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Clinical, Angiographic, and Sonographic Findings After Structured Treatment of Cerebral Vasospasm and Their Relation to Final Outcomes

J. Fandino[1], **B. Schuknecht**[2], **C. Yüksel**[2], **H.-G. Wieser**[3], **A. Valavanis**[2], and **Y. Yonekawa**[1]

[1] Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland
[2] Institute of Neuroradiology, University Hospital Zurich, Zurich, Switzerland
[3] Department of Neurology, University Hospital Zurich, Zurich, Switzerland

Summary

Objective. To report the early clinical results, quantitative angiographic and sonographic findings, and final outcome in patients with symptomatic vasospasm who had undergone surgical occlusion of the aneurysm and a structured protocol including aggressive intensive care management, endovascular procedures (EP), and barbiturate coma (BC).

Results. Thirty consecutive patients (19 women, 11 men, age: 51 ± 8 years) underwent 38 EP for the treatment of 81 vascular territories (15 balloon dilatations and 66 papaverine infusions). Overall angiographic vasospasm in the intradural ICA improved significantly from 44.7 ± 19.8% to 16.5 ± 16%, in the MCA from 44.2 ± 14.7% to 14.4 ± 14%, and in the ACA from 38.7 ± 18.6% to 13.3 ± 12%. Mean flow velocities (Vm) in the MCA and ACA decreased significantly from 135 ± 48 cm/sec to 87 ± 32 cm/sec and from 110 ± 36 cm/sec to 84 ± 30 cm/sec, respectively. No significant Vm improvement in the ICA could be demonstrated. Six patients (20%) developed intractable vasospasm after repeated EP and five patients underwent BC. The correlation coefficient between percentage of angiographic vasospasm and Vm increase was −0.19 ($p = NS$) for the ICA, 0.2 ($p < 0.001$) for the MCA, and 0.3 ($p < 0.05$) for the ACA. Correlation coefficient between percentages of angiographic and sonographic improvement was −0.12 ($p = NS$) for the ICA, 0.42 ($p < 0.001$), and 0.1 ($p < 0.05$) for the ACA. Early clinical improvement after EP was observed in 73% of patients and was significantly associated with favourable outcome (GOS 4–5). Sixteen patients (53%) had a GOS 5, six patients (20%) a GOS 4, six patients (20%) a GOS 3, and two patients (6.6%) died as consequence of devastating vasospasm.

Conclusions. Changes in vessel diameter and increases of Vm during vasospasm correlate weakly. In spite of the fact that significant differences in vessel diameter and Vm were demonstrated after treatment, a moderately good correlation between percentages of angiographic and Vm improvement was observed only in the M1 segments. In our experience, a reduction of mortality and disabilities can be achieved with a maximal structured treatment of vasospasm. Early clinical improvement after endovascular treatment is strongly associated with favourable outcome, nevertheless, cost-benefit and controlled trials are necessary to evaluate these techniques.

Keywords: Intensive care; endovascular therapy; barbiturate coma; cerebral vasospasm.

Introduction

In contemporary series, 15% to 20% who developed delayed ischaemic neurological deficit (DIND) caused by cerebral arterial vasospasm suffered stroke or died despite maximal therapy [22, 25, 26, 34, 38, 63]. At the present, the most common therapeutic tools considered in the treatment of vasospasm include hypertensive hypervolaemic haemodilution (HHH) [4, 34, 56, 62], endovascular procedures such as percutaneous transluminal angioplasty (PTA) [5, 14–16, 26, 39, 76, 83] and intra-arterial papaverine hydrochloride infusion (PPV) [8, 32, 33, 43, 44, 55], calcium-channel antagonists such as nimodipine [64, 83], lipid peroxidation inhibitors [23, 36], and barbiturates [3, 18]. These treatment modalities remain controversial [13, 58, 59] and have not all been subjected to controlled clinical trials. Recent studies, nevertheless, have reported improvements in cerebral oxygenation, cerebral blood flow (CBF) and metabolic patterns. [17, 18, 19, 42, 56]. In addition, improvements in angiographic vasospasm and mean flow velocities (Vm) measured by transcranial Doppler sonography (TCD) after PTA or PPV infusion have been observed to the order of 50 to 80% [8, 13, 26, 33, 49, 52, 55].

Most of the published studies have focused on the evaluation of one specific therapeutic modality. We believe that assessing the treatment of vasospasm should primarily include clinical features and that each therapy must not be evaluated separately nor exclude other therapeutic steps, which are almost always complementary. In this report we summarized our experience in the management of symptomatic vasospasm

using a structured and multidisciplinary management protocol including aggressive intensive care management, PTA, PPV infusion, and barbiturate therapy. In addition, early clinical results, quantitative angiographic and sonographic findings, and final outcome are discussed.

Patients and Methods

Patient Population

A total of 30 consecutive patients with symptomatic vasospasm after aneurysm rupture were included in this study. Table 1 provides a summary of the clinical data. The patient population included 19 women (63%) and 11 men (37%), ranging in age from 30 to 74 years (mean 51 $\pm$ 8). The initial neurological condition was assessed according to the grading scales of Hunt and Hess [30] and of the World Federation of Neurological Surgeons [11]. Fifteen patients (50%) were assigned a Hunt and Hess grade II, eight (26%) a grade III and five (16%) a grade IV. Computed tomography scans were classified according to Fisher *et al.* [20]. Thirteen patients (43.3%) were classified as SAH grade 3 and ten (33.3%) as grade 4. Most of the aneurysms were located in the anterior circulation (93.3%). Two patients (27 and 28) had aneurysms located in the posterior circulation. In Patient 29 fibromuscular dysplasia was diagnosed. All patients underwent surgical treatment of the ruptured aneurysm within the first 48 hours after admission using Yasargil® clips (Aesculap, Tuttlingen, Germany). Minimal removal of subarachnoid clot was intended intra-operatively [82]. Final outcome was assessed three months after SAH according to the Glasgow Outcome score (GOS) [31].

Intensive Care Monitoring and Medical Treatment of Vasospasm

All patients were admitted and treated in our neurosurgical intensive care unit until they exhibited signs of clinical recovery and improvement of TCD vasospasm signs. If rapid deterioration of the level of consciousness was evident (GCS < 8), the patient was sedated, paralysed, and mechanically ventilated. Haemodynamic monitoring included an arterial line and a Swan-Ganz catheter for measuring the central venous pressure (CVP), pulmonary artery wedge pressure (PCWP), pulmonary artery pressure (PAP), cardiac output (CO), stroke volume index (SVI), systemic (SVR), and pulmonary vascular resistance (PVR). CO was determined by the thermodilution technique. CO, SVR, PVR were indexed with the body surface area calculated in square meters. Mixed venous oxygen saturation ($S\bar{v}O_2$), arteriovenous oxygen difference ($avDO_2$), oxygen delivery, and oxygen consumption were measured using fiberoptic technology or blood sampling from the pulmonary artery (PA). Hypovolaemia was avoided during the early postoperative days based on CVP measurements. As soon as symptomatic vasospasm was evident, and before any endovascular procedures were undertaken, HHH-therapy [34, 56] was initiated, maintaining a PCWP between 14 and 16 mmHg. Haematocrit level was held constant between 30% and 32%. Cathecolamine support (dobutamine, norepinephrine, and dopamine) was added to the therapy in order to induce hypertension, raising the systolic blood pressure up to 160 to 200 mm Hg, and to maintain a cardiac index (CI) higher than 3 L/min/m^2. Haemodynamic parameters and measurements were documented in a "haemodynamic data-sheet" every eight hours. Arterial blood gases were analysed every six hours or within shorter intervals when necessary. Pulse oxymetry was continuously monitored. Hypervolaemic therapy was maintained mainly with colloids and 5% albumin. If the urine output was extremely high (greater than 200 ml/h), the diuresis was suppressed with intravenous boluses of vasopressin (DDAVP). Nimodipine was administrated intravenously (2 mg/hour) in all patients during the first week and orally during the second and third week after SAH. All patients received phenytoin, dexamethasone, and low-weighted heparin postoperatively as prophylaxis for deep venous thrombosis and pulmonary embolism. Ten patients received tiralazad mesylate intravenously as part of a controlled study [36]. In 8 out of 30 patients (26.6%), either ventriculostomy or an open-ended catheter placed in the subdural space allowed intracranial pressure (ICP) monitoring. In these cases, cerebral perfusion pressure (CPP) of over 70 mm Hg was maintained.

Endovascular Treatment of Vasospasm

Indications for PPV infusion and PTA included: 1) onset of ischaemic neurological deficit not attributable to other causes, 2) neurological deficit not successfully treated with the conventional medical and pharmacological therapies, 3) mean flow velocity in the affected vessel greater than 100 cm/sec or an increase in Vm greater than 30 cm/sec within 24 hours, 4) no evidence of infarction in the CT scan, and 5) correlation between the spastic vessel seen on angiography and the neurological deficit. As required for endovascular treatment modalities, we insured a well-monitored HHH-therapy as mentioned above.

All endovascular procedures were performed via the transfemoral approach without heparinization, under general anaesthesia or neuroleptic analgesia, and according to the technique described elsewhere [5, 14, 15, 26, 32, 33, 43, 44, 76, 77, 83, 84]. Balloon dilatation with a silicone microballoon (diameter: 1.5–2.5 mm, Target Therapeutics Inc., Fremont, CA) was performed as a first step only if proximal vessel narrowing was observed in the C1/2 segments of the ICA and/or M1 portion of the MCA. Otherwise papaverine alone was infused superselectively through a Tracker-18 catheter which was advanced coaxially close to the spastic vessels. PPV was diluted with normal saline to a concentration of 0.3% and a total dose of 300 mg/100 ml to 360 mg/120 ml was infused supraselectively at a rate of 0.1 ml/sec (20 minutes in each vascular territory), under monitoring by digital subtraction angiography (DSA). Infusion of PPV was continued until the vessels were dilated to nearly normal caliber size. Early clinical results were assessed in the intensive care unit within a 6-hour period after the procedure when sedation and relaxation was discontinued.

Intractability Criteria and Protocol for Barbiturate Coma

The following criteria were considered to define medical intractability of vasospasm: 1) persisting or recurring clinical signs of vasospasm (decreased level of consciousness with focal neurological deficit); 2) persisting or recurring of mean flow velocity in the middle cerebral artery (Vm MCA) higher than 100 cm/s with pulsatility indices (PI) greater than 1 and a MCA/ICA index more than 3; 3) sustained and well-monitored HHH-therapy throughout the intensive care management and, 4) the need for the patient to have undergone at least two endovascular treatment sessions (balloon angioplasty with or without intra-arterial PPV infusion) within a 48-hours period.

According to an ongoing study [18], a subgroup of patients with *intractable vasospasm* who were included in this series underwent barbiturate coma (BC), unless a contraindication was identified (acute heart failure, myocardial infarction six months prior to SAH, or fever of unknown origin and uncontrolled infectious conditions). Prior to the initiation of BC, the patients were orally intubated, mechanically ventilated, and kept under sedation until suppression of cortical activity was recorded on EEG. In addition, a baseline

Table 1. *Summary of Demographic Characteristics, Endovascular Procedures, Early Results, and Final Outcome*

Patient	Sex/ age	Aneurysm location	H & H grading	Fisher's CT group	WFNS classifi-cation	Days to vaso-spasm	Balloon angioplasty	PPV	Neurological deficit	Early results	Final GOS	Comments
1	m/57	AcomA	II	2	2	11.13	–	++	DLC	improved	4	–
2	m/42	lt MCA	II	2	1	7	–	+	DLC	improved	5	transient lt arm paresis
3	m/43	AcomA	II	3	2	10	–	+	rt hemiparesis	improved	4	–
4	f/74	lt PcomA	II	4	2	12	–	+	DLC, lt arm paresis	improved	5	–
5	f/52	rt ICA	II	2	2	2	–	+	DLC, rt hemiparesis, aphasia	improved	3	–
6	m/42	rt PcomA	I	2	1	5, 7	–	++	DLC	improved	5	–
7	m/29	AcomA	IV	4	5	5, 7	rt C1/2, rt M1 (++)	+	DLC, rt hemiparesis	improved*	1	–
8	m/33	AcomA	III	4	3	5	–	+	DLC	improved	5	–
9	f/55	AcomA	IV	4	4	6	–	+	comatose	unchanged	3	rt ACA infarction
10	f/48	lt ACA	II	2	2	6	–	+	DLC, dysphasia	improved	4	–
11	f/68	rt ICA	III	3	4	4, 6, 8	–	+++	DLC	unchanged	5	BC
12	m/65	lt MCA	IV	4	4	5	lt C1/2	+	DLC, aphasia, hemiplegia	comatose	1	–
13	f/49	rt PcomA	II	2	2	10	–	+	DLC	improved	5	–
14	f/48	AcomA	II	3	2	4	lt C1/2	+	DLC, rt arm plegia	improved	5	BC
15	f/45	lt MCA	II	3	2	9	lt C1/2	+	DLC, rt hemiparesis, aphasia	improved	5	BC
16	f/47	rt MCA	III	3	2	10	–	+	DLC, lt hemiplegia	unchanged	3	rt MCA infarction
17	m/69	PcomA	III	3	3	6, 7	lt C1, lt M1	–	DLC	improved	5	–
18	f/65	AcomA	IV	4	5	12	–	+	DLC, rt hemiparesis	improved	5	–
19	m/48	AcomA	II	3	2	10	rt M1	+	DLC	unchanged	4	BC
20	f/55	rt PcomA	II	3	2	9	rt M1	–	DLC	improved	4	–
21	f/42	AcomA	IV	4	5	4,7	lt C1/2, lt M1 (++)	+	DLC	unchanged	3	BC, multiple infarctions
22	f/46	AcomA	II	4	1	5	lt C1/2, lt M1	+	DLC	improved	5	–
23	f/50	AcomA	III	3	4	9	–	+	DLC	improved	5	–
24	f/30	lt OphA	II	3	3	10	–	+	DLC	improved	5	–
25	f/64	rt MCA	III	3	4	6	–	+	DLC	improved	5	–
26	f/58	lt MCA	III	3	2	7	lt M1	+	aphasia	improved	5	–
27	m/55	rt SCA	II	2	2	8	–	+	DLC, lt hemiparesis	unchanged	3	rt MCA infarction
28	m/70	BA tip	II	3	2	7	–	+	DLC, lt hemiparesis	improved	3	–
29	f/49	rt MCA	IV	4	5	6, 10, 14	–	+++	DLC, lt hemiparesis	improved	5	FMD
30	f/57	AcomA	III	4	4	4	lt M1	–	DLC, rt hemiparesis	improved	4	–

rt Right; *lt* left; *m* male; *f* female; *H&H* Hunt and Hess grading [30]; *WFNS* World Federation of Neurological Surgeons's classification for subarachnoid haemorrhage [11]; *PPV* papaverine; *GOS* Glasgow outcome scale [31]; *BC* barbiturate coma; *DLC* decreased level of consciousness; *FMD* fibromuscular dysplasia; *ICA* internal carotid artery; *AcomA* anterior communicating artery; *MCA* middle cerebral artery; *ACA* anterior cerebral artery; *M1* 1st segment of the MCA; *PcomA* posterior communicating artery; *OphA* ophthalmic artery; * only initial improvement; endovascular procedures (PTA or PPV infusion): + one session, ++ two sessions, +++ three sessions.

EEG was registered and responsiveness to exteroceptive painful and acoustic stimuli was assessed. BC was induced by giving a bolus of sodium thiopental (Pentothal®) of 5–11 mg/kg body weight, followed by a continuous infusion of 4–6 mg/kg/h to maintain a burst-suppression pattern of 4–6 burst/min. Efforts were made to maintain PCWP between 12–16 mm Hg and CI greater than 3 L/min/m^2 throughout the treatment by means of volume expansion and cardiovascular pressor agents such as dopamine, dobutamine, and norepinephrine. During BC, continuous EEG monitoring was performed using a bedside 12-channel computerized EEG apparatus (Nicolet Instrument Corporation, Madison, WI). The dose of the continuous infusion of thiopental was based on EEG findings. Serum levels of thiopental were not measured routinely. BC was maintained for four to five days in all patients. After this period, thiopental was abruptly stopped and EEG monitoring was maintained during the following 12 to 48 hours.

Angiographic and Sonographic Evaluation

It is our policy to perform on day 7 after SAH postoperative angiograms in all patients treated surgically in our department. In the presence of clinical or TCD signs of vasospasm, a diagnostic angiogram was indicated and focused on the territory or territories corresponding to the clinical findings. Bilateral angiography was performed only in patients without focal neurological deficits or if high flow velocities indicated vasospasm in the contralateral vessels. In order to evaluate effectively the percentages of vasospasm severity and improvement of vessel narrowing after the treatment, angiograms were evaluated retrospectively by a neuroradiologist who was unaware of the clinical and TCD findings. The vessel diameters of the C1/2, M1, and A1 portions were measured in millimeters on the admission angiograms and in the angiograms before and after endovascular procedures. In order to be able to compare the vessel diameters, a magnification correction factor was calculated, comparing the diameter of the C4/C5 segment of the ICA in each angiogram, and taking into consideration that extradural carotid portions are not significantly affected during vasospasm. The resulting magnification factor was used to correct changes in the diameter of the C1/2, M1 and A1 segments unrelated to the development of vasospasm. *Percentage of angiographic vasospasm* was calculated by comparing the vessel diameter in the initial angiogram performed on admission with the diameter measured prior to the endovascular procedure. *Percentage of angiographic improvement of vasospasm* was calculated by comparing the diameter of the affected and treated vessel before and after the endovascular procedure.

Flow velocities were measured by TCD, using a 2 MHz sector probe with a colour Doppler device (Acuson, Mountain View, CA). The examination was performed through the transtemporal window by the same investigator (B.S.). The TCD parameters revealed the time-averaged Vm of the affected vessel at high-pulse repetition frequencies which were obtained at different depths, typically at the point of colour wrap-around (aliasing), on the colour flow image. The angle of insonation was orientated based on the colour flow image. The baseline TCD values were obtained within the first 24 hours after the diagnostic angiogram. Daily TCD follow-up was performed throughout the intensive care management. Flow velocities were measured before and after the endovascular procedures. *Percentage of sonographic vasospasm* was calculated by comparing the Vm in the baseline evaluation with the values obtained prior to the endovascular procedure. *Percentage of sonographic improvement of vasospasm* was calculated by comparing the Vm of the affected vessel before and after the endovascular procedure. Angiographic and sonographic findings during vasospasm and after the treatment were then correlated.

Statistical Methods

Summary data are reported as the mean $\pm$ standard deviation. Student's t-test was used to compare group means. The Fisher exact test was used to analyse association between clinical findings after endovascular therapy and final outcome. The level used to determine statistical significance was 0.05. The Pearson correlation coefficients between angiographic and sonographic findings were illustrated in scatterlot graphs with linear regressions. The circles, boxes, and whisker plots in Figs. 1, 2, and 3 represent respectively mean, standard deviation, and range values.

Results

Early Clinical Results and Final Outcome

The interval from SAH to development of vasospasm signs was 7 $\pm$ 2.6 days and ranged between day 4 and 14. Fourteen patients (47%) presented as the only clinical sign a decreased level of consciousness (DLC). In addition to this, 16 patients (53%) presented focal neurological deficits such as hemiparesis, arm paresis, hemiplegia or aphasia (Table 1). A total of 38 endovascular procedures or "sessions" were performed in 30 patients. Eighty-one vessels (12 intradural ICA-segments, 42 M1-segments, and 27 A1-segments) were treated with PPV infusion and/or PTA under aggressive HHH-therapy. PTA was performed in 15 vessels in 11 patients and PPV was infused in 66 vessels in 27 patients. A total of eight patients (26%) underwent PTA and PPV infusion in the same treatment session, and three patients (Patients 16, 19, and 30) underwent PTA without PPV, as vasospasm compromised M1 segments but not peripheral vessels. Vasospasm occurred ipsilateral to the rupture of the aneurysm in 46 out of 58 vessels (79.3%). Vasospasm contralateral to the ruptured aneurysm was recognized in 20.7% of the vessels. Six patients (20%) of this series developed intractable vasospasm according to our criteria (Patients 1, 6, 7, 11, 21, and 29) and five of them were treated with BC (Table 1). The recurrence of vasospasm was more common in the A1 segments treated only with PPV (4 patients, 19 segments) than in the M1 segments treated with PTA and/or PPV (4 patients, 24 segments). Only in one patient was vasospasm recurrence seen in the supraclinoid ICA after PTA. Four patients underwent two or three PPV-infusion sessions and two patients underwent two PTA procedures in the M1 segment.

A total of 22 patients (73.3%) improved from their clinical deficits after EP under aggressive HHH-therapy. One patient (3.3%) required re-intervention

Table 2. *Clinical Outcome According to Early Clinical Improvement After Endovascular Procedures*

Outcome[1] (GOS)	Early improvement no. patients (%)	No improvement no. patients (%)
Favourable	20 (90.9%)	2 (25%)
GR	15	1
MD	5	1
Poor	2 (9.1%)	6 (75%)
SD	2	4
VS	–	–
D	–	2
Total	22 (100%)	8 (100%)

GOS Glasgow outcome scale [31]; *GR* good recovery; *MD* moderately disabled; *SD* severely disabled; *VS* vegetative state; *D* death.
[1] The association between outcome groups and clinical findings was statistically significant ($p = 0.0011$, Fisher exact test).

after transient improvement (Patient 7), six patients (20%) remained clinically unchanged, and one (3.3%) became comatose after the procedure (CPP deterioration). In four patients who remained clinically unchanged, a transient elevation of ICP was demonstrated during the first two hours following the procedure. As shown in Table 2, a strong association was demonstrated between clinical improvement and final outcome ($p = 0.0011$). Twenty patients (90.9%) who improved clinically after EP had favourable outcomes (GOS 4–5). In contrast, six patients (75%) who did not improve after EP had poor outcomes (GOS 1–3). In addition, mortality was observed only among patients who did not show early clinical improvement.

The only complication in this series was observed in Patient 2, who developed a transient left arm paresis after PPV infusion. The mean overall GOS of this series was 4 ± 1.2. Sixteen patients (53.3%) could resume their previous job and daily activities (GOS 5). Six patients (20%) were able to live independently and partially resume their previous life activities (GOS 4). Six patients (20%) were severely disabled three months after SAH (GOS 3). No patient remained in a vegetative state (GOS 2) and two patients (6.6%) died as a consequence of devastating vasospasm. The patients who died both presented with a Hunt and Hess grade IV and were classified with a Fisher's grade 4. The 3-month follow-up CT scans showed ischaemic lesions as a consequence of vasospasm in four patients (13.3%): three patients presented infarctions involving only one vascular territory and in one patient multiple infarctions could be demonstrated (Patient 21). Finally, the outcome in patients who received BC

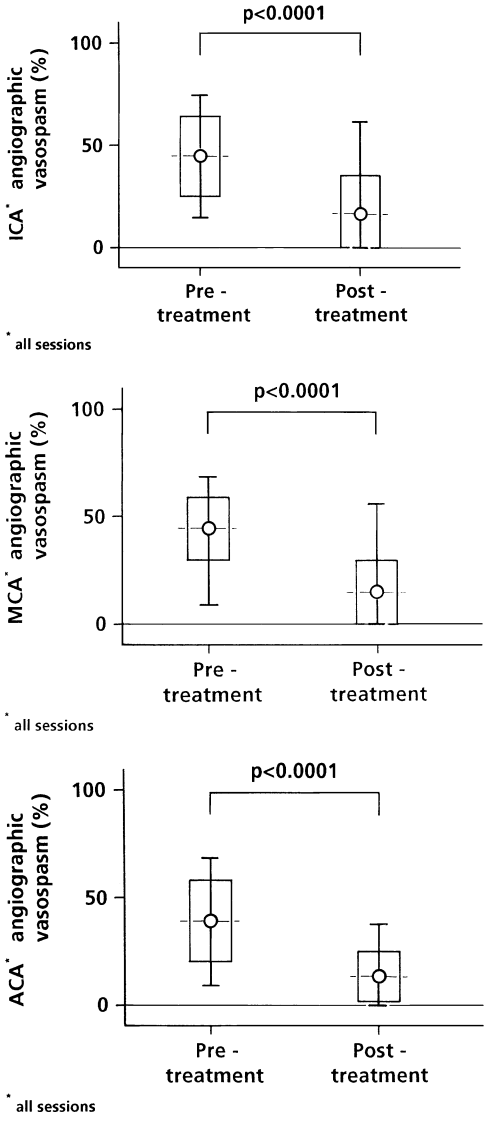

Fig. 1. Overall percentage of angiographic vasospasm before and after endovascular treatment under HHH-therapy in 30 patients who underwent one or more sessions of endovascular procedures (*circle* mean, *box* mean $\pm$ 1.00 standard deviation, *whisker plot* range). *ICA* Internal cerebral artery; *MCA* middle cerebral artery; *ACA* anterior cerebral artery

included three patients with GOS 5, one with GOS 4, and one patient moderately disabled (GOS 3). A detailed analysis of this subgroup of patients is the objective of another study and will be reported in the near future.

Quantification of Angiographic Findings

Figure 1 shows the overall percentage of angiographic vasospasm before and after all endovascular procedures or "sessions" (PTA and/or PPV) under

HHH-therapy. The graphs include the 12 intradural ICA in 10 patients, 42 MCA (M1) in 26 patients, and 27 ACA (A1) segments in 17 patients. The percentage of angiographic vasospasm or caliber reduction in the intradural ICA was 44.7 ± 19.8% (range: 15–75%). In the M1, it was 44.2 ± 14.7% (range: 9–69%), and in the A1 segments it was 38.7 ± 18.6% (range 9–69%). After the endovascular procedures under HHH-therapy (Figure 1), the diameter reduction in the ICA was 16.5 ± 16% ($p < 0.0001$), in the M1 segments the diameter was 14.4 ± 14% ($p < 0.001$), and in the A1 segments it was 13.3 ± 12% ($p < 0.0001$). The overall mean angiographic improvement of caliber in the ICA was 83.5 ± 18.5% (range: 63–100%), in the M1 it was 85.9 ± 15% (range: 44–100%), and in the A1 it was 86.7 ± 12.1% (range: 62–100%). A total of 28 out of 81 vessels (34.5%) treated returned to their original calibers (100% improvement). In addition, a total of 44 vessels (49.4%) had a caliber improvement of 90% or greater in the post-treatment angiograms.

The analysis of angiographic findings from 10 M1 segments (6 patients) and 7 A1 segments (4 patients) which were treated two or three times at different sessions under HHH-therapy and additional BC (five patients) is illustrated in Figure 2. After the second or third session, the 10 M1 segments which were treated showed an improvement of caliber reduction from 43.2 ± 14.7% to 10.5 ± 9.9%, implying a significant improvement of angiographic vasospasm of 89.5 ± 9.9% ($p < 0.005$). The caliber reduction in the A1 segments improved from 47.3 ± 17% to 14.7 ± 11% after repeated endovascular treatment, which implies an improvement of 85.3 ± 11% ($p < 0.005$). Percentages of vasospasm in this subgroup of vessels were similar to the percentage of vasospasm seen in the vessel treated in a first session (ICA: 42.7 ± 20.4%, M1: 44.9 ± 13.9%, and A1: 36 ± 18.6%).

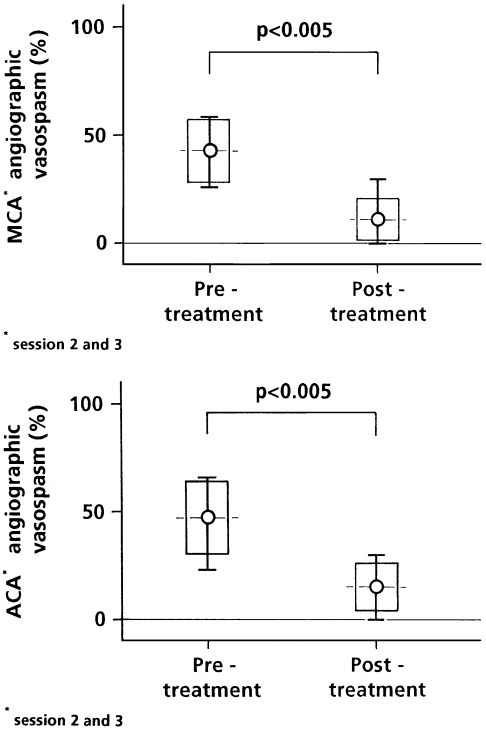

Fig. 2. Percentage of angiographic vasospasm before and after endovascular treatment under HHH-therapy in six patients who underwent two or three sessions of endovascular procedures (*circle* mean, *box* mean ± 1.00 standard deviation, *whisker plot* range). *MCA* Middle cerebral artery; *ACA* anterior cerebral artery

Quantification of Sonographic Findings

Figure 3 illustrates the sonographic findings during vasospasm and after the endovascular procedures in terms of Vm increases (cm/sec) or "sonographic vasospasm" measured in the intradural ICA, M1, and A1. The initial Vm in the intradural ICA portions (C1–C2) increased from 73 ± 12.2 cm/sec (range: 60–88) to 112 ± 41 cm/sec (range: 66–211). After all sessions, the Vm ICA dropped to 83 ± 30 cm/sec (range: 51–151); nevertheless, the observed 73.8 ± 22.7% improvement of Vm ICA was not statistically significant ($p = 0.06$). In the M1 segments, the range of Vm was greater than in the ICA and A1 portions (Figure 3). The baseline Vm MCA on admission was 64 ± 14 cm/sec (range 44–90) and increased significantly to 135 ± 48 cm/sec (range 73–287) during vasospasm (118.9 ± 91.4%). After endovascular procedures under HHH-therapy, these values decreased significantly to 87 ± 32 cm/sec (range: 33–171). Finally, the Vm in the A1 segments increased from 61 ± 21 cm/sec (range 28–93) to 110 ± 37 cm/sec during vasospasm and decreased significantly to 84 ± 30 cm/sec, showing an improvement of 61.3 ± 20.3% ($p < 0.005$).

Correlations between Angiographic and Sonographic Findings

The percentages of angiographic vasospasm related to increases in flow velocities are presented in Table 3. Low correlation between angiographic and sonographic vasospasm in the ICA ($r = -0.19, p = \text{NS}$), M1 segments ($r = 0.2, p < 0.05$), and A1 segments ($r = 0.3, p < 0.05$) were demonstrated. Figure 4 shows

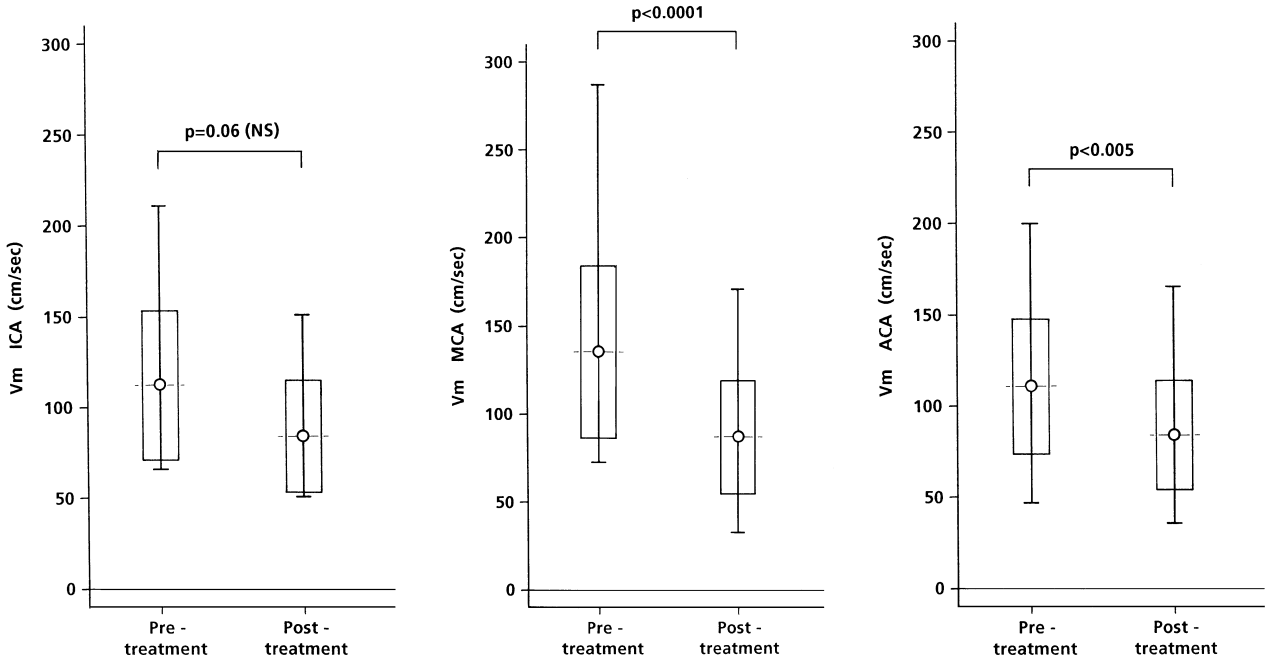

Fig. 3. Overall percentage of sonographic vasospasm in terms of mean flow velocity changes before and after endovascular treatment under HHH-therapy in 30 patients who underwent one or more sessions of endovascular procedures (*circle* mean, *box* mean ± 1.00 standard deviation, *whisker plot* range). *Vm* Mean flow velocity; *ICA* internal cerebral artery; *MCA* middle cerebral artery; *ACA* anterior cerebral artery

Table 3. *Correlation of Angiographic Vasospasm and Vm Increases During Vasospasm**

Artery	No. of vessels treated	Angiographic vasospasm (%)	Vm increase (%)	Correlation coefficient	p-value
ICA	12	44.7 ± 19.8	49.1 ± 34.6	−0.19	NS
MCA	42	42.2 ± 14.7	118.9 ± 91.4	0.2	$p < 0.001$
ACA[1]	27	38.7 ± 18.6	147.7 ± 170.5	0.3	$p < 0.05$

* Including all sessions; *Vm* mean velocity.
[1] Only PPV infusion.

in scatterplot graphs the correlation between the percentage of angiographic vasospasm in the M1 and A1 segments and the percentage of Vm increases.

The Pearson correlation coefficient between angiographic and sonographic improvement was moderately good for the M1 segments and weak for the ICA and A1 segments (Table 4). In addition, no statistically significant differences between angiographic and sonographic improvement in the intradural segments of the ICA could be demonstrated. Figure 5 shows scatterplot graphs for the correlation of angiographic and sonographic improvement percentages in 42 treated M1 segments ($r = 0.42, p < 0.001$) and 26 A1 segments ($r = 0.1, p < 0.05$).

Discussion

Structured Treatment of Vasospasm

The aim of this study was the evaluation of clinical, angiographic and sonographic results in patients undergoing a structured treatment protocol including all available modern therapeutic tools for the treatment of cerebral vasospasm. We attempted, therefore, to report the results in patients undergoing a maximal therapy schema rather than evaluate each therapeutic modality *per se*. Considering the technical difficulties and lack of prospective, controlled studies evaluating emerging treatment and techniques in the management

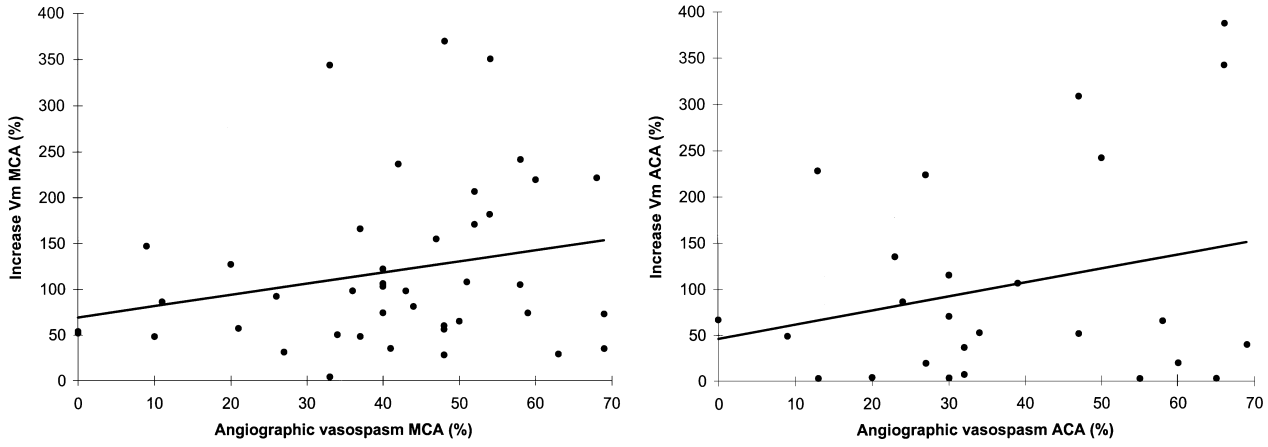

Fig. 4. Linear regressions showing correlations between the percentage of increases of flow velocities during vasospasm and the percentage of angiographic vasospasm (MCA: n: 26, number of vessels treated (M1): 42, $r = 0.2, p < 0.001$; ACA: n: 17, number of vessels treated (A1): 26, $r = -0.3, p < 0.05$) *Vm* mean flow velocity; *MCA* middle cerebral artery; *ACA* anterior cerebral artery

Table 4. *Correlation of Angiographic and Sonographic Improvement After Endovascular Treatment**

Artery	No. of vessels treated	Angiographic improvement (%)	Sonographic improvement (%)[1]	Correlation coefficient	p-value
ICA	12	83.5 ± 18.5	73.8 ± 22.7	−0.12	NS
MCA	42	85.9 ± 15	37.9 ± 21.5	0.42	$p < 0.001$
ACA[2]	27	86.7 ± 12.1	61.3 ± 20.3	0.1	$p < 0.05$

* Including all sessions.
[1] In terms of percentage of mean flow velocity (Vm) reduction.
[2] Only PPV infusion.

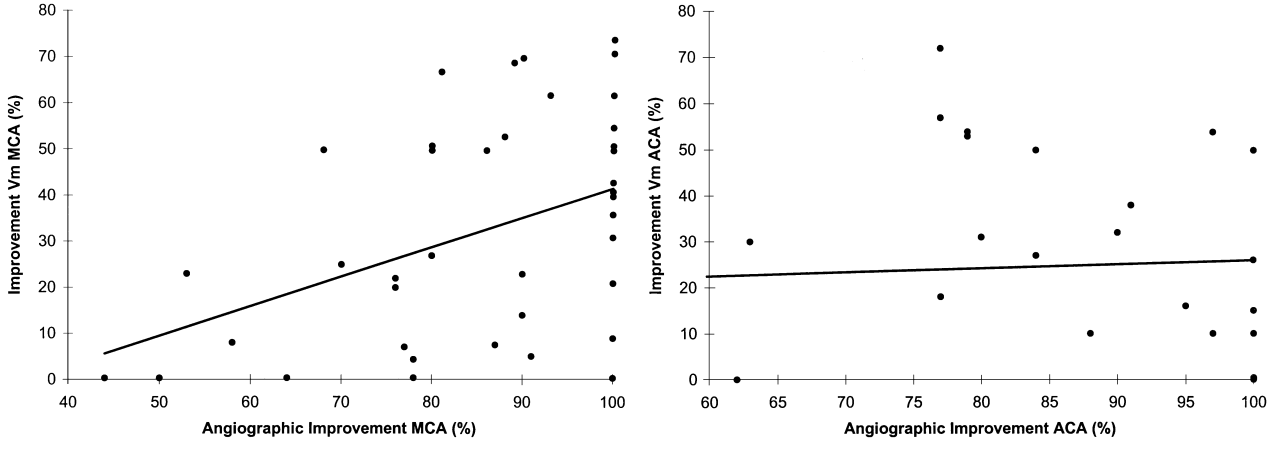

Fig. 5. Linear regressions showing correlations between the percentage of improvement of flow velocities during vasospasm and the percentage of angiographic improvement of vessel diameter (MCA: n: 26, number of vessels treated (M1): 42, $r = 0.42, p < 0.001$; ACA: n: 17, number of vessels treated: 26, $r = 0.1, p < 0.05$); *Vm* mean flow velocity; *MCA* middle cerebral artery; *ACA* anterior cerebral artery

of cerebral vasospasm, the importance of retrospective studies reporting results in patients who underwent all available therapies should not be underestimated. These reports deserve the attention of the worldwide medical community, which have the responsibility to apply or adjust management protocols based on financial, technological, and human resources available in their milieus.

Our management protocol is based on the prevention of early rebleeding of the ruptured aneurysm [38,

82] and DIND caused by cerebral vasospasm. HHH-therapy constitutes the basis of the intensive care treatment after aneurysmal SAH since its introduction by Kassell *et al.* [34] in the early 1980's. In spite of the fact that this therapy has not been proven in controlled studies, several reports demonstrated improvement of neurological deficits during vasospasm [4, 62], probably as a consequence of a sustained increase of CBF [56]. If HHH-therapy is to be employed, careful monitoring of the patient is necessary, involving an arterial line and either a central venous line or, preferably, a pulmonary catheter to guide vasopressor and volume management. In our series we did not observe any complications due to PA catheterization and PCWP monitoring. We believe, therefore, that the haemodynamic information obtained from Swan-Ganz catheters allows the prevention of other more common complications such as pulmonary oedema or cardiac failure, which might severely compromise the CBF and cerebral oxygenation [18]. In our series, HHH-therapy and haemodynamic monitoring were continued beyond the period of risk for vasospasm or until abatement of vasospasm by clinical and TCD parameters.

Nimodipine, which consistently reduces poor outcome due to vasospasm [2], constitutes the only calcium-channel antagonist routinely included in our protocol. The free radical scavenger tiralazad was given to ten patients in this series, nevertheless, based on the controversy that emerged from the European-Australian [36] and North American [23] trials and considering cost-benefit aspects, we decided to exclude this medication from our protocol after a one-year period of routine administration in men.

Neuro-interventional procedures such as PTA and intra-arterial PPV infusion constitute the next step in the treatment of cerebral vasospasm [16]. These modalities, which were routinely introduced in our hospital in 1993, must be considered only with optimal medical and well-monitored intensive care management that is maintained during and after the procedures in order to sustain the achieved improvements of cerebral oxygenation patterns [17].

The concept of *medical intractability* has been added recently to our management protocol. This group includes patients in whom vasospasm signs recurred or became refractory after maximal medical and endovascular therapy. In our series, vasospasm recurrence could be documented angiographycally in six patients (20%) who were treated in two or three PTA/PPV sessions. Three patients (50%) who underwent repeated endovascular treatment could resume their previous jobs (GOS 5) and no evidence of cerebral infarction could be demonstrated. These observations coincide with the study by Numaguchi *et al.* [55], who observed clinical improvement in half of the patients who underwent a second session of PPV infusion, we believe, nevertheless, based on our experience, that better final outcome could be achieved if PPV were combined with PTA in cases of proximal vessel narrowing.

In addition, we reported in this study the clinical results of five patients with intractable vasospasm who underwent repeated endovascular treatment combined with barbiturate therapy as *ultima ratio*. Early experiments and clinical experiences in the 1970's have shown that barbiturates might be useful in the treatment of cerebral oedema [7, 68, 69]. The effects of barbiturates have been studied mainly in brain oedema caused by head injury [46, 54, 57, 60, 61, 67, 75, 78, 79], and metabolic coma [45, 61], and in the spinal cord [27]. The use of barbiturates in cerebral ischaemia and stroke is still controversial, considering that most of the studies have focused on the reduction of ischaemic brain oedema [9, 10, 28, 51, 70, 72, 81] rather than a cerebral protection mechanism [29, 65, 63, 66]. Large doses of barbiturates during intracranial aneurysm surgery were reported to be safe in cases in whom a compromised cerebral circulation could be anticipated [6, 73]. Kassell *et al.* [35] reported alterations in CBF, EEG and oxygen metabolism in dogs receiving high-dose barbiturate therapy [36]. Based on these results, the authors treated 12 patients with progressive ischaemic neurological deficits caused by cerebral vasospasm after SAH [37]. The results of this study were discouraging since 11 of the 12 patients died due to medical complications or uncontrolled intracranial hypertension. The patients included in this study were, however, comatose due to ischaemic lesions and were probably in irreversible (infarction) vasospasm stages. Considering the advances in neuromonitoring techniques and neuro-interventional procedures, we began a study of intractable vasospasm cases combining early/repeated PTA/PPV infusion with BC. Early results of this ongoing study have been reported elsewhere [18] and have been recently supported by Armonda *et al.* [3], who reported 32 patients in whom high-dose pentobarbital administration was part of combined therapy. The renaissance of barbiturate therapy in vasospasm (combined with modern neuromonitoring and therapeutic tools such as PTA and PPV) should,

nevertheless, be evaluated in controlled studies and deserves careful cost-benefit analysis.

Clinical, Angiographic, and Sonographic Results

Since the introduction of PTA by Zubkov *et al.* [84] in 1984, numerous reports describing profound neurological improvement have been described worldwide [5, 14, 15, 19, 39, 41, 42, 52, 76, 77]. The improvement after PTA, which has been demonstrated angiographically [14, 26, 52], in terms of CBF [19, 42], and by transcranial Doppler [13], seems to be sustained. PTA, nevertheless, has limitations in the treatment of distal or sharply angled vessels. PPV has been introduced as an alternative therapeutic tool in these cases [32, 33, 43] and early clinical improvement in as much as 80% of the cases has been reported [8, 32, 33, 44, 47, 47–50]. Milburn *et al.* [49] reported an increase in proximal, intermediate and distal arterial diameters after PPV infusion, ranging from 2.8 to 73.9%, with a mean increase of 26.5%. We found in the present series higher angiographic improvement, especially in the M1 and A1 segments. Our results, however, might be influenced by the fact that combined therapy with PTA and PPV was undertaken in 26% of the cases. In addition, the timing of EP probably played an important role in our protocol since 47% of the patients presented exclusively with DLC and were treated in a very early stage of vasospasm where vasodilator mechanisms of PPV might be more effective [21]. PPV improves cerebral oxygenation and might prevent stroke during severe vasospasm [17], nevertheless; its short-term vasodilator effects have brought into question its consequences on final outcome [21, 32, 33, 44, 49, 55].

The clinical significance of endovascular treatment of vasospasm has not been evaluated in controlled studies. In an effort to evaluate the clinical significance of PPV, Polin *et al.* [58] retrospectively examined a subgroup of patients of the North American Trial of Tiralazad [23] who received PPV and were matched with individuals who exhibited similar clinical characteristics but received medical management alone. The authors found no statistical difference in outcome after three months. More recently, the same author reported the short-term neurological improvement after PPV and PTA analysing subgroups of patients from the aforementioned trial [59]. In spite of the fact that improvement in TCD could be demonstrated in both treatment groups, there was no significant difference in clinical improvement on days 1 and 4 postprocedure. Heterogeneity in treatment protocols, intensive care monitoring, and timing of therapy among centers might influence these valuable retrospective studies. In addition, the authors evaluated PPV effects based on the motor GCS. These results can hardly be extrapolated to series such as ours, in which endovascular therapy was indicated in 47% of the patients based exclusively on decreased levels of consciousness without any motor deficit. According to our experience and considering that this study was intended to evaluate our management protocol and not endovascular procedures, we believe that EP has contributed to the decrease of mortality and the improvement favourable outcomes in our center. In the present series, 73% of the patients had favourable outcomes, and mortality due to devastating vasospasm was 6.6%. In addition, we believe that the major social and financial impact lies with the 20% severe disability which could be demonstrated in our patients. Our results differ from those reported by Polin *et al.* [58], where favourable outcomes (GOS 4–5) in the 31 patients receiving PPV was observed in 45% of the cases, severe disability in 29%, and mortality in 25% of the patients. For these reasons we believe that results of retrospective and multicentric trials must be carefully analysed and should not be extrapolated without considering the outcome in each center. Until new medical therapeutic tools arise, endovascular procedures cannot be categorically excluded from the management of vasospasm.

Early clinical results after EP must be evaluated not only in terms of early clinical results but also in terms of final outcome. In our series, 73.3% of the patients improved from their clinical deficits after EP. We found a significant association between early clinical improvement and favourable outcome, which other authors have also observed. In a series of cases undergoing PTA, Newell *et al.* [52] reported that the only two deaths occurred in patients who showed only transient improvement or no improvement. Moreover, in the series published by Higashida *et al.* [26], three out of the four patients who died were clinically unchanged after PTA. Le Roux *et al.* [41] reported that in 5 cases where PTA was performed after surgery, the only death occurred in one patient who did not improved immediately after PTA. Kaku *et al.* [32] observed that poor outcome was associated with no clinical improvement in patients who underwent PPV infusion without PTA [32].

The impact of repeated infusion of PPV on final

outcome is still controversial. Four out of six patients in our series who underwent repeated EP could resume their daily activities or previous jobs. Numaguchi *et al.* [55] reported, however, that only two of nine patients undergoing repeated PPV infusion had a good recovery. The timing of the treatment might influence the effects on final outcome after PPV infusion or repeated PPV infusions and could constitute a significant bias in the recent controversy about additional benefits of PPV in vasospasm [58, 59]. Most of the patients in our series who underwent only PPV infusion presented only with DLC due to distal vessel narrowing and, therefore, probably were treated at an earlier stage than those who were included in other studies [8, 13, 55].

TCD was introduced in 1982, enabling the understanding of cerebral haemodynamic mechanisms [1]. The time course of Vm changes during vasospasm has been described [24]; however, its impact for predicting neurological deficit and improve outcome remains controversial [40, 80]. In this study we evaluated the sonographic improvements and significant decreases of Vm, which could only be demonstrated in the M1 and A1 segments. Sustained improvement of TCD findings in a consecutive series of 50 patients undergoing PTA was reported by Eskridge *et al.* [14]; nevertheless, precise information regarding Vm values angiographic findings was not available in his report. In patients receiving PPV who were enrolled in the North American Trial of Tirilazad, TCD values did not correlate with improved clinical outcomes [58]. Recently, higher decreases of Vm after PTA compared to PPV have been reported (PPV: Vm decrease -18.4 cm/sec, PTA: Vm decrease: -26.04 cm/sec, $p = 0.55$); however, no correlation with short-term neurological improvement could be demonstrated [59]. In the present series, Vm decreased significantly from 135 ± 48 cm/sec to 87 ± 32 cm/sec in the MCA and 110 ± 37 cm/sec to 84 ± 30 cm/sec in the ACA. In spite of the fact that we observed clinical improvement associated with Vm decreases, we evaluated the TCD findings regardless of the type of endovascular therapy that the patient received, considering that the aim of this study was an evaluation of our management protocol and not the comparison of different therapeutic tools.

Finally, complications after EP have to be divided into those caused by mechanical factors during catheterization such as spasm or rupture of the vessel, and those secondary to reperfusion mechanisms as consequence of improvement of vessel diameter or vasodilator effects of PPV. Eskridge *et al.* [14] reported mortality in two patients after vessel rupture during PTA. Transient neurological deterioration, pupil dilatation, and increase of ICP have been reported after PPV infusion [33, 47, 49]. In our series, one patient developed a transient left arm paresis after PPV infusion and four patients developed ICP increases after PPV infusion.

Conclusions

In our experience, a reduction of mortality and disability after cerebral vasospasm can be achieved with a maximal structured treatment of vasospasm. In this series, weak correlation coefficients between vessel diameter and increases of Vm during vasospasm were observed. In spite of the fact that significant differences in vessel diameters and flow velocities could be demonstrated, a moderately good correlation between percentages of angiographic and sonographic improvement after treatment was observed only in the M1 segments. Early clinical improvement after endovascular treatment is strongly associated with a favourable outcome, nevertheless, cost-benefit and controlled trials are necessary to evaluate these techniques.

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Comments

The paper describes and retrospectively analyses the treatment protocol used in a series of patients with symptomatic vasospasm secondary to aneurysmal subarachnoid haemorrhage. The protocol includes an aggressive intensive care management, endovascular procedures and barbiturate coma. The aim of the study was to evaluate the outcome of patients submitted to a structured treatment protocol, rather than evaluate a specific treatment.

The management of cerebral vasospasm is still controversial. There is to date no large prospective controlled clinical trial that validates any of the therapeutic modalities available to the treatment of vasospasm. We agree with the authors when they state the importance of studies which could report retrospectively and in a rational basis the outcome of patients submitted to different available therapies. The paper describes a favourable outcome (GOS 4 and 5) in 73% of patients and a surprisingly good outcome for cases considered ''intractable'' who were submitted to barbiturate coma. Their overall favourable outcome is superior to those described in previous reports and may be related to the proper timing of the introduction of the treatment as described in the paper. A very logical sequence of treatment based on strict clinical and sonographic criteria is described. The close monitoring of such patients is well stressed.

Cerebral vasospasm is due to the presence of blood clot in the subarachnoid space. Contrary to the authors's attitude, it is our policy to attempt total removal of blood clot from the basal cisterns during surgery. We believe that it could help in preventing vasospasm and also the occurrence of late hydrochephalus.

The authors report on the CT findings according to Fisher's grading scale but do not report on the presence of acute ventricular dilatation. This finding could eventually influence the choice of the more appropriate device to measure the intracranial pressure. Incracranial pressure measurement was undertaken in 8 out of 30 patients but its indication was not described.

All patients were operated on within 48 hours after hospital admission. The time interval from SAH to the development of vasospasm is described in the paper. However the time interval from SAH to surgery is not described and one can only surmise about the influence of surgical timing on the final outcome.

We look forward to hearing about the results of the ongoing study which will analyse the outcome of a larger subgroup of patients submitted to barbiturate coma for the treatment of refractory vasospasm. We hope it could establish the potential benefit of that treatment as a tool in the management of this entity.

Evandro de Oliveira,
Hung Tzu Wen,
M. Ferreira

Correspondence: Javier Fandino, M.D., Department of Neurosurgery, University Hospital Zurich, Frauenklinikstrasse 24, 8091 Zurich, Switzerland.