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BACKGROUND AND PURPOSE: **Cerebral vasospasm remains a major problem in patients recovering from aneurysmal subarachnoid hemorrhage despite advances in medical, surgical, and endovascular care. Our purpose was to assess the efficacy of intra-arterial nimodipine, a calcium-channel blocker acting mainly on cerebral vessels, in preventing delayed neurologic deficits in patients with symptomatic vasospasm.**

METHODS: **Clinical charts of 25 consecutively treated patients were retrospectively reviewed. A multifactorial decision tree was used to determine the indication for angiography and subsequent endovascular treatment. Nimodipine was infused intra-arterially via a diagnostic catheter in the internal carotid artery or vertebral artery at a rate of 0.1 mg/min. Angiographic vasospasm before endovascular treatment, immediate vessel caliber modifications, and short- and long-term clinical efficacy of the procedure were assessed.**

RESULTS: **Thirty procedures were performed in 25 patients. Clinical improvement was observed in 19 (76%), 16 of whom improved after the first endovascular procedure, two after the second intra-arterial treatment, and one after the third. Of these 19 patients, only 12 (63%) had notable vascular dilatation at postprocedural angiography. Dilatation of infused vessels occurred in only 13 (43%) of 30 procedures. After follow-up of 3–6 months, 18 (72%) of 25 patients had a favorable outcome (Glasgow outcome scale score of 1–2 and modified Rankin scale score of 0–2). No complications were observed.**

CONCLUSION: **Intra-arterial nimodipine is effective and safe for the treatment of symptomatic vasospasm after subarachnoid hemorrhage. Further prospective randomized studies of cerebral blood flow are needed to confirm these results.**

Cerebral vasospasm is one of the main causes of mortality and morbidity following aneurysmal subarachnoid hemorrhage (SAH) (1). Neurocritical care has been greatly improved over the past decades and the use of both medical and surgical measures has reduced the incidence of clinical deficits in patients recovering from SAH (2). However, poor outcome attributed to secondary ischemia remains a major problem. For this reason, endovascular treatment of refractory cerebral vasospasm has become part of the standard treatment protocol in many neurosurgical centers (3). The most frequently used techniques aim to achieve arterial vessel dilatation by means of mechanical balloon angioplasty, local intra-arterial administration of papaverine, or a combination of the two.

Mechanical angioplasty has demonstrated permanent reversal of vasospasm in treated vessels, but it can be applied to only proximal vessel segments, and it must be performed by experienced interventional neuroradiologists (4, 5). Pharmacologic dilation by means of intra-arterial papaverine has the advantage of also acting on smaller distal branches and diffuse vasospasm. However, its beneficial effects are transient, and repeat treatment sessions are often necessary (6). Moreover, both techniques are frequently associated with considerable risks, and reports have

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From the Departments of Neuroradiology (A.B., G.K.R., J.C.), Anesthesiology (L.P., L.A.) and Neurosurgery (R.V.E.), Pitié-Salpêtrière Hospital–Paris VI University, Paris, France, and the Department of Radiology, University of Messina, Italy (M.L.).

Address reprint requests to Alessandra Biondi, MD, Departement of Neuroradiology, Pitié-Salpêtrière Hospital, Paris VI University, 47/83 Boulevard de l'Hôpital, 75651 Paris, Cedex 13, France.

demonstrated that their superiority to medical management for symptomatic cerebral vasospasm is questionable (7–9). Evidence from a rat model indicates that reperfusion of parenchyma injured by an ischemic insult may lead to further injury (10). This phenomenon could be one of the reasons why the use of angioplasty and intra-arterial papaverine are in some instances associated with unsatisfactory clinical results despite substantial vessel dilatation.

Nimodipine is a calcium antagonist that reduces the influx of calcium in the smooth muscle cell through the blockage of the voltage-operated calcium channels. This may lead to reduced vascular smooth muscle constriction and a decrease in the release of vasoactive substances from endothelium and platelets (11). It has also been hypothesized that nimodipine may have direct neuroprotective properties (10, 12–14). Many previous studies have proved the efficacy of prophylactic oral or intravenous nimodipine in reducing the evidence of cerebral infarction and improving outcomes after SAH (15–18). Results of a study analyzing the effect of clinically relevant doses of nimodipine on cerebral blood flow and mean arterial pressure confirmed the absence of adverse effects and a maintained cerebral blood flow regulation (19).

Another calcium antagonist, verapamil, has recently been demonstrated to be safe when administered intra-arterially for the treatment of cerebral vasospasm; it also has short-term beneficial effects in some patients (20). The administration of nimodipine by the arterial route has previously been reported for the treatment of symptomatic vasospasm only in small groups of patients. No complication following this treatment has been reported (2, 21–23). However, the long-term clinical efficacy of intra-arterial nimodipine has not yet been assessed. On the basis of anecdotal experience concerning the resolution of vasospasm during endovascular procedures, we have used intra-arterial nimodipine for symptomatic cerebral vasospasm due to a ruptured aneurysm for the past 4 years. The purpose of our study was to review the clinical charts of patients treated with intra-arterial nimodipine in our institution over an 18-month period to determine the safety and clinical benefits of this treatment for cerebral vasospasm.

Methods

Patient Population

In our department, all patients admitted for SAH, as confirmed by CT or lumbar puncture, are examined by means of four- or six-vessel angiography or, in rare cases, CT angiography. During the 18 months between July 2000 and January 2002, 181 patients presented with SAH due to a ruptured intracranial aneurysm. Endovascular treatment was performed in 119 aneurysms, and surgical treatment was given in 62. Among the 181 patients, 32 (17.7%) had findings compatible with symptomatic cerebral vasospasm. Therefore, these patients underwent cerebral angiography for intra-arterial nimodipine treatment. Seven patients had no signs of angiographic vasospasm despite clinical or transcranial Doppler (TCD) findings, and endovascular vasospasm treatment was not performed. Twenty-five patients treated with intra-arterial nimodipine for symptomatic aneurysmal cerebral vasospasm were included in the study. We retrospectively reviewed their clinical records, procedural reports, and anesthesiologic charts.

TABLE 1: Patient characteristics

Patient/ Sex/ Age, y	WFNS Grade at Admission	Fischer Score	Location of Aneurysm*	Aneurysm Treatment
1/F/42	II	3	R Pcom	Endovascular
2/M/48	IV	4	L MCA	Surgery
3/M/50	III	3	Acom	Surgery
4/F/48	I	2	L MCA	Surgery
5/F/46	V	4	Acom	Endovascular
6/F/37	V	4	L MCA	Surgery
7/M/55	II	3	L MCA	Endovascular
8/F/38	I	3	L Pcom	Surgery
9/F/47	IV	3	Acom	Surgery
10/M/51	III	2	Acom	Endovascular
11/M/44	I	4	R MCA	Surgery
12/F/51	I	3	BA	Endovascular
13/F/53	II	3	R MCA	Surgery
14/F/46	I	3	R PCA	Endovascular
15/F/43	II	4	Acom	Endovascular
16/F/32	II	4	R Pcom	Endovascular
17/F/34	IV	2	R MCA	Endovascular
18/F/55	II	3	Acom	Surgery
19/M/57	II	3	Acom	Endovascular
20/F/32	IV	3	L Pcom	Endovascular
21/F/39	I	3	AchoA	Surgery
22/F/63	IV	4	Acom	Surgery
23/F/51	I	3	R Pcom	Surgery
24/F/52	I	4	Acom	Surgery
25/F/57	II	3	L MCA	Surgery

* AchoA indicates anterior choroidal artery; Acom, anterior communicating artery complex; BA, basilar artery apex; MCA, middle cerebral artery; PCA, posterior cerebral artery (P1 segment); and Pcom, posterior communicating artery.

In 14 (56%) of 25 patients, the aneurysm was treated by surgical clipping, whereas 11 patients (44%) underwent coil endovascular treatment. Aneurysm treatment was performed within the first 48 hours after hemorrhage in all patients except three who were referred from other institutions. In these three patients, endovascular vasospasm treatment was performed before the aneurysm was treated. In two of these patients, the aneurysm was treated by endovascular occlusion in the same session, and in one patient, it was treated with surgical clipping after the spasm resolved.

Thirty endovascular treatments were performed in 25 patients (19 female, six male) aged 32–63 years (mean, 47 $\pm$ 8 years). Patients experienced symptomatic vasospasm from day 4 through day 15 after SAH (mean number of days after SAH, 7 $\pm$ 3 days).

At admission, the patients' neurologic condition was assessed by using the World Federation of Neurologic Surgeons (WFNS) grading scale. Eight patients (32%) had a grade I condition; eight, grade II (32%); two, grade III (8%); five, grade IV (20%); and two, grade V (8%).

CT scans were evaluated according to the Fisher classification (24), as follows: 14 patients (56%) had group 3 SAH; eight (32%), group 4 SAH; and three (12%), group 2 SAH. Twenty-three aneurysms were located in the anterior circulation, and two were in the posterior circulation. Patient characteristics are summarized in Table 1.

In the neurosurgical intensive care unit, standard medical management included preventive, well-monitored hypertensive, hypervolemic, and hemodilution (triple-H) therapy maxi-

mized to the point of elevating systolic arterial pressure to 150–170 mm Hg. Triple-H therapy was implemented just after surgical or endovascular treatment of the aneurysm. All patients received intravenous nimodipine (Nimotop, Bayer AG, Leverkusen, Germany) with a dose of 2 mg of nimodipine per hour by means of continuous infusion beginning when the diagnosis of aneurysmal SAH was established. This treatment was continued until the 21st day in patients developing vasospasm. The drug was temporarily suspended only if refractory hypotension or hypoxemia developed.

Arterial blood pressure, central venous pressures, intracranial pressure, and cerebral perfusion pressures were measured continuously in patients with grade III or IV conditions via arterial, central venous, Swan-Ganz, and ventricular catheters. TCD study was performed at least once every 2 days through a transtemporal approach for 12–18 days. Mean flow velocities in the supraclinoid internal carotid artery (tICA), middle cerebral arteries (MCAs), and ipsilateral extracranial internal carotid arteries (eICAs) were measured.

Indication for Treatment

Patients were considered eligible for angiography and pharmacologic angioplasty if they showed at least one of the following conditions: 1) altered consciousness or clinical worsening based on Glasgow Coma Scale scores, 2) new motor deficits (monohemiparesis or cranial nerve palsy), 3) speech disturbances (aphasia-dysphasia), 4) Mean flow velocity in the MCA >140 cm/s and/or mean flow velocity in the anterior cerebral artery (ACA) > 120 cm/s with a ratio of MCA- to-eICA mean flow velocities greater than 3 (ie, Lindegaard ratio), or 5) increase in blood velocity above 50 cm/s/day. A body temperature of over 38°C without other explanation or EEG abnormalities suggesting brain ischemia, were also part of the multifactorial decision tree to perform angiography (2). Increased flow velocity suggesting vasospasm, a criterion used to select patients for treatment, was adapted from other publications reporting the correlations between elevation of mean arterial flow velocity and vasospasm (25–27). Another criterion used to select patients for possible treatment was the presence of fever; this was based on the fact that, in SAH, fever is associated with vasospasm and poor outcome independent of hemorrhage severity or presence of infection (28). In addition, fever, which is probably caused by vasospasm, can potentiate vasospasm-mediated brain injury.

When vasospasm was suspected, cerebral CT scanning was first performed to exclude other causes of clinical deficits, such as hydrocephalus or rebleeding. Afterward, the patient underwent diagnostic angiography to confirm vasospasm. If the patient was not under deep sedation and receiving assisted mechanical ventilation because of his or her clinical state, a systemic opioid and local anesthesia were given before obtaining transfemoral arterial access with a 4F, or rarely a 5F, sheath. Intra-arterial nimodipine was administered only in patients with angiographic evidence of spasm in a territory compatible with the neurologic deficit or in those with substantially elevated mean flow velocity, as determined with TCD study.

Fifteen of the 25 patients presented with clinical worsening, based on Glasgow Coma Scale scores, which usually included a decreased level of consciousness and/or disorientation. Four had hemiparesis, two had other motor disturbances, and two had speech disturbances. In two patients, a mean flow velocity above 150 cm/s was the only indication for angiography. All patients with a poor clinical condition at admission—five patients with a grade IV condition and two with a grade V condition based on the WFNS scale—improved within a few days after SAH but subsequently deteriorated because of vasospasm.

In three patients, the selective intra-arterial infusion of nimodipine was performed twice, and in one patient, it was done three times. Their clinical and TCD findings, which were unchanged after endovascular treatment, continued to worsen the following day. Therefore, a total of 30 endovascular procedures were performed.

Velocities of the affected vessels within 24 hours before and after endovascular nimodipine treatment were available in 25 of 30 procedures. In two patients, reliable assessment could not be performed because of poor transtemporal windows. TCD values were the main indication for treatment in two cases and were significantly elevated in 14 of the patients treated.

The mean TCD-measured blood flow velocity in the proximal MCA increased from an admission reference value of 78 ± 12 cm/s to 154 ± 31 cm/s in the 24 hours preceding treatment.

Angiographic Findings and Endovascular Treatment of Vasospasm

Diagnostic angiography and subsequent treatment was performed within 24 hours of the onset of symptomatic vasospasm in all cases and the mean delay time after the occurrence of symptoms was 18 ± 6 hours.

As in previous studies (6, 7, 29), a spasm on pretreatment angiograms was assessed semiquantitatively and subjectively by two neuroradiologists (A.B., G.K.R.). Spasm was graded as mild when arterial narrowing was <25%, moderate when 25–50% constriction was present, and severe when narrowing was >50%. In 23 patients, the initial admission arteriograms, without obvious vasospasm, were used as a reference and were compared with pretreatment and post-treatment angiograms. The initial angiograms in the remaining two patients were not available for review. Both readers separately evaluated all angiograms and then compared their findings. In cases of disagreement, another neuroradiologist, blinded to the findings of both readers, evaluated the angiograms, and disagreements in grading were resolved by consensus.

The degree of vasospasm was severe in 11 cases, moderate in 16, and mild in three. In 10 patients (13 procedures), substantial vasospasm of tICA, MCA, and ACA was found. Vasospasm involved the tICA and MCA in three patients and the tICA and ACA in other three. Vasospasm involved only the ACA in three cases, only the MCA in one case, and both the MCA and ACA in another one. Both the anterior and posterior circulations were diffusely affected in three cases (four procedures), whereas isolated posterior circulation vasospasm was found in one patient (two procedures). Distal vasospasm (arterial branches distal to the circle of Willis) was also present in nine patients (36%).

The internal carotid artery on the side of vasospastic cerebral vessels was the only vessel infused in 21 of 30 procedures (Figs 1 and 2). Nimodipine was injected into both right and left internal carotid arteries in seven procedures, and in three of these, one vertebral artery was also injected because of associated posterior circulation vasospasm (Fig 3). In one patient (two procedures), the left vertebral artery was the only vessel infused (Table 2).

The procedure was performed via a 4F, or in rare cases a 5F, diagnostic catheter placed into the cervical internal carotid artery or the vertebral artery. A dose of 1–3 mg of nimodipine (5–15 mL of Nimotop) per vessel was infused after it was diluted with physiologic saline (15–45 mL) to obtain a 25% dilution. Slow continuous infusion of the solution at a rate of 2 mL/min (0.5 mL/min Nimotop, 0.1 mg/min nimodipine) was achieved by means of an electric pump. Consequently, the intra-arterial administration of nimodipine lasted 10–30 minutes per vessel. The total dose of nimodipine injected intra-arterially for a given patient was maintained within 5 mg and was determined by judging the severity of initial spasm, the degree of vessel dilatation, and the initial systemic blood pressure.

Because of the reported undesirable effects of some vasoactive drugs on systemic blood pressure and intracranial pres-

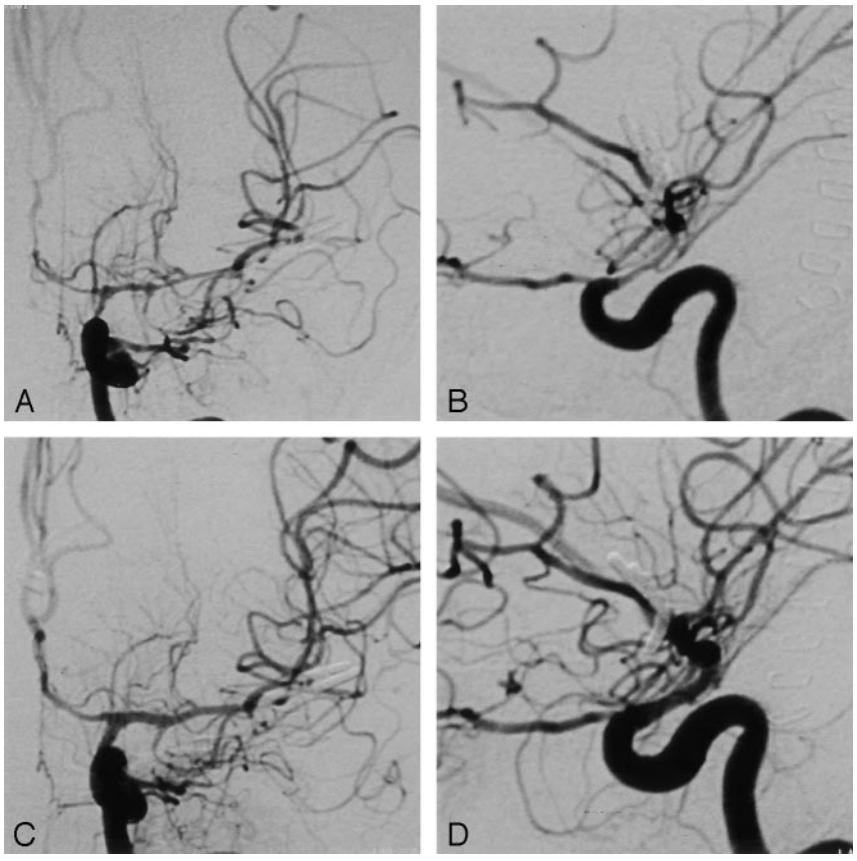

FIG 1. Case 25. This patient presented with a decreased level of consciousness and was treated with intra-arterial nimodipine for symptomatic cerebral vasospasm following SAH.

A and *B*, Anteroposterior (*A*) and lateral (*B*) angiograms of the left internal carotid artery show vasospasm at the level of the carotid siphon, the terminal internal carotid artery, the A1 segment of the ACA, and the MCA.

C and *D*, Anteroposterior (*C*) and lateral (*D*) angiograms obtained after intra-arterial injection of nimodipine 3 mg into the internal carotid artery demonstrate an increased diameter of the vessels. The patient's clinical condition rapidly improved after treatment.

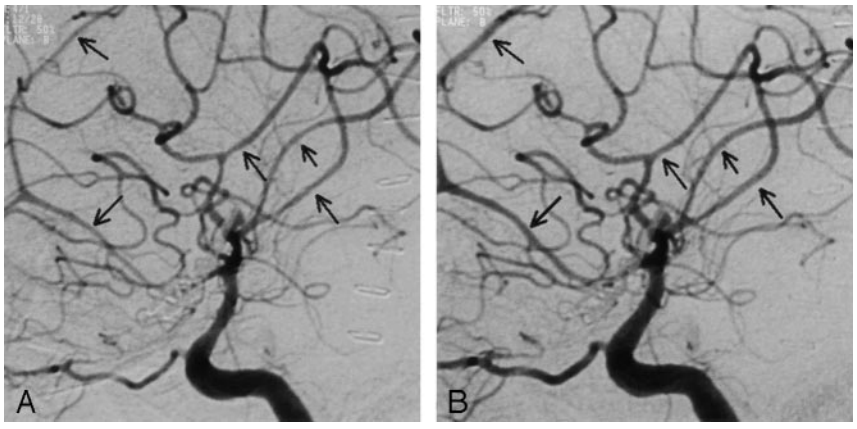

FIG 2. Case 4. This patient with right hemiparesis was treated with intra-arterial nimodipine for symptomatic cerebral vasospasm following SAH. This patient had moderate vasospasm of tICA, ACA and MCA on the left side.

A, Lateral angiogram of the left internal carotid artery shows vasospasm involving also the distal cerebral branches (*arrows*).

B, Lateral angiogram of the left internal carotid artery obtained after the intra-arterial injection of nimodipine 2 mg shows a slight increase in the size of the distal arteries (*arrows*) and the internal carotid system. Despite the poor angiographic results, the patient's condition improved significantly within 12 hours, and no recurrence of symptoms was observed.

sure, routine neurophysiologic monitoring was always performed while the patients were being treated. Arterial blood pressure was continuously monitored to record the maximum systolic blood pressure and the total decrease from the beginning of the procedure. Recording continued for at least 20 minutes after the intra-arterial injection was over. Continuous intravenous infusion of nimodipine was not suspended during the procedure unless the patient's systolic blood pressure dropped below 110 mm Hg or decreased by more than 40 mm Hg. Direct monitoring of intracranial pressure was performed only in those patients who, because of their severe neurologic condition, had a ventricular catheter. In the other patients, indirect signs of increased intracranial pressure (eg, sudden rise in blood pressure, bradycardia, or rapid neurologic deterioration) were monitored instead.

In no case was systemic heparinization or additional sedation necessary to perform the treatment. To assess the angiographic effects of intra-arterially administered nimodipine, angiography was repeated 10 minutes after the end of the injection.

Post-Treatment Angiographic Evaluation

In all cases, two neuroradiologists (A.B., G.K.R.) separately evaluated the angiographic results of nimodipine treatment. The angiographic response was graded as *poor* if there was no improvement or only mild improvement in vessel caliber, *good* if all or most of the treated vessels improved by at least one angiographic grade (eg, severe to moderate or moderate to mild), and *excellent* if vessels with marked spasm improved by two grades or if it normalized. Worsening of vasospasm after the procedure was graded as a *negative* response. As in the pretreatment evaluation, disagreements in grading between the two neuroradiologists were resolved by consensus and included

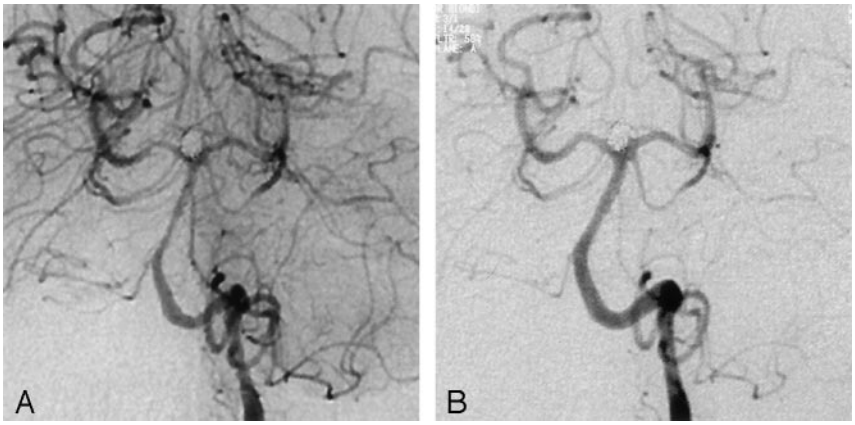

FIG 3. Case 12. Patient presenting with left hemiparesis and diffuse and severe vasospasm. After an intra-arterial injection of 3 mg of nimodipine into both carotid arteries and the basilar artery, angiographic and clinical results were poor. A second session with injection of 5 mg of nimodipine into the same vessels achieved good angiographic results and clinical improvement.

A, This angiogram obtained before the intra-arterial injection of nimodipine shows a moderate vasospasm of the left vertebral artery. (Vasospasm was severe in the other vessels, not shown.)

B, After nimodipine therapy, this left vertebral artery angiogram shows increased size of the basilar artery. Despite these results, the patient later died from cardiopulmonary complications.

an evaluation by another neuroradiologist blinded to the findings of both readers.

Post-Treatment Clinical Evaluation

After the procedure, all patients returned to the neurosurgical intensive care unit, and standard parameters were continuously monitored. Clinical assessments were performed every 3 hours for the first 24 hours. Triple-H therapy was continued after nimodipine intra-arterial infusion. All patients remained in the neurosurgical intensive care unit until they recovered or their clinical and TCD criteria stabilized. They were then transferred to the neurosurgical ward. Clinical follow-up data were obtained from the case notes for each patient on their discharge from the hospital and at the first postdischarge clinical assessment, which was usually 3–6 months later.

The anesthesiologic records of all patients were analyzed for undesired systemic effects due to intra-arterial nimodipine. Clinical improvement, determined within 24 hours after nimodipine therapy, was defined as the disappearance of findings or an improvement in the clinical condition that had led to endovascular treatment. Improvement included an increase in motor power (Substantial improvement was defined as increase of motor power by two grades), improvement in mental status, the possibility of reducing sedative drugs or antiedematous treatments, and a reduction of mean velocities at TCD in those cases in which this was the indication for treatment. Anesthesiologists, who were not blinded to the patient's therapy, performed the neurologic examination. The level of consciousness and the neurologic status were evaluated by using the Glasgow Coma Scale.

The patients were discharged from hospital and then clinically reassessed within 3–6 months by the neurosurgeon or interventional neuroradiologist in charge, whether their aneurysm had been treated surgically or endovascularly. Long-term outcomes were assessed by using the Glasgow Outcome Scale (GOS) (30) and the modified Rankin scale (Oxford Handicap Scale) (31). A favorable outcome consisted of a GOS score indicating good recovery or moderate disability (grades 1 and 2). Unfavorable outcomes were severe disability, a vegetative state, and death (grades 3, 4, and 5). According to the modified Rankin scale, 0 indicated no symptoms; 1, minor symptoms; 2, some restriction in lifestyle; 3, significant restriction in lifestyle; 4, partial dependence; 5, full dependence; and 6, death.

Post-Treatment TCD Evaluation

Assessment of flow velocity in major intracerebral vessels by means of TCD monitoring was performed in all 25 patients as part of our standard management, but complete results were available for review in only 18.

Data Collection and Analysis

We entered all data into a database, taking care to maintain patient anonymity. The results were analyzed by using a commercially available statistical package (InStat version 3; GraphPad Software, Inc, San Diego, CA). Statistical analysis was performed by using paired and unpaired t tests; significance was set at a P value of $<.05$. All data were presented as mean $\pm$ SD.

Results

Angiographic Results

Notable vascular dilatation was observed in 13 (43%) of 30 procedures. The angiographic response, as previously assessed, was excellent in two (7%) and good in 11 (37%) of the 30 endovascular procedures. Angiographic responses were judged as poor in the remaining 17 procedures (57%) (Fig 1–3). Vasospasm never worsened after the selective injection of intra-arterial nimodipine. Systolic blood pressure did not decrease by more than 40 mm Hg during nimodipine infusion (mean -18 ± 11 mm Hg) and was never below 100 mm Hg. Pressure decrease rapidly normalized within a short time (5–10 minutes) after the end of the procedure. In no case did a notable elevation of intra-arterial pressure occur during or immediately after the endovascular treatment.

In five cases, the patient presented with a patent aneurysm (three ruptured and two unruptured). No modifications of the aneurysmal diameter were observed after the vasospasm endovascular treatment. No changes of the intracranial pressure was observed during the treatment in 12 patients who, because of their neurologic condition, had a ventricular catheter. There were no clinically evident complications or deaths that could be linked to the procedure (Table 2).

Clinical Results

Nineteen (76%) of 25 patients had substantial and stable improvement in their clinical condition during the 24 hours following vasospasm treatment with intra-arterial nimodipine. Clinical improvement was observed after the first endovascular procedure in 16 patients, after the second procedure in two patients, and after the third in one patient. Consequently, three of the four patients who had multiple proce-

TABLE 2: Data in 25 patients treated with intra-arterial nimodipine for symptomatic cerebral vasospasm after SAH

Pt/No. of Tx	Indication for Angiography	Days after SAH	Symptom Onset after Spasm, h	Vessel with Spasm	Side	Spasm Severity	Vessel Infused	Nimodipine Dose per Session, mg	SAP Change, mm Hg	Angio-graphic Results	Clinical Results	GOS Score	Modified Rankin Score
1/1	Decreased LOC	6	18	tICA, MCA	R	Moderate	ICA R	1.0	0	Good	Improved	2	2
2/1	Decreased LOC	7	18	tICA, MCA, ACA	L	Severe	ICA L	1.0	−10	Excellent	Improved	1	1
3/1	Decreased LOC	6	24	tICA, MCA, ACA	R/L	Moderate	ICA R/L	3.0	−15	Poor	Unchanged	3	3
4/1	R hemiparesis	7	18	tICA, MCA, ACA	L	Moderate	ICA L	2.0	−10	Poor	Improved	1	0
5/1	L hemiparesis	8	24	ACA	R	Mild	ICA R	1.0	0	Good	Improved	2	2
6/2	L MCA > 200 cm/s	7	6	tICA, MCA, ACA	L	Severe	ICA L	2.0	−20	Poor	Unchanged		
6*	R hemiparesis	9	24	tICA, MCA, ACA	L	Severe	ICA L	3.0	−20	Good	Unchanged*	3	3
7/1	Dysphasia	10	12	MCA	L	Mild	ICA L	3.0	−15	Poor	Improved	1	0
8/1	Disorientation	9	24	tICA, MCA, ACA	L	Severe	ICA L	2.0	−20	Poor	Improved	1	0
9/1	Decreased LOC	5	18	tICA, MCA	L	Moderate	ICA L	1.0	10	Good	Improved	3	3
10/1	R-leg monoparesis	15	18	ACA	L	Mild	ICA L	2.0	−15	Good	Improved	1	0
11/1	Decreased LOC	6	24	tICA, ACA	R	Moderate	ICA R	2.0	−30	Good	Improved	2	2
12/2	L hemiparesis	7	12	Diffuse	R/L	Severe	ICA R/L, VA L	3.0	−20	Poor	Unchanged		
12*	L hemiparesis	8	24	Diffuse	R/L	Severe	ICA R/L, VA L	5.0	−30	Good	Improved*	5	6
13/1	Decreased LOC	4	12	tICA, MCA, ACA	R/L	Moderate	ICA R/L	3.0	−30	Poor	Unchanged	5	6
14/2	Cranial nerve III paresis	11	18	BA, PCA	R	Moderate	VA L	3.0	−20	Poor	Unchanged		
14*	Cranial nerve III paresis	12	24	BA, PCA	R	Moderate	VA L	2.0	−25	Poor	Improved*	1	0
15/1	Dysphasia, temp >38°C	7	12	MCA, ACA	R/L	Moderate	ICA R/L	2.0	−10	Poor	Unchanged	2	2
16/1	Decreased LOC, disorientation	5	12	Diffuse	R/L	Severe	ICA R/L, VA	3.0	−20	Good	Improved	2	2
17/1	Decreased LOC disorientation	10	24	tICA, MCA, ACA	R	Moderate	ICA R	2.0	0	Good	Improved	1	1
18/1	R/L MCA > 190 cm/s	11	18	tICA, MCA, ACA	L	Moderate	ICA L	2.0	−20	Poor	Unchanged	3	3
19/1	Decreased LOC	10	24	Diffuse	R/L	Severe	ICA R/L VA	5.0	−35	Excellent	Improved	2	2
20/3	Decreased LOC	4	12	tICA, MCA, ACA	L	Moderate	ICA L	2.0	−30	Poor	Unchanged		
20*	Decreased LOC, L MCA > 140 cm/s	5	24	tICA, MCA, ACA	L	Moderate	ICA L	3.0	−25	Poor	Unchanged*		
20†	Decreased LOC, L MCA > 160 cm/s	6	48	tICA, MCA, ACA	L	Severe	ICA L	3.0	−40	Poor	Improved†	1	0
21/1	L hemiparesis	8	24	tICA, MCA	R	Moderate	ICA R	3.0	−10	Poor	Improved	2	2
22/1	Decreased LOC	5	12	ACA	R	Severe	ICA R	3.0	−15	Good	Improved	2	2
23/1	Decreased LOC	6	6	tICA, ACA	R	Moderate	ICA R	3.0	−25	Poor	Improved	1	0
24/1	Decreased LOC	10	24	tICA, ACA	L	Moderate	ICA L	2.0	−30	Poor	Unchanged	3	3
25/1	Decreased LOC	5	12	tICA, MCA, ACA	L	Severe	ICA L	3.0	−20	Good	Improved	2	2

Note.—ACA indicates anterior cerebral artery; BA, basilar artery; GOS, Glasgow Outcome Scale (5 indicates death); ICA, internal carotid artery; LOC, level of consciousness; PCA, posterior cerebral artery; SAP, systolic artery pressure; Tx, treatment; and VA, vertebral artery.

* Second treatment.

† Third treatment.

dures improved. Six patients (five of the patients treated only once and one with two treatments) remained clinically unchanged after the procedure.

After follow-up of 3–6 months, 18 patients (72%) had a good GOS score (nine with a score of 1, and nine had a GOS score of 2) and a good modified Rankin scale score (seven patients with a score of 0, two with score of 1, and nine with a score of 2). Five patients had severe disability, while two patients died. One patient (case 18) had a WFNS grade of II at admission and had a poor long-term outcome, with a GOS score of 3 and a modified Rankin scale score of 3; this patient had an impairment of memory and superior functions most likely caused by vasospasm developing after surgical treatment of the aneurysm. There were no cases of vegetative survival.

Among the 19 patients with clinical improvement after nimodipine treatment, 17 (89.5%) had good

long-term outcomes. In the six patients without clinical improvement after treatment, only one patient had a good outcome (16.5%) (Table 2).

Angiographic-Clinical Correlation

Of 19 patients with clinical improvement after nimodipine infusion, only 12 (63%) had notable vascular dilatation on postprocedural angiograms. Seven patients (37%) had no vascular dilatation. Of six patients who remained unchanged after treatment; one had vascular dilatation. Among the 18 patients with good long-term outcomes, 17 (94%) experienced clinical improvement after the procedure (10 with vessel dilatation and seven without vessel dilatation). Only one patient (6%) with no clinical improvement and no angiographic dilatation had a good outcome (Table 2).

TCD Results

After the 30 procedures, mean velocities decreased by at least 20 cm/s in seven cases, changed only slightly after 20, and increased by at least 20 cm/s in three. Velocities decreased to 142 ± 31 cm/s during the 24 hours following selective intra-arterial nimodipine. Flow-velocity modifications were not correlated with either angiographic modifications of vascular caliber or with immediate clinical effects of the treatment.

Discussion

We investigated the clinical effects of intra-arterial nimodipine on ischemic deficits in patients with symptomatic vasospasm after aneurysmal SAH. In many institutions, angioplasty and intra-arterial papaverine, performed either alone or together, are the primary methods of endovascular treatment of vasospasm when maximized medical therapy fails to reverse symptoms (3). The main aim of both techniques is to improve cerebral blood flow by reversing angiographically visible vessel vasospasm.

Angioplasty is widely considered to be the most effective endovascular procedure because of the excellent, and nearly always permanent, angiographically confirmed reversal of vasospasm, which is often followed by high rates of clinical improvement (4). Although the safety of the procedure has greatly increased with greater experience and better technical devices, a potential for severe complications still exists (8). These include vessel rupture, branch occlusion, displacement of surgical clips, and rebleeding of unclipped aneurysms. Moreover, angioplasty is applicable to only proximal, segmental vasospasm in the ICA, the M1 segment of the MCA, and (more rarely) the A1 segment of the ACA. In addition, because angioplasty is technically demanding, it should be performed only in centers with experience in endovascular procedures (32).

Because of fewer technical difficulties, intra-arterial administration of papaverine has long been an attractive approach as the only endovascular treatment. In addition, it is more effective than angioplasty in cases of distal vasospasm. However, to prevent complications during the procedure, current protocols require close monitoring and heparinization of patients. Moreover, many teams intubate their patients and monitor intracranial pressure before the procedure (32, 33). Reported complications include monocular blindness, brain stem dysfunction (including respiratory arrest), transient focal neurologic deficits, and formation of crystal emboli (34, 35). In addition, many studies have demonstrated that papaverine infusion often does not provide permanent reversal of vasospasm, and a rebound effect can occur. Consequently, repeated procedures, which have associated risks with each catheterization, are required (7, 9, 32).

Other treatments, such as the intra-arterial infusion of milrinone (36) and verapamil (20), the intrathecal delivery of nitric-oxide donors, the systemic administration of endothelin receptors antagonists or various inhibitors of phosphodiesterase enzymes, are also under intensive investigation, but their clinical efficacy has not yet been demonstrated (37).

In our department, nimodipine has been used for the last 5 years in the treatment of catheter-induced vasospasm during the endovascular treatment of aneurysms and arteriovenous malformations. Our anecdotal experience has shown that catheter-induced vasospasm resolves rapidly after the local injection of 0.5–1 mg of nimodipine from the guiding catheter. In addition, in difficult vascular procedures, the incidence of vasospasm is greatly reduced when nimodipine was preventively injected intra-arterially as soon as the catheter is placed in the internal carotid artery or vertebral artery. At present, to prevent vasospasm and to make the endovascular procedure easier, we preventively inject 0.5–1 mg of nimodipine from the guiding catheter before and during the treatment of ruptured intracranial aneurysms.

Four years ago, we also started treating postaneurysmal SAH vasospasm with nimodipine and, for the last 2 years, the intra-arterial injection of nimodipine has been the elective endovascular treatment performed in our department in cases of cerebral vasospasm refractory to medical treatment. Balloon angioplasty is more rarely performed and was never used in this series of consecutive 25 patients.

The utility of injecting nimodipine intra-arterially in patients already receiving a continuous intravenous administration of the same drug may be questionable. Nevertheless, the cerebral concentration of nimodipine may be higher when injected locally, and this could allow the persistence of therapeutic drug concentration for longer periods than through the intravenous route. As in the case of intravenous injection, the systemic effects of intra-arterial nimodipine are short-lived, as evidenced by the rapid recovery of decreases in blood pressure experienced by all patients in this study.

Although the efficacy of prophylactic intravenous nimodipine in improving outcomes after SAH and in

reducing the frequency of secondary neurologic deficits has been repeatedly demonstrated (16), the intermediate factors by which nimodipine exerts its beneficial effects remain uncertain. There have been many hypotheses about possible mechanism by which nimodipine exerts its positive effects. The effects may be due to direct neuroprotective properties induced by the blockage of free-radical attack on the intraneuronal mitochondria (11, 12), an improvement of CO_2 reactivity and cerebral oxygen metabolism (13), or a reduction of tissue damage caused by calcium overload at reperfusion (10).

One meta-analysis failed to show a statistically significant reduction in angiographically detected cerebral vasospasm among patients treated with intravenous nimodipine (17); this was confirmed with an in vitro study in which nimodipine failed to promote relaxation in the spastic vascular smooth muscle (38). On the other hand, previous studies have demonstrated that, after nimodipine, the magnitude of vasodilatation in isolated rat arterioles was greater, and the duration of dilation after washout longer in intracerebral penetrating arterioles than in pial arterioles (39). This finding may lead to the hypothesis that, in humans, nimodipine could be more effective in dilating small perforating branches than angiographically visible larger arteries (14). In our study, a significant reduction of angiographic cerebral vasospasm was found only in 13 (52%) of 25 patients (43% of procedures), and this effect was visible in both the proximal and distal vessels (Fig 2). We were not able to assess modifications in parenchymography or cerebral circulation time, which would have required specific data collection. Another aspect to be considered is the utility of intra-arterial nimodipine infusion in patients in whom vasospasm is suspected but not confirmed by angiography. Although seven of 32 patients in our series did not receive intra-arterial nimodipine, the cause of delayed deterioration in these cases was thought to be vasospasm of small vessels; consequently, intra-arterial nimodipine could have been beneficial.

Zygmunt and Delgado-Zygmunt (40) demonstrated, in a small group of patients, that high-dose continuous intravenous nimodipine (4 mg/h) may improve clinical outcomes and promote the angiographic resolution of vasospasm. Roda et al (10) found that a maximized dose of intra-arterially injected nimodipine given just before and during reperfusion reduced the cortical infarct volume in rats subjected to partially reversible focal cerebral ischemia. On the basis of data from previous studies and ours, it could be hypothesized that a supplementary dose of nimodipine injected directly into the territories where vasospasm has developed improves the survival of patients with hypoperfused cerebral parenchyma.

Regarding a possible rebound effect after intra-arterial nimodipine, we did not observe clinical deterioration (due to vasospasm) following an improvement after intra-arterial nimodipine. Consequently, further angiographic study, which could have demonstrated an angiographic rebound effect, was not performed. On the other hand, in some cases we observed no angiographic findings of dilatation after intra-arterial nimodipine, with or without clinical improvement.

In the six patients who remained clinically unchanged after intra-arterial nimodipine administration (only one with vessel dilatation), the treatment was not repeated. Multiple treatments were performed in four patients whose conditions were unchanged after endovascular treatment and who presented with progressive worsening the following day despite the first infusion of nimodipine. The treatment was repeated in an attempt to prevent progressive deterioration.

Because ethyl alcohol is an excipient used by the manufacturer of Nimotop, the presence of a local effect of alcohol must be considered. The alcoholic titer of the drug is of 23.5% V/V (0.185 g of alcohol per milliliter of Nimotop). However, we diluted the mediation in normal saline at 25%; consequently, the dose of ethyl alcohol was 0.046 g/mL of solution. The dose administered to our patients was 0.9–2.7 g per vessel, and the infusion lasted 10–30 minutes. The total dose never exceeded 4.5 g per procedure. These doses are negligible and, with slow infusion of the solution at a rate of 2 mL/min (0.092 g of ethyl alcohol per min), the alcohol did not cause vascular injury. In the treatment of vascular malformations, only a high dose of absolute ethyl alcohol (98%) is reported to be harmful to the vascular endothelium (41).

Our study was limited to some extent: 1) data collection was retrospective; 2) the number of patients was relatively small; 3) no control group was treated concurrently with placebo infusions or other methods. However, only 31 and 38 patients were enrolled in the two multicenter studies of the efficacy of intra-arterial papaverine (7) and angioplasty (8), respectively. The investigators retrospectively evaluated findings in a series of patients who were part of a prospective, multicenter, clinical trial designed for other purposes, not primarily to investigate these treatment methods. The authors pointed out that a long time would be required to gather enough patients at a single institution or a small group of institutions to achieve adequate statistical power.

Another possible problem in our study is that we assessed only the immediate and long-term clinical efficacy of the treatment. Immediate clinical results suggest that intra-arterial nimodipine is effective in the treatment of these patients. Long-term clinical efficacy may be influenced by many factors, so the positive trend toward symptom reversal and good outcome is not sufficient to claim efficacy of treatment. Ideally, cerebral blood flow should be continuously monitored, before and after treatment, in patients recovering from aneurysmal SAH to optimize the timing and indication of the endovascular procedure and to assess the real efficacy of the treatment in preventing cerebral ischemia (9). However, the patients in the present study were monitored with the standard tools currently used at our institution; these tools do

not include the routine assessment of cerebral perfusion.

TCD values were the main indication for treatment in two cases and were significantly elevated in 14 of the patients treated. However, modifications in flow velocity after treatment were not correlated with either the angiographic results or the immediate clinical picture. Different studies have recently highlighted this problem in assessing results of patients treated with papaverine or angioplasty (7, 9, 29). One explanation may be that this technique does not assess tissue microcirculation and, even in presence of indexes aimed at correcting for systemic modifications, it is unpredictably influenced by hyperdynamic treatment strategies. Furthermore, velocity measurements truly reflect flow only if the diameter of the conductance vessels does not change at the same time. Consequently, TCD study is no longer an accurate tool to measure flow if the diameter of the conductance and resistance vessels change concomitantly.

In conclusion, although our data have some limits, results of this retrospective analysis suggest that intra-arterial nimodipine is effective and safe in select cases of vasospasm following aneurysmal SAH. Prospective, randomized studies evaluating cerebral blood flow are needed to confirm these results and to determine whether this therapy is truly cost-effective and superior to intensive medical care.

References

1. Weir B, MacDonald L. **Cerebral vasospasm.** *Clin Neurosurg* 1993; 40:40–55
2. Paoletti C, Dematons C, Bellec C, et al. **Medical management of vasospasm and hemodynamic alterations in the neurosurgical ICU.** In: Connors JI, Wojak J, eds. *Interventional Neuroradiology: Strategies and Practical Techniques.* Philadelphia: WB Saunders Company; 2000; 602–612
3. Song JK, Elliott JP, Eskridge JM. **Neuroradiologic diagnosis and treatment of vasospasm.** *Neuroimaging Clin N Am* 1997;7:819–835
4. Rosenwasser RH, Armonda RA, Thomas JE, Benitez RP, Gannon PM, Harrop J **Therapeutic modalities for the management of cerebral vasospasm: timing of endovascular options.** *Neurosurgery* 1999;44:975–979; discussion 979–980
5. Livingston K, Guterman LR, Hopkins LN. **Intraarterial papaverine as an adjunct to transluminal angioplasty for vasospasm induced by subarachnoid hemorrhage.** *AJNR Am J Neuroradiol* 1993;14: 346–347
6. Numaguchi Y, Zoarski GH, Clouston JE, et al. **Repeat intra-arterial papaverine for recurrent cerebral vasospasm after subarachnoid haemorrhage.** *Neuroradiology* 1997;39:751–759
7. Polin RS, Hansen CA, German P, Chadduck JB, Kassell NF. **Intra-arterially administered papaverine for the treatment of symptomatic cerebral vasospasm.** *Neurosurgery* 1998;42:1256–1264; discussion 1264–1257
8. Polin RS, Coenen VA, Hansen CA, et al. **Efficacy of transluminal angioplasty for the management of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage.** *J Neurosurg* 2000;92:284–290
9. Vajkoczy P, Horn P, Bauhuf C, et al. **Effect of intra-arterial papaverine on regional cerebral blood flow in hemodynamically relevant cerebral vasospasm.** *Stroke* 2001;32:498–505
10. Roda JM, Carceller F, Diez-Tejedor E, Avendano C. **Reduction of infarct size by intra-arterial nimodipine administered at reperfusion in a rat model of partially reversible brain focal ischemia.** *Stroke* 1995;26:1888–1892
11. Pickard JD, Walker V, Vile J, Perry S, Smythe PJ, Hunt R. **Oral nimodipine reduces prostaglandin and thromboxane production by arteries chronically exposed to a periarterial haematoma and the antifibrinolytic agent tranexamic acid.** *J Neurol Neurosurg Psychiatry* 1987;50:727–731
12. Hongo K, Kobayashi S. **Calcium antagonists for the treatment of vasospasm following subarachnoid hemorrhage.** *Neurol Res* 1993; 15:218–224
13. Rasmussen G, Bergholdt B, Dalh B, Sunde N, Cold G, Voldby B. **Effect of nimodipine on cerebral blood flow and cerebrovascular reactivity after subarachnoid hemorrhage.** *Acta Neurologica Scandinavica* 1999;99:182–186
14. Meyer FB. **Calcium antagonists and vasospasm.** *Neurosurg Clin N Am* 1990;1:367–376
15. Pickard JD, Murray GD, Illingworth R, et al. **Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial.** *BMJ* 1989;298: 636–642
16. Barker FG II, Ogilvy CS. **Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a meta-analysis.** *J Neurosurg* 1996;84:405–414
17. Feigin VL, Rinkel GJ, Algra A, Vermeulen M, van Gijn J **Calcium antagonists in patients with aneurysmal subarachnoid hemorrhage: a systematic review.** *Neurology* 1998;50:876–883
18. Ohman J, Servo A, Heiskanen O. **Long-term effects of nimodipine on cerebral infarcts and outcome after aneurysmal subarachnoid hemorrhage and surgery.** *J Neurosurg* 1991;74:8–13
19. Schmidt JF, Waldemar G. **Effect of nimodipine on cerebral blood flow in human volunteers.** *J Cardiovasc Pharmacol* 1990;16:568–571
20. Feng L, Fitzsimmons BF, Young WL, et al. **Intraarterially administered verapamil as adjunct therapy for cerebral vasospasm: safety and 2-year experience.** *AJNR Am J Neuroradiol* 2002;23: 1284–1290
21. Bracard S, Arrue P, Barral FG, et al. **Management of vasospasm from subarachnoid hemorrhage: Attitude of French centers—French Society of Neuroradiology [French].** *J Neuroradiol* 1999;26: S44–S47
22. Grotenhuis JA, Bettag W, Fiebach BJ, Dabir K. **Intracarotid slow bolus injection of nimodipine during angiography for treatment of cerebral vasospasm after SAH: a preliminary report.** *J Neurosurg* 1984;61:231–240
23. Boker DK, Solymosi L, Wassmann H. **Immediate postangiographic intraarterial treatment of cerebral vasospasm after subarachnoid hemorrhage with nimodipine: report on 3 cases.** *Neurochirurgia (Stuttg)* 1985;28:118–120
24. Fisher CM, Kistler JP, Davis JM. **Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning.** *Neurosurgery* 1980;6:1–9
25. Burch CM, Wozniak MA, Sloan MA, et al. **Detection of intracranial internal carotid artery and middle cerebral artery vasospasm following subarachnoid hemorrhage.** *J Neuroimaging* 1996;6:8–15
26. Wozniak MA, Sloan MA, Rothman MI, et al. **Detection of vasospasm by transcranial Doppler sonography: the challenges of the anterior and posterior cerebral arteries.** *J Neuroimaging* 1996;6: 87–93
27. Treggiari-Venzi MM, Suter PM, Romand JA. **Review of medical prevention of vasospasm after aneurysmal subarachnoid hemorrhage: a problem of neurointensive care.** *Neurosurgery* 2001;48: 249–261; discussion 261–242
28. Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. **Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome.** *Neurology* 2001;56:1299–1304
29. Schuknecht B, Fandino J, Yuksel C, Yonekawa Y, Valavanis A. **Endovascular treatment of cerebral vasospasm: assessment of treatment effect by cerebral angiography and transcranial colour Doppler sonography.** *Neuroradiology* 1999;41:453–462
30. Jennett B, Bond M. **Assessment of outcome after severe brain damage.** *Lancet* 1975;1:480–484
31. Lindley R, Waddel F, Livingstone M, et al. **Can simple questions assess outcomes after stroke?** *Cerebrovasc Dis* 1994;4:314–324
32. Elliott JP, Newell DW, Lam DJ, et al. **Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage.** *J Neurosurg* 1998;88:277–284
33. Milburn JM, Moran CJ, Cross DT III, Diringer MN, Pilgram TK, Dacey RG, Jr. **Increase in diameters of vasospastic intracranial arteries by intraarterial papaverine administration.** *J Neurosurg* 1998;88:38–42
34. Mathis JM, Jensen ME, Dion JE. **Technical considerations on intra-arterial papaverine hydrochloride for cerebral vasospasm.** *Neuroradiology* 1997;39:90–98
35. Clouston JE, Numaguchi Y, Zoarski GH, Aldrich EF, Simard JM, Zitnay KM. **Intraarterial papaverine infusion for cerebral vaso-**

spasm after subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 1995;16:27–38
36. Arakawa Y, Kikuta K, Hojo M, Goto Y, Ishii A, Yamagata S. **Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: report of seven cases.** *Neurosurgery* 2001;48:723–728; discussion 728–730
37. Chow M, Dumont AS, Kassell NF. **Endothelin receptor antagonists and cerebral vasospasm: an update.** *Neurosurgery* 2002;51:1333–1342
38. Clark J, Pyne G, Choutka O, et al. **In vitro therapy with dobutamine, isoprenaline and sodium nitroprusside protects vascular smooth muscle metabolism from subarachnoid hemorrhage induced cerebral vasospasm.** *Acta Neurochir (Wien)* 2001;143:721–728
39. Takayasu M, Bassett JE, Dacey RG, Jr. **Effects of calcium antagonists on intracerebral penetrating arterioles in rats.** *J Neurosurg* 1988;69:104–109
40. Zygmunt SC, Delgado-Zygmunt TJ. **The haemodynamic effect of transcranial Doppler-guided high-dose nimodipine treatment in established vasospasm after subarachnoid hemorrhage.** *Acta Neurochir (Wien)* 1995;135:179–185
41. Yakes WF, Krauth L, Ecklund J, et al. **Ethanol endovascular management of brain arteriovenous malformations: initial results.** *Neurosurgery* 1997;40:1145–1152; discussion 1152–1144