accurately diagnose proximal vessel spasm, it cannot detect distal vessel vasospasm (e.g., A2 arteries) which is present in a minority of cases (13). Blood flow studies may complement TCD findings and improve the accuracy of diagnosis; these include Xenon computed tomography (XeCT) (14) and single photon emission computed tomography (SPECT) (15). Using XeCT, regions of interest with a cerebral blood flow (CBF) of <20 cc/100gm/min are considered at risk for ischemia (14).

We have found CBF studies to be particularly useful in high-grade patients in whom it may be difficult to detect clinical deterioration or responsiveness to HHH therapy. Both TCD and blood flow studies may be used after endovascular therapy to monitor the efficacy of the treatment and to diagnose recurrent vasospasm (10, 15, 16).

We treat all patients with nimodipine and utilize HHH therapy as indicated by transcranial Doppler velocities. We proceed to endovascular therapy only if the patient deteriorates clinically or develops perfusion deficits on SPECT despite maximal medical treatment. As discussed below, however, the timing of endovascular intervention is critical and should be instituted within 12 hours of onset of symptoms (17, 18).

ENDOVASCULAR TECHNIQUES

Angioplasty of cerebral arteries as a treatment for vasospasm was first described by Zubkov in 1984 (19). In their landmark paper, Zubkov et al. performed angioplasty on 105 major cerebral arteries in 33 consecutive patients without any complications, although 28 of these patients underwent angioplasty before definitive treatment of the ruptured aneurysm. Since that time, refinement in techniques and improvement in balloon catheters have confirmed the safety and angiographic efficacy of angioplasty (17, 20, 21). In addition, intra-arterial papaverine infusion has been used to both as an adjunct to angioplasty and as a treatment for distal arterial vasospasm (22-24).

Endovascular therapy is performed under general anesthesia after a head CT is done to exclude a large infarct or hemorrhage. Arterial blood pressure and intracranial pressure are monitored throughout; a head CT is repeated immediately after therapy to rule out hemorrhagic transformation. Systemic anticoagulation with 5000-7000 IU heparin is instituted prior to angioplasty. Using a transfemoral approach, a low pressure (0.5 atm) silicon microballoon catheter is placed at the site of vessel narrowing and gradually inflated. The balloon is inflated only to 25% of its maximal size initially, and then deflated; the degree of inflation is the increased and repeated until vessel dilatation is com-

plete. It is important to avoid overinflation beyond the normal diameter of the artery, as this may result in vessel rupture (17). All significantly narrowed vessels are treated with angioplasty, not just the vessel responsible for the clinical symptoms.

The mechanism of action of balloon angioplasty has been studied in animal models although the reason for its sustained effect is still not known. Electron microscopy has revealed stretched and torn collagen fibers (25), endothelial denudation, and rupture of the internal elastic lamina (8) and stretched smooth muscle fibers (8). In vitro studies on canine vasospastic vessels indicate significant impairment in vascular reactivity following angioplasty which persists for 2 to 3 weeks (8). Thus, angioplasty disrupts the ability of smooth muscle cells to contract for a period of time by mechanisms as yet unknown.

Intra-arterial papaverine is given via a superselective catheter positioned just proximal to the affected area (10, 26). A total of 300 milligrams of papaverine is infused per side gradually over 30–60 minutes, with careful monitoring of the ICP and arterial blood pressure. Papaverine is an alkaloid compound which causes smooth muscle relaxation through phosphodiesterase inhibition and possibly by decreasing the level of intracellular calcium (27, 28). Macdonald et al. found that, in a rabbit model, the efficacy of papaverine was influenced by the duration of the vasospasm and the degree of vessel narrowing (29). Conversely, Milburn et al. found no correlation between duration of vasospasm and response to papaverine (28). The limitations of papaverine treatment are still under consideration; a major drawback has been the recurrence of vasospasm following treatment (10). In vessels with severe vasospasm, papaverine may be infused first to facilitate microcatheter entry into a spastic vessel.

RESULTS OF ENDOVASCULAR THERAPY

The results of endovascular therapy for vasospasm have been reported in multiple case series with variable selection criteria, follow-up, and outcomes (10, 17, 18, 20, 30–34). To date, no controlled, prospective trial has been conducted to assess the impact of endovascular treatment on outcome; without a true untreated comparison group, any conclusions regarding this treatment modality must be interpreted with caution. The results of treatment with angioplasty have been found to be consistently better than with papaverine infusion alone (10, 34).

Balloon Angioplasty

In most series to date, balloon angioplasty has been studied with regard to its immediate effect on neurological deficit, as well as on long-

term outcome. In 1992, Higashida et al. reported the clinical results of 28 patients treated with balloon angioplasty, with immediate improvement in 60.7% and favorable long-term outcomes in 60.7% (20). In two cases, vessels ruptured during the procedure with devastating consequences. In contrast, Coyne et al. in 1994 reported an immediate improvement in only 31% of their 13 patients and a favorable long-term outcome in only 38%, although they had no complications related to the procedure itself. They attributed 5/6 deaths to vasospasm (31). In analyzing their results, they felt that the poor grade of many of the patients (Grade 4-5) and the long duration (18 hours) between development of DINDs and treatment may have contributed to the worse outcomes. Since then, however, multiple series have confirmed an immediate improvement in neurologic deficit in at least 60% of patients (10, 16-18, 30, 32).

In Eskridge et al.'s series of 50 consecutive patients with symptomatic vasospasm, 61% were improved post-treatment; the complications included two vessel ruptures, with subsequent death of both patients, one branch vessel occlusion, and two aneurysmal rebleeds 4 and 12 days following treatment (17). Long-term follow-up was not reported. The authors did note a tendency towards better responsiveness in patients treated within 12 hours of onset of clinical symptoms but a worse outcome in patients with a GCS score of less than 12.

Bejjani et al. also in 1998 described 31 patients who were treated with angioplasty. Although they used different criteria for improvement post-therapy, they found that 72% of patients were better after treatment. Importantly, they too found time to be a predictor of short-term results: angioplasty performed within 24 hours of onset of neurologic symptoms resulted in 90% of patients having marked or moderate improvement, whereas angioplasty after 24 hours resulted in only 36% of patients having moderate improvement. However, this stratification did not extend to long-term outcome; 25/29 patients in follow-up had a Glasgow outcome scale (GOS) of 1 regardless of timing of angioplasty. Given the small number of patients, the actual long-term impact of timing of angioplasty is difficult to determine (30).

In 1999, Rosenwasser et al. further investigated the effect of early treatment of clinical vasospasm. In their series of 84 patients treated with cerebral angioplasty, they found a 70% early favorable outcome in 51 patients treated within 2 hours of symptom onset and a 40% good outcome in patients treated after 2 hours. At 6 month follow-up, 33/84 (39.2%) had a good outcome and 30/84 (35.7%) a fair outcome; no distinction was made as to the effect of the timing of treatment on late outcomes (18). They reported no complications related to the angioplasty procedure.

In 2000, Polin et al. summarized the results of angioplasty in patients enrolled in the tirilizad in SAH trial. Unlike the previous single center studies, these patients were treated at 15 different centers without a consistent vasospasm treatment protocol. Of these 38 patients, only 4 improved after treatment and 53% achieved a good/fair long-term outcome. When compared to a matched control group who had a 60% favorable outcome, angioplasty had no beneficial effect (33). However, there were numerous drawbacks to this study. Most importantly, no pre-treatment CT scan was reported and yet large hemispheric infarctions were seen on 22/29 late follow-up CT scans. Of the seven patients with normal CT scans, five had made a favorable outcome. Because no standardization of treatment was attempted, the maximum vasospasm was judged to be severe in only 13/38 cases; the indications for angioplasty were variable and other causes for clinical deterioration not well documented. The extent of medical treatment was also inconsistent. Fifteen of 38 patients were treated >12 hours after onset of symptoms and a high vasospasm recurrence rate was noted, contrary to other published reports. It is difficult to interpret the comparison of outcomes given the limitations of the study.

When Le Roux et al. analyzed 224 patients with a Grade I-III SAH, they found symptomatic vasospasm in 17.4% (39 patients). In the 17 patients for whom angioplasty was not used or not available, 76.5% achieved a good outcome. This is in contrast to the 22 remaining patients, who had a 96.6% good outcome. Not all of these patients were treated with angioplasty, so the improved outcome may in part be accounted for by aggressive medical therapy for vasospasm (4).

These results are summarized in *Table 14-1*.

Papaverine Infusion

Multiple small case series evaluating papaverine have been reported in the literature (10, 22, 23, 34). The results have been mixed. In 1992, Kassell et al. described 12 patients treated with intra-arterial papaverine; although 57% had marked reversal of angiographic vasospasm, only 25% had dramatic neurologic improvement (23).

Firlik et al. evaluated 15 consecutive patients treated with papaverine, alone (10 cases) or combined with angioplasty (5 cases). These patients were selected on the basis of development of a delayed neurologic deficit and XeCT documentation of ischemic regions of interest (ROI) with CBF <20 cc/100gm/min. Although 78% had some angiographic reversal of vasospasm, only 26% had clear neurologic improvement. Of the 9 patients who underwent XeCT after treatment, only 46% had augmentation of CBF; there was poor correlation between clinical change and increased CBF (34). There were several complications: one patient

TABLE 14.1
A comparison of current studies on the results of balloon angioplasty for treatment of vasospasm

Author	# of Patients	Early Outcome	Long-term Outcome	Complications
Bejjani (30) (1998)	31	72% improved PTA <24hrs: 90% improved PTA >24hrs: 36% improved	25/29 independent PTA time ns	1 death from vasospasm 2 groin/1 retroperitoneal hematoma 5/6 deaths due to vasospasm
Coyne (31) (1994)	13	31% improved	38% independent 46% dead	
Eskridge (17) (1998)	50	61% improved	N/A	2 vessel ruptures 2 aneurysmal rebleeds (4 and 12 days after PTA)
Firlik (16) (1997)	14	86% improved	N/A	1 MCA branch occlusion 1 patient no PTA possible due to technical difficulty 1 hemorrhagic transformation
Fujii (32) (1995)	19	63% improved	68% good- excellent at discharge	
Higashida (20) (1992)	28	60.7% improved	60.7% good- excellent	2 vessel ruptures
Polin (33) (2000)	38	11% improved	53% good or moderate disability	
Rossenwasser (18) (1999)	84	PTA <2hrs: 70.5 improved PTA >2hrs: 40% improved	39% good 36% fair 8.3% dead (no distinction made in timing of PTA)	None

had a paradoxical angiographic narrowing following papaverine infusion, with a resultant hemispheric infarction, one experienced transient brainstem depression during infusion of the vertebral artery, and one developed a seizure and hypotension with carotid artery infusion.

Elliot et al. compared the efficacy of papaverine infusion (13 patients) with balloon angioplasty (39 patients). Using serial TCD examinations, the velocities of the internal carotid arteries (ICA) and middle cerebral arteries (MCA) before and after treatment were documented. Prior to angioplasty, the mean ICA/MCA velocity increased from a baseline of 95 ± 12 cm/sec to 166 ± 9 cm/sec just prior to treatment; following angioplasty, the velocity decreased to 92 ± 4 cm/sec and remained stable (*Fig. 14-1*). Just prior to papaverine infusion, the mean TCD velocity increased to 158 ± 8 cm/sec and decreased to 127 ± 13 cm/sec on post treatment day 1; significantly, however, the velocities returned to pretreatment levels by day 2 (*Fig. 14-2*). Clinically, 67% of patients treated with angioplasty demonstrated some neurologic recovery. Although 62% of papaverine treated patients ultimately made a favorable outcome, five of these eight patients required re-treatment or conversion to balloon angioplasty. The sustained effects of angioplasty were not seen with papaverine therapy. Using SPECT scanning in 37 patients, angioplasty resulted in increased perfusion in 71% of patients, whereas papaverine improved perfusion in only 31%. There were no treatment related complications in this series (10).

Fandino et al. measured jugular bulb vein oxygen saturation (SvjO₂) and arteriovenous differences in lactate (AVDL) before and after papaverine infusion in 10 patients. Three patients also underwent angioplasty and endovascular therapy was instituted soon after failure of medical treatment, although the duration of neurologic deterioration was not given. All 10 patients had early neurologic improvement and no re-treatment was required. Nine of the 10 patients had an improvement in SvjO₂ following papaverine, which was maintained with aggressive HHH therapy; however, there were no significant differences in AVDL before and after therapy. Overall, seven patients made a favorable outcome. The precise indications for angioplasty and the small number of patients bring into question the validity of these findings, in particular the sustained effect of papaverine infusion. Nevertheless, this study does document improved global perfusion following papaverine vasodilatation (35).

CEREBRAL BLOOD FLOW STUDIES

The diagnosis and treatment of vasospasm may be monitored by cerebral blood flow studies. Lewis et al. used SPECT scanning in 10 patients and showed a significant increase in CBF in eight patients

who had neurologic improvement whereas there was no change in CBF in the two patients who had no clinical change (15).

Firlik et al. successfully used XeCT to diagnose clinical vasospasm in 14 patients. Prior to angioplasty, the mean number of ROIs at risk was 11.4 ± 4.3 with a mean CBF of 13 ± 2.1 ml/100gm/min. Angioplasty was possible in 13 patients; 12 (92%) demonstrated clinical improvement. The number of at-risk regions of interest decreased to 0.9 ± 1.6 and the average CBF increased to 44 ± 13.1 ml/100gm/min, well above the ischemic threshold. One patient required repeat angioplasty in a different vessel 3 days after initial treatment; she did not respond to the second course of treatment. One patient suffered a hemorrhagic transformation and expired after angioplasty. Using specific CBF criteria, these authors were able to obtain a high response rate to endovascular treatment (16).

LONG-TERM EFFECTS OF ANGIOPLASTY

As described above, both angioplasty and papaverine infusion, although safe procedures, are associated with some immediate risks. The long-term consequences of cerebral angioplasty, unlike coronary angioplasty, are benign. We studied 28 patients an average of 44 months following angioplasty with transcranial Doppler. All patients had normal TCD examinations without evidence of intracranial vessel stenosis or occlusion. When autoregulatory function was assessed in the MCA territories, no difference was found between the previously treated and untreated territories; autoregulation was normal, indicating that no significant cerebrovascular occlusive disease had developed (36). The lower pressure used to dilate cerebral arteries (0.5 atm) compared to coronary arteries (3–4 atm) likely leads to less vessel remodeling and therefore fewer vessel occlusions.

FUTURE STUDIES

Despite advances in endovascular technology, the efficacy of treatment is dependent on appropriate and timely identification of symptomatic vasospasm. Megyesi et al. performed transluminal angioplasty on one internal carotid artery (ICA) in 12 dogs; they then exposed both ICAs to blood clot. Angiography performed after 7 days revealed that the vessels which had undergone angioplasty did not develop vasospasm, whereas the untreated vessels did (37). Thus, angioplasty prevented the development of vasospasm. The safety of prophylactic balloon angioplasty was then evaluated in a pilot study of 13 patients. In this series, Fisher grade 3 patients were treated with angioplasty

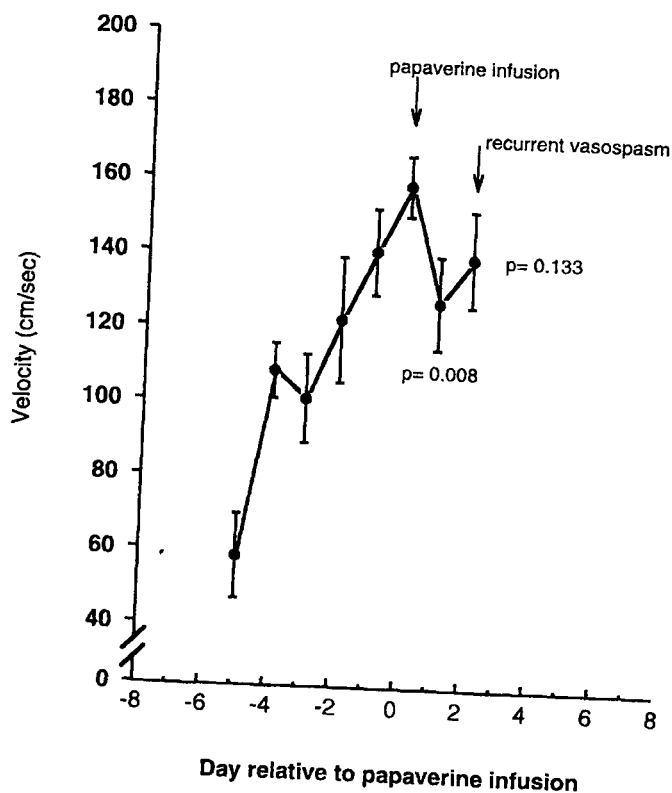


FIG. 14.2 Graph illustrating the results of papaverine infusion as a treatment for distal ICA or MCA velocity in 13 patients. Although there was an initial decrease in velocity following treatment, the velocities failed to reach normal levels and increased again within two days after treatment. From Elliott JP, Newell DW, Lam DJ, et al.: Comparison of balloon angioplasty and papaverine infusion for treatment of vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 88:277-284, 1998, with permission.

within 3 days after bleeding and after securing of the ruptured aneurysm. One patient died secondary to a vessel rupture during angioplasty, but no patient developed a delayed neurologic deficit. Overall, eight patients made a good recovery and two a moderate recovery. The other two deaths were secondary to poor outcomes in grade 4-5 patients. Although TCD velocities did increase in some patients, none of these increases was considered severe. The role of prophylactic angioplasty in high risk patients will be assessed in a randomized, prospective study currently underway (38).

A final consideration is determination of which patients will become symptomatic from vasospasm. Although many patients have angio-

graphic evidence of vasospasm, DINDs are less frequent. Ratsep et al. found that a significant proportion (60%) of patients have perturbed autoregulation following subarachnoid hemorrhage; however, only those who had impaired autoregulation distal to the arterial vasospasm developed ischemic deficits (39). The ability to identify at risk patients early may improve the response to endovascular therapy. It is also possible that prophylactic angioplasty may be useful in this subset of patients.

CONCLUSIONS

Over the past two decades, treatment of vasospasm following subarachnoid hemorrhage has advanced with the advent of calcium channel blockers, HHH therapy, and endovascular treatment. At the current time, balloon angioplasty appears to be the therapy of choice for symptomatic vasospasm, provided it is instituted within 12 hours of development of neurologic decline and before CT appearance of an infarct. Despite the many reports of its efficacy, no prospective trial has been conducted to date. Papaverine has more limited utility for the treatment of distal vessel vasospasm and as an adjunct to balloon angioplasty; however, its effects are frequently transient and multiple treatments may be required. As our understanding of the pathophysiology of vasospasm increases, the effectiveness of this therapy will likely improve.

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